INVESTIGATIONS OF NEW SYNTHETIC APPROACHES TO
IMIDAZO[4,5-e]-1,2,4-TRIAZINE (6-AZAPURINE)
AND PYRIMIDO[4,5-e]-1,2,4-TRIAZINE (6-AZAPTERIDINE)
DERIVATIVES AND RELATED POLYAZA HETEROCYCLES

By

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Thesis presented for the degree of Doctor of Philosophy

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To Nanna and Grandpa
DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record was carried out by me and that it has not been submitted in any previous application for a Higher degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1985 and September 1988.
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Dr. I. H. Sadler (University of Edinburgh)

"Mass Spectrometry"
Several speakers (Kratos Ltd.)

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ABSTRACT

This thesis is concerned with the development of new, general, synthetic approaches to aza- and deaza-aza-pteridines and purines of potential biological interest. The construction of derivatives of four such ring systems, all containing a 1,2,4-triazine nucleus was studied.

Synthesis of two types of aza- and deaza-aza-pteridines were investigated, namely 6-azapteridines and 6-aza-1-deaza-pteridines. The formation of both types involved the use of appropriately functionalised 1,2,3-triazolylhydrazones, cyclisation of which afforded the corresponding 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives as key starting materials. In the case of 6-azapteridine synthesis, subsequent annulation gave the respective tricyclic 1,2,3-triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine derivatives, acid-catalysed triazole scission of which to the respective pyrimido[4,5-e]-1,2,4-triazine (6-azapteridine) derivatives was unsuccessful. However, general access to the latter was provided by acid-catalysed scission of the precursor 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives followed by annulation.

In the case of 6-aza-1-deaza-pteridine synthesis, annulation of the appropriate bicyclic 1,2,3-triazolo-[1,5-b]-1,2,4-triazine derivatives afforded the corresponding 1,2,3-triazolo[1,5-b]pyrido[4,3-ε]-1,2,4-triazines. The latter underwent smooth acid-catalysed triazole scission providing a general route to variously functionalised pyrido[4,3-ε]-1,2,4-triazine (6-aza-1-deazapteridine)
derivatives.

Syntheses of the two classes of aza- and aza-deaza-purines investigated were based on a common type of 1,2,3-triazolo[1,5-b]-1,2,4-triazine intermediate, bearing a readily displaceable benzenesulphonyl moiety ortho to an amino-group in the triazine ring. The construction of 6-azapurines was approached by nucleophilic displacement of the benzenesulphonyl group with cyanamide anion with concomitant cyclisation of the resulting ortho-amino cyanamide products giving the corresponding tricyclic 1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine derivatives. However, attempts to obtain molecules of the latter type appropriate for acid-catalysed triazole scission to imidazo[4,5-e]-1,2,4-triazines (6-azapurines) were unsuccessful.

Synthesis of 6-aza-7-deaza-purines used a similar approach to that investigated for 6-azapurines, namely nucleophilic displacement of the benzenesulphonyl group in ortho-amino-benzenesulphonyl 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives but using stabilised carbanions rather than amide ions. Acid-catalysed triazole scission of the resulting tricyclic 1,2,3-triazolo[1,5-b]-pyrrolo[2,3-e]-1,2,4-triazine derivatives then afforded a new and potentially general route to pyrrolo[2,3-e]-1,2,4-triazine (6-aza-7-deazapurine) derivatives.
CONTENTS

Preface 1

Chapter One

A survey of Synthetic Routes to 1,2,4-Triazine Analogues of Aza and Deaza-aza Purines and Pteridines 4

Chapter Two

New Synthetic Approaches to Pyrimido[4,5-e]-1,2,4-triazine (6-Azapteridine) Derivatives Based on Triazole Scission Reactions of 1,2,3-Triazolo-[1,5-g]pyrimido[4,5-e]-1,2,4-triazine Derivatives. 24

Experimental 66

Chapter Three

New Synthetic Approaches to Pyrido[4,3-e]-1,2,4-triazine (6-Aza-1-deazapteridine) Derivatives Based on Triazole Scission Reactions of 1,2,3-Triazolo-[1,5-b]pyrido[4,3-e]-1,2,4-triazine Derivatives 148

Experimental 176
Chapter Four

Investigations of the Synthesis and Reactivity of 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine Derivatives en Route to Imidazo-[4,5-ε]-1,2,4-triazine (6-Azapurine) and Pyrrolo-[2,3-ε]-1,2,4-triazine (6-Aza-7-deazapurine)

Derivatives 223

Experimental 243

General Experimental Data 270

Bibliography 272
PREFACE

Of all the naturally occurring heterocyclic compounds known, derivatives of the pyrimido[4,5-\textit{d}]pyrazine (pteridine) and imidazo[4,5-\textit{d}]pyrimidine (purine) systems (1) and (2) are perhaps of greatest biological importance. The pteridine ring system (1) for example is found in tetrahydrofolic acid (3) which functions as a co-enzyme in purine biosynthesis.

\[
\begin{align*}
\text{(1)} & \quad \text{(2)} \\
\end{align*}
\]

Biopterin\textsuperscript{1} (4), a co-factor of three very important mammalian enzymes also contains the pteridine ring system.

\[
\begin{align*}
\text{(3)} \\
\end{align*}
\]

\[
\begin{align*}
\text{(4)} \\
\end{align*}
\]
As components of nucleic acids, the purine bases adenine (5) and guanine (6) are essential for cell growth and replication. Substances structurally related to such nucleic acid bases [e.g. tubercidin (7)] have been applied successfully in cancer chemotherapy as they act by incorporation as isosteres of nucleic acid bases thus resulting in the blockade or modification of nucleic acid synthesis.

The biological activity of polyazaheterocyclic isosteres of the aforementioned purine and pteridine systems has not previously been comprehensively investigated. The present thesis is concerned with the development of new, general methodology for the construction of novel aza- and deaza- purine and pteridine ring systems. By way of introduction, chapter 1 provides a survey of literature methods for the synthesis of derivatives of such ring
systems as well as a discussion of their biological properties. This is followed in chapters 2 to 4 by an account of the results obtained in the present studies.
Chapter 1

A Survey of Synthetic Routes to 1,2,4-Triazine Analogues of Aza and Deaza-aza Purines and Pteridines
A Survey of Synthetic Routes to 1,2,4-Triazine Analogues of Aza and Deaza-aza Purines and Pteridines

The following literature survey of synthetic routes to aza- and deaza- azapteridine and azapurine analogues is concerned only with bicyclic 6:6 and 6:5 ring systems relevant to the subject material of subsequent chapters i.e. pyrimido-1,2,4-triazines, pyrido-1,2,4-triazines, imidazo-1,2,4-triazines and pyrrolo-1,2,4-triazines. Condensed 1,2,4-triazine ring systems containing bridgehead-fused nitrogen atoms are excluded from the survey.

1.1 PYRIMIDO-1,2,4-TRIAZINES

Two azapteridine ring systems of the pyrimido-1,2,4-triazine type are possible (Scheme 1) wherein the ring nitrogen atoms in the pteridine nucleus remain unscrambled, namely the pyrimido[5,4-e]-1,2,4-triazine (8) or 7-azapteridine ring system and the pyrimido[4,5-e]-1,2,4-triazine (9) or 6-azapteridine ring system. These structures arise from the incorporation of nitrogen atoms in place of methine groups as indicated by the arrows at the 6- or 7- position of the pteridine ring (according to the numbering system adopted for pteridine (1) in Chemical Abstracts).
Scheme 2
1.1.1 Synthetic Routes to Pyrimido[5,4-e]-1,2,4-triazines (7-Azapteridines)

A number of naturally occurring antibiotics exist which contain the 7-azapteridine structure (Scheme 2) notably fervenulin (10), toxoflavin (11) and reumycin (12). Toxoflavin (11) was first isolated by Van Veen and Mertens\(^3\) from the bacterium *Pseudomonas cocovenans* and has subsequently been connected with outbreaks of food poisoning.\(^4\) The potency of these 7-azapteridine derivatives as antibacterial agents is tempered by their extreme toxicity, but despite this a variety of 7-azapteridine derivatives have been synthesised with the hope of producing compounds with beneficial biological properties. Certain analogues have been shown to be effective as herbicides\(^5\) and inhibition of *Mycobacterium tuberculosis* by dihydrofolate...
(13) \[ \rightarrow \] (14)

(i) \[ HC(OEt)_3, \text{ heat.} \]

(ii) \[ Ag_2O, BaO, THF, 25^\circ. \]

Scheme 3
\((15)\) + \((16)\) 

(i) EtOH, NH\(_3\) 

\[(17)\] 

(ii) NH\(_3\), DMF, EtOH, 60\(^\circ\). 

(i) dioxane, H\(_2\)O, room temp. 

(ii) NH\(_3\), DMF, EtOH, 60\(^\circ\).

Scheme 4
reductase analogues was demonstrated by Werbel, Elslager and Johnson.

In theory, two synthetic approaches to pyrimido[5,4-e]-1,2,4-triazines are possible involving respectively the formation of the pyrimidine ring from appropriately substituted triazines or alternatively annulation of the triazine ring on to a preformed pyrimidine derivative. In practice, the latter is the method most commonly used. The former approach based on monocyclic triazines was first carried out only recently in 1985.

(a) Synthetic Routes to Pyrimido[5,4-e]-1,2,4-triazines
Based on Pyrimidine Precursors

The first synthesis of the parent of the pyrimido[5,4-e]-1,2,4-triazine series, 7-azapteridine (8) (Scheme 3) was reported by Biffin, Brown and Sugimoto and involved the reaction of 5-amino-1,2,4-triazin-6-ylhydrazine (13) with triethyl orthoformate to give a dihydro derivative (14) followed by oxidation with silver oxide in the presence of barium oxide [(14) -> (8)].

This type of approach involving the annulation of an ortho-aminopyrimidylhydrazine is also illustrated (Scheme 4) by the condensation of the 4-benzylthio-5-amino-1,2,4-triazin-6-ylhydrazine (15) with a range of aryl imidates [e.g. (16)] to afford the corresponding 5-benzylthiopyrimido [5,4-e]-1,2,4-triazines (17) ammonolysis of which affords...
Scheme 5

(i) MeNHNNH₂, heat.

Scheme 6

(i) H₂, Pd-C.

(ii) Ag₂O, MeOH, heat.
\[(26)\] + \[(27)\] \rightarrow \[(28)\] \rightarrow \[(29)\] \rightarrow \[(30)\]

(i) conc. HCl, EtOH, heat.

Scheme 7
the respective pyrimido[5,4-e]-1,2,4-triazine-5,7-diamines (18) in moderate yields.

Ring closure through formation of the 2,3-bond of the triazine ring (Scheme 5) led to the first total synthesis of toxoflavin (11). This approach involved the reaction of 6-chloro-5-formamido-3-methylpyrimidine-2,4(1H,3H)-dione (19) with methylhydrazine to give the hydrazino derivative (20). On heating, water was eliminated and cyclisation gave the dihydro derivative (21) which spontaneously oxidised to the final product (11).

A similar approach is illustrated (Scheme 6) based on an ortho-acylhydrazino-nitropyrimidine (22). Reduction of the nitro group to amino and subsequent cyclisation of the amine (23) affords the dihydro derivative (24) which readily oxidises to yield the 7-azapteridine (25). In contrast to the previous example, the group in the 6-position of the pyrimidine ring contains the carbonyl functionality.

Alternatively, pyrimido[5,4-e]-1,2,4-triazines can be synthesised by cyclisation of 2-alkylidene- or 2-arylidenehydrazinopyrimidines. An example of this method is shown (Scheme 7) where the nitrosopyrimidine derivative (26) is condensed with the benzaldehyde (27) to afford an intermediate (28) which undergoes acid-catalysed cyclisation. Elimination of water from the cyclic intermediate (29) affords the 7-azapteridine derivative (30).

A more recent approach employing a similar strategy
(i) N-bromosuccinimide, CHCl₃, reflux.

(ii) AcOH, reflux.

Scheme 8
Scheme 9

(i) RNCS.

(ii) N-bromosuccinimide.
Etc9X

N,SMe\(_2\) (i)

Cl (40)

(i)

RCNC

N\(_2\) Sme

(41)

(ii)

R

B

a; \text{NH}_2

b; \text{Ph}

(\text{i}) (H\textsubscript{2}N)\textsubscript{2}C=NH or Ph (H\textsubscript{2}N)C=NH, EtOH, room temp.

(\text{ii}) K\textsubscript{2}CO\textsubscript{3}, DMF, heat.

\textbf{Scheme 10}
(Scheme 8) has been reported by Kanazawa, Nishigaki and Senga.\textsuperscript{12} Bromination of the 1,3-dimethyluracil derivative (31) with N-bromosuccinimide followed by acid catalysed hydrolysis of the bromo derivative (32) afforded the 5-bromo-6-hydrazino derivative (33). This then reacted with one molecule of the precursor (32) to give a dimeric uracil intermediate (34) which cyclised to (35). Elimination of 5-bromo-1,3-dimethyl-6-methylaminouracil and subsequent acid-catalysed demethylation and aromatisation afforded 3-phenyl fervenulin (36) in 12\% yield.

The 7-azapteridine system has also been shown (Scheme 9) to be accessible by ring closure of the 1,2- bond of the triazine ring.\textsuperscript{13} The di-amino pyrimidine (37) was reacted with an isothiocyanate to yield the thiourea (38). Oxidative cyclisation using N-bromosuccinimide gave the dihydro- derivative (39).

(b) Synthetic Routes to Pyrimido[5,4-e]-1,2,4-triazines
Based on 1,2,4-Triazine Precursors

Syntheses of pyrimido[5,4-e]-1,2,4-triazines involving 1,2,4-triazine derivatives prior to 1984 utilised triazine precursors derived by ring-closure of other pyrimido[5,4-e]-1,2,4-triazines (prepared from pyrimidine derivatives by synthetic routes of the type already described). Huang\textsuperscript{7} however in 1985 devised a route (Scheme 10) to 7-azapteridines (and 6-azapteridines) based on a
monocyclic 1,2,4-triazine derivative (40). Reaction of this triazine with guanidine in ethanol at room temperature affords the 5-guanidinoacyltriazone derivative (41a) which cyclises in refluxing dimethylformamide containing potassium carbonate to yield the pyrimido[5,4-e]-1,2,4-triazine derivative (42a) in 42% yield. Similarly, reaction with benzamidine leads to the corresponding 5-benzamidinoacyltriazone (41b) and finally the 7-phenyl derivative (42b) in 28% yield.

1.1.2 Synthetic Routes to Pyrimido[4,5-e]-1,2,4-triazines (6-Azapteridines)

Although no naturally occurring 6-azapteridines have been reported to date, many synthetic 6-azapteridines exhibit both antibacterial and antiviral activity. In addition, several reports in the literature describe the analgesic and antiinflammatory properties of 6-azapteridines. At present, available synthetic routes to 6-azapteridines fall into three categories namely annulation of a triazine ring to a preformed pyrimidine and vice versa and less commonly, the oxidative ring expansion of certain purine derivatives.

(a) Synthetic Routes to Pyrimido[4,5-e]-1,2,4-triazines Based on Pyrimidine Precursors

The first synthesis of a 6-azapteridine derivative
(i) AcOH, room temp.

(ii) pyridine, heat.

Scheme 11
(i) Pb(OAc)$_4$, AcOH, 50 - 55°.

(ii) POCI$_3$, heat.

(iii) H$_2$NNH$_2$, H$_2$O, room temp.

(iv) HgO, H$_2$O, room temp.

Scheme 12
Scheme 11) was reported by Heinisch and his co-workers in 1964.\textsuperscript{15} Reaction of the alloxan derivative (43) with S-ethylthiosemicarbazide (44) affords the intermediate dihydroxy compound (45) which is readily dehydrated in refluxing pyridine to yield the 3-ethylthiopyrimido[4,5-e]-1,2,4-triazinedione (46), useful via nucleophilic displacement reactions as a precursor of other 6-azapteridine derivatives.

The commonest preparation of 7-azapteridines involving the construction of the 1,2,4-triazine moiety from orthoaminopyrimidinylhydrazines has also been applied to 6-azapteridine synthesis. Thus (Scheme 12) the orthoaminopyrimidinylhydrazine (47) undergoes oxidative cyclisation on treatment with lead tetraacetate in glacial acetic acid to afford the pyrimido[4,5-e]-1,2,4-triazinetrione (49) via the probable intermediacy of the N-ethoxycarbonyl derivative (48).\textsuperscript{16} Treatment of the pyrimidotriazinetrione with phosphoryl chloride results in its smooth conversion into the chloro-compound (50) hydrazinolysis of which followed by oxidative deamination of the resulting hydrazine product (51) provides a convenient route (49\% yield) to the 3-unsubstituted pyrimidotriazine (52).

(b) Synthetic Routes to Pyrimido[4,5-e]-1,2,4-triazines
Based on 1,2,4-Triazine Precursors

The second general approach to pyrimido[4,5-e]-1,2,4-
Scheme 13

(i) \((\text{EtO})_2\text{C}=\text{O}, \text{NaOEt, EtOH, heat.}\)

(ii) \(\text{H}_2\text{NCH}=\text{O, NaOEt, heat.}\)

Scheme 14

(i) \((\text{H}_2\text{N})\text{C}=\text{NH or Ph( NH}_2\text{)C}=\text{NH, EtOH, 0° then room temp.}\)
(i) $\text{H}_2\text{NOSO}_3\text{H}$.

(ii) $\text{Pb(OAc})_4, \text{CH}_2\text{Cl}_2$.

*Scheme 15*
triazines involves the annulation of a pyrimidine ring to a preformed 1,2,4-triazine ring and in contrast to the case of 7-azapteridines this method is more successful for the synthesis of 6-azapteridines. In 1965, Taylor and Morrison\textsuperscript{17} reported the first synthesis of this type as illustrated by the condensation reactions of 3,5-diamino-1,2,4-triazine-6-carboxamide (53) outlined in Scheme 13 to afford the 6-azapteridines (54) and (55). More recently, Huang\textsuperscript{7} reported a synthesis of 6-azapteridines also based on 1,2,4-triazines. Treatment of the monocyclic triazine derivative (56) with guanidine or benzamidine (Scheme 14) afforded the corresponding guanidino- and benzamidinoacyltriazines (57a) and (57b). Cyclisation gave the 6-azapteridines (58a) and (58b) in moderate yield which are isomers of the 7-azapteridines (42a) and (42b) prepared in the same manner (See Scheme 10).

(c) Synthetic Routes to Pyrimido[4,5-e]-1,2,4-triazines Based on Purine Precursors

Perhaps the most unorthodox synthesis of a pyrimido[4,5-e]-1,2,4-triazine (Scheme 15) has been described recently by Pozharskii and his co-workers\textsuperscript{18} who showed that oxidation of 7-aminootheophylline (60) with lead tetraacetate in methylene chloride resulted in its ring expansion to isofervenulin (52). Since 7-aminootheophylline (60) is readily accessibly by amination of theophylline (59)
with hydroxylamine-O-sulphonic acid, Pozharskii's method represents a potentially general synthesis of 6-azapteridines from purine derivatives.

1.2 PYRIDO-1,2,4-TRIAZINES

Four pyrido-1,2,4-triazine ring systems whose structures are shown in Scheme 16 can be categorised as deaza-azapteridine structures, their aza/deaza relationship to the basic pteridine nucleus (1) being denoted by arrows to indicate the insertion (aza-) or deletion (deaza-) of nitrogen atoms involving the pteridine framework (1).

Scheme 16
The four ring systems are named systematically according to Chemical Abstracts as pyrido[3,4-e]-1,2,4-triazine (or 1-deaza-7-azapteridine) (61), pyrido[4,3-e]-1,2,4-triazine (or 1-deaza-6-azapteridine) (62), pyrido[3,2-e]-1,2,4-triazine (or 8-deaza-4-azapteridine) (63) and pyrido[2,3-e]-1,2,4-triazine (or 5-deaza-4-azapteridine) (64).

A survey of the literature indicates that derivatives of the four pyrido-1,2,4-triazine ring systems [(61) - (64)] appear to be almost exclusively synthesised from appropriately substituted pyridines. However, two interesting exceptions (which are discussed in detail later) are the formation of certain pyrido[3,2-e]-1,2,4-triazines by a photochemical rearrangement of 3-methylisoaxazolo[4,5-e]pyridines\(^\text{19}\) and the annulation of a 5,6-disubstituted 1,2,4-triazine to give a pyrido[2,3-e]-1,2,4-triazine\(^\text{20}\)

1.2.1 The Biological Activity of Pyrido-1,2,4-triazines

(a) Pyrido[4,3-e]-1,2,4-triazines (62)

The only report relating to the biological activity of this ring system is that of Lewis and Sheperd\(^\text{21}\) who have described the usefulness of 3-amino derivatives and the corresponding N-oxides as antibacterial, antifungal and antiinflammatory agents.
(b) Pyrido[3,4-e]-1,2,4-triazines (61)

The use of pyrido[3,4-e]-1,2,4-triazine derivatives as antimicrobial agents was reported in 1973. Two years later Wright, Bayless and Grey described the synthesis of 3-benzyl- and 3-phenoxyethylpyrido[3,4-e]-1,2,4-triazines which inhibited skin-infecting fungi in vitro. More recently, Hungarian chemists have prepared pyrido[3,4-e]-1,2,4-triazine derivatives which are reputed to be analgesics, tranquilisers and antidepressants.

(c) Pyrido[3,2-e]-1,2,4-triazines (63)

As in the case of pyrido[3,4-e]-1,2,4-triazines, pyrido[3,2-e]-1,2,4-triazine derivatives have been extensively studied for biological activity and have been found to possess antimicrobial, antibacterial, anti-inflammatory and antifungal properties. A more unusual effect of one derivative was the inhibition of locomotor activity in mice.

(d) Pyrido[2,3-e]-1,2,4-triazines (64)

As might be expected, pyrido[2,3-e]-1,2,4-triazines derivatives have also been found to exhibit biological activity most notably as antibacterial agents and tranquilisers.
(i) \((\text{H}_2\text{N})_2\text{C} = \text{NH}\). HCl, NaOMe, MeOH, 45 - 50°.

(ii) heat.

(iii) \(\text{H}_2\), Pd - C.

(iv) \(\text{H}_2\), Ni, EtOH.

(v) \(\text{K}_3^+ [\text{Fe} (\text{CN})_6]^{3-}\), KOH, H\(_2\)O, 0 -5°.

Scheme 17
(i) $\text{(H}_2\text{N})_2\text{C}=\text{NH}, \text{t-BuOH, reflux.}$

(ii) 1-5% w/v NaOH, H$_2$O, 100$^\circ$.

(iii) >5% w/v NaOH, H$_2$O.

Scheme 18
1.2.2 Synthetic Routes to Pyrido-1,2,4-triazines

With only one or two noteworthy exceptions which will be discussed later, existing general synthetic approaches to derivatives of the four possible pyrido-1,2,4-triazine ring systems have been repetitive in their use of substituted nitropyridines as starting materials. Syntheses have been reported for the construction of all four ring systems in which the nitro-group of variously orientated nitropyridines becomes N-1 in the annulated triazine ring.\(^3\)

One such synthesis\(^3\) is illustrated (Scheme 17) by the formation of a pyrido[4,3-e]-1,2,4-triazine derivative (68) involving the reaction of 4-methoxy-3-nitropyridine (65) with guanidine hydrochloride in the presence of sodium methoxide to afford the N-oxide derivative (66). Catalytic reduction of the latter yields the 3-aminopyrido[4,3-e]-1,2,4-triazine (67), which can be further reduced with Raney nickel in ethanol to the dihydro species (68). This second reduction is reversible and derivative (67) may be regenerated by oxidation of the dihydro product in aqueous potassium hydroxide.

A further illustration of this mode of cyclisation (Scheme 18) is an extension of the Arndt synthesis\(^3\) of benzo-1,2,4-triazine N-oxides applied to pyrido[2,3-e]-1,2,4-triazines as reported by Carbon and Tabata.\(^2\) The reaction of a 2-chloro-3-nitropyridine [e.g.
\[(74) \xrightarrow{\text{(i)}} (75) \]

\[(74) \xrightarrow{\text{(ii)}} (76) \xrightarrow{[\text{O}] - \text{H}_2} (75)\]

(i) \(\text{P}_2\text{O}_5 - \text{H}_3\text{PO}_4, \text{heat}\).

(ii) \(\text{HCl (aq.)}\).

Scheme 19
(69)] with guanidine gives an isolable 2-guanidino derivative [e.g. (70)] which can be cyclised in 1-5% aqueous sodium hydroxide to give the corresponding N-oxide derivative [e.g. (71)]. However, at greater alkali concentrations, ring contraction of the N-oxide derivative [e.g. (71)] occurs resulting in the formation of triazolopyridine derivatives [e.g. (72) and (73)].

An alternative synthetic strategy for pyrido-1,2,4-triazines based on substituted nitropyridines in which the nitro- group nitrogen atom becomes N-4 of the triazine moiety avoids the formation of N-oxide derivatives. Thus, introduction of an ortho-hydrazino substituent in nitropyridines followed by reduction of the nitro group to an amino group opens up two routes for formation of various pyrido-1,2,4-triazine derivatives, namely intramolecular cyclodehydration of ortho-amino-acylhydrazinopyridines or intermolecular cyclisation of ortho-amino-hydrazinopyridines with one-carbon electrophilic reagents. The former approach has been employed in a synthesis of 3-substituted pyrido[3,2-e]-1,2,4-triazines (Scheme 19)\textsuperscript{33} involving the acid-catalysed dehydration of a 3-amino-2-(2-acylhydrazino) pyridine (74). Cyclisation was achieved in one step with polyphosphoric acid to give the pyrido-1,2,4-triazine (75). However, in an alternative strategy, cyclisation with hydrochloric acid gave the dihydro derivative (76) which subsequently oxidised to give the same product.

The intermolecular formation of pyrido-1,2,4-triazines
(i) EtOH, heat.

(ii) Mel, H₂O, pH > 7, room temp.

Scheme 20
(i) $\text{K}^+ \cdot \text{OBu}^+ , \text{Bu}^+\text{OH}, \text{toluene}, \text{room temp.}$

(ii) $\text{NEt}_3, \text{CHCl}_3, 0 - 10^\circ$.

(iii) $\text{Br}_2, \text{CHCl}_3, 0 - 10^\circ$ then at room temp.

Scheme 21
Scheme 22
from ortho-amino-hydrazino pyridines has been carried out with insertion of electrophilic reagents. One interesting example leads to the formation (Scheme 20) of a pyrido[2,3-e]-1,2,4-triazine (79) containing a useful thiomethyl group in the 3-position which is nucleophilically displaceable. The ortho-amino-hydrazinopyridine (77) reacts with carbon disulphide with elimination of hydrogen sulphide to afford the thiol (78). Methylation occurs readily with methyl iodide to give the thiomethyl derivative (79) in 50% yield.

The alternative and less orthodox synthetic approach to pyrido-1,2,4-triazines involving the annulation of a pyridine ring to a preformed 1,2,4-triazine derivative has apparently been achieved in only a single instance. Thus (Scheme 21) base-catalysed cyclisation of the 1,2,4-triazine derivative (80) gave a product (81) bromination / dehydrobromination of which yielded the pyrido[2,3-e]-1,2,4-triazine product (83).

A completely unorthodox synthetic route to a pyrido-1,2,4-triazine derivative (Scheme 22) was reported by Adembri and his co-workers in 1981. These workers showed that photolysis of the isoxazolo[4,5-c]pyridine derivative (84) resulted in its rearrangement to the dihydropyrido[3,2-e]-1,2,4-triazine product (87). This novel transformation is suggested to occur by initial ring-opening of the isoxazole ring in (84) to afford a resonance-stabilised nitrene intermediate (85) followed by
rearrangement of the latter to a dipolar species (86), cyclisation of which through the hydrazine substituent accounts for the observed product (87).

1.3 IMIDAZO-1,2,4-TRIAZINES

Azapurines containing a 1,2,4-triazine nucleus are represented (Scheme 23) by the imidazo[4,5-e]-1,2,4-triazine or 6-azapurine ring system (89) which is formally derived by the insertion of a nitrogen atom at the 6-position in purine (88) [see arrow in structure (89)]. Basically there have been

![Scheme 23](image)

three synthetic approaches to this ring system, namely annulation of an imidazole moiety to 1,2,4-triazine derivatives and the reverse, annulation of a triazine nucleus to imidazole derivatives and less orthodoxly, ring contraction of pyrimido[5,4-e]-1,2,4-triazine derivatives.

As yet, no biological activity has been attributed to derivatives of the imidazo[4,5-e]-1,2,4-triazine ring
(i) NaH, DMF, 0°.

(ii) K₂CO₃, DMF, heat.

Scheme 25
1.3.1 Synthetic Routes to Imidazo[4,5-e]-1,2,4-triazines

An obvious route to imidazo[4,5-e]-1,2,4-triazines involves the intermolecular cyclisation of 5,6-diamino-1,2,4-triazines with one-carbon electrophilic reagents. This approach is illustrated (Scheme 24) by the reaction of 5,6-diamino-3-methylthio-1,2,4-triazine (90) with triethyl orthoformate which

\[
\begin{array}{c}
\text{H}_2\text{N} \quad \text{N} \quad \text{N} \\
\text{H}_2\text{N} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{SMe} \\
\end{array}
\]

(90) \quad \text{(i)} \quad (91)

(i) H\text{C(OEt)}_3, \text{conc. HCl, heat.}

Scheme 24

provided the first 6-azapurine (91) lacking substituents on nitrogen.\(^{35}\) A similar synthesis employing benzaldehyde to close the imidazole ring has been reported\(^{36}\)

6-Azapurines can also be synthesised through the intramolecular cyclisation of amidino-1,2,4-triazines\(^7\) as demonstrated (Scheme 25) by the conversion of the readily accessible 5-benzamidino-1,2,4-triazine (94) into the imidazo[4,5-e]-1,2,4-triazine derivative (95) by heating under reflux with potassium carbonate in dimethylformamide.
(i) AcOH.

(ii) EtO₂CN=NCO₂Et, fusion.

(iii) NaOEt, EtOH, heat.

Scheme 26
(i) 10% KOH, EtOH, reflux.

(ii) R\(^2\), K\(_2\)CO\(_3\), DMF, room temp.

(iii) EtO\(_2\)CN=NCO\(_2\)Et, 175 - 180\(^\circ\).

Scheme 27
Finally, 6-azapurines have been prepared by routes involving alkali-mediated ring contraction of arylidene pyrimidinylhydrazines and of pyrimido[5,4-e]-1,2,4-triazines. The latter method was used in the first 6-azapurine synthesis (Scheme 26) by Yoneda and his co-workers\textsuperscript{37} who demonstrated that treatment of pyrimido[5,4-e]-1,2,4-triazine N-oxides [e.g. (99)] with ethanolic sodium hydroxide gave rise to the corresponding imidazo[4,5-e]-1,2,4-triazine [e.g. (101)] through the presumed intermediacy of carboxy derivatives such as (100). The synthesis of the pyrimido[5,4-e]-1,2,4-triazine starting materials [e.g. (99)] was achieved by the cyclisation of ortho-nitroso-arylidene pyrimidinylhydrazines [e.g. (96)] in acetic acid followed by in situ oxidative aromatisation of the resulting dihydro derivatives such as (98) with diethyl azodicarboxylate (D.A.D.). An interesting extension (Scheme 27) of this type of imidazo[4,5-e]-1,2,4-triazine synthesis was described by Yoneda et al\textsuperscript{38} in 1980 whereby ortho-nitroso-arylidene pyrimidinylhydrazines (102) are ring-contracted by treatment with ethanolic potassium hydroxide to give 4,5-diiminoimidazolidinone intermediates (103), the N-alkyl derivatives (104) of which can be oxidatively cyclised by D.A.D. to imidazo[4,5-e]-1,2,4-triazine derivatives (105) in high yield.

1.4 PYRROLO-1,2,4-TRIAZINES
Deaza-azapurines containing a non-bridgehead-fused 1,2,4-triazine nucleus are represented (Scheme 28) by the pyrrolo[2,3-\(e\)]-1,2,4-triazine (106) and pyrrolo[3,2-\(e\)]-1,2,4-triazine (107) ring systems, also designated as 7-deaza-6-azapurine and 9-deaza-6-azapurine respectively corresponding to the insertion of a nitrogen atom at the 6-position in purine (88) [see arrows in structures (106) and (107)] and deletion of the nitrogen atom at position 7 or 9 in purine (88) [see arrows in structures (106) and (107)].

![Scheme 28](image)
The literature to date contains no reference to derivatives of either of the pyrrolo-1,2,4-triazine ring systems (106) or (107), though a pyrrolo[3,4-e]-1,2,4-triazine derivative has been reported.⁸⁹
Chapter 2

New Synthetic Approaches to Pyrimido[4,5-e]-1,2,4-triazine (6-Azapteridine) Derivatives Based on Triazole Scission Reactions of 1,2,3-Triazolo[1,5-g]-pyrimido[4,5-e]-1,2,4-triazine derivatives
(108)  

(109)  

(110)  

(111)  

(112)  

(113)  

\( R^1 = \text{H or Me} \)  

\( X = \text{OH; OCO.Me; CI; Br} \)  

Scheme 29
New Synthetic Approaches to Pyrimido[4,5-e]-1,2,4-triazine (6-Azapteridine) Derivatives Based on Triazole Scission Reactions of 1,2,3-Triazolo[1,5-\(b\)]pyrimido[4,5-e]-1,2,4-triazine derivatives

2.1 Introduction

In view of the biological interest\(^{14}\) in the 6-azapteridine ring system (see chapter 1, page 10), studies into the development of a new, versatile, general route to 6-azapteridine derivatives were undertaken. Existing synthetic routes to such heterocycles are based primarily on annulation reactions of appropriate pyrimidine or 1,2,4-triazine derivatives and are severely limited due to the difficulty of incorporating the suitable degree of functionalisation into either the pyrimidine or the 1,2,4-triazine ring prior to annulation. This chapter is concerned with an alternative synthetic strategy (Scheme 29) which involved the construction of tricyclic bridgehead-fused 1,2,3-triazolo-heterocycles containing the 6-azapteridine framework, which it was believed could ultimately be readily unmasked via acid-catalysed triazole scission to afford the corresponding 6-azapteridine itself.

Thus, suitably aminated 1,2,3-triazolo[1,5-\(b\)]-1,2,4-triazine derivatives (111) are available by the coupling\(^{40}\)
of 1H-1,2,3-triazole-5-diazonium derivatives (108) with acetonitrile derivatives (109) via the corresponding hydrazone derivatives (110) as outlined in Scheme 29. The acid-catalysed triazole scission of bridgehead-fused 1,2,3-triazole derivatives is a well known process\textsuperscript{41-43} which has been used for the efficient construction of a variety of otherwise inaccessible or difficultly accessible heterocycles, an example particularly pertinent to the present studies (Scheme 29) being the acid-catalysed conversion of compounds originally formulated as 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives but now believed on the basis of the present studies (see later) to be the isomeric 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives [see (111)] into otherwise inaccessible 1,2,4-triazine derivatives. In the present studies it was anticipated that cyclisation of appropriately functionalised 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives (111) to tricyclic 1,2,3-triazolo[1,5-b]pyrimido-1,2,4-triazine derivatives (112) then acid-catalysed scission of the 1,2,3-triazole nucleus in the latter would provide a viable, new, general route for the synthesis of usefully functionalised pyrimido[4,5-e]-1,2,4-triazine (6-azapteridine) derivatives (113).
(i) NaOMe, MeOH, reflux.

(ii) Na, NH\textsubscript{3} (liq.).

(iii) NaNO\textsubscript{2}, 2M H\textsubscript{2}SO\textsubscript{4}, H\textsubscript{2}O, 0\degree.

(iv) 10M NaOH, H\textsubscript{2}O, heat.

scheme 30
2.2 The Investigation of 5-Amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide Derivatives as Synthetic Precursors en route to Pyrimido[4,5-e]-1,2,4-triazine (6-azapteridine) Derivatives

Application of the general synthetic strategy outlined in the introduction to this chapter (see Scheme 29) requires suitably functionalised 5-amino-1H-1,2,3-triazoles as precursors of the 1H-1,2,3-triazole-5-diazonium species involved as key starting materials. Initially (Scheme 30) the known\textsuperscript{44} compound 5-amino-1,2,3-triazole-4-carboxylic acid (119) was chosen since it was known\textsuperscript{41} that though electron-withdrawing carbonyl substituents such as alkoxy carbonyl or carboxamide stabilise the 1,2,3-triazole ring in bridgehead-fused 1,2,3-triazoles to acid-catalysed scission, carboxyl substituents, due to their concomitant loss by decarboxylation, do not.

5-Amino-1H-1,2,3-triazole-4-carboxylic acid (119) was readily prepared (Scheme 30) as described in the literature\textsuperscript{44} by alkaline hydrolysis of 5-amino-1H-1,2,3-triazole-4-carboxamide (117) derived by debenzylation of the N-benzyl triazole (116)\textsuperscript{45} readily accessible by the sodium methoxide catalysed condensation of benzyl azide (114) with cyanoacetamide (115). Diazotisation (Scheme 30) of the amino-acid (119) afforded the known\textsuperscript{46} diazonium betaine (120) in excellent yield (94%). Though the detailed structure of the diazonium betaine (120) has not been
(i) NaNO$_2$, 2M HNO$_3$, H$_2$O, 0$^\circ$.
(ii) NaOAc, EtOH, H$_2$O, room temp.
(iii) DMF, H$_2$O, reflux.

Scheme 31
established, it is assumed that it is ionised at the carboxyl group rather than at the less acidic NH of the triazole ring. An attempt to obtain the diazonium betaine (120) more directly by concomitant deamination-diazotisation of the amino-triazole-amide (117) gave only a moderate yield (58%) of a product identical in all respects to an authentic sample\(^{47}\) of the amidotriazole diazonium betaine (118).

The strategy generalised in scheme 29 was initially investigated (Scheme 31) using cyanoacetamide (115) which coupled under weakly basic conditions with the diazonium betaine (120) to give a product in high yield (72%) that showed i.r. NH and cyano absorption at 3420-3170 and 2210 cm\(^{-1}\) as well as bands at 2700-2300 and 1680 cm\(^{-1}\) due to a carboxyl group and NH amidic carbonyl absorption at 1650 cm\(^{-1}\), features consistent with its formulation as the triazolylhydrazone (121). However this structure could not be confirmed by combustion analysis since on attempted purification by crystallisation, the compound underwent cyclisation and thermal decarboxylation yielding the triazolotriazine derivative (123), which analysed correctly and showed spectroscopic properties consistent with its assigned structure.

It was found (Scheme 31) that diazotative coupling of the aminotriazole carboxylic acid (119) with cyanoacetamide (115) led, via the presumed intermediacy of the diazonium betaine (120) to two products in good total yield one of
Scheme 32
which was identified as the triazolylhydrazone (121) obtained before. The second product lacked absorption due to a cyano- group but contained i.r. bands at 3150-2500 and 1700 cm\(^{-1}\) attributable to the hydroxyl and carbonyl absorption of a carboxyl group allowing its formulation as the triazolotriazine carboxylic acid (122). Again however, this structure could not be confirmed by combustion analysis due to the compound's ready thermal decarboxylation on attempted crystallisation to give the triazolotriazine derivative (123) obtained before.

The triazolotriazine (123) was also the end-product obtained in variable yield (37 - 71%) by heating either the crude triazolylhydrazone (121) or the crude triazolotriazine carboxylic acid (122) or their respective sodium salts in dimethylformamide. The end-product of all of these reactions is formulated (Scheme 32) as the linear 1,2,3-triazolo[1,5-b]-1,2,4-triazine structure (123) rather than the angular 1,2,3-triazolo[5,1-c]-1,2,4-triazine structure (127) expected on the basis of direct ring closure of the triazolylhydrazone (121) followed by decarboxylation. The linear formulation (123) for this product and indeed for all such 1,2,3-triazolo-1,2,4-triazine derivatives described in the present studies is based on analogy with a related compound whose linear 1,2,3-triazolo[1,5-b]-1,2,4-triazine structure has been unambiguously established by X-ray analysis as described later (see chapter 3, page 173). The establishment of this structure also has the consequence
(i) AcCl, AcOH, reflux.

(ii) HCl (g.), AcOH, reflux.

(iii) AcOH, reflux.

Scheme 33
that other products derived by coupling of triazolediazonium salts with acetonitrile derivatives in the literature as 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives should be reformulated as 1,2,3-triazolo[1,5-b]-1,2,4-triazines. In the present context the formulation (Scheme 32) of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (122) and hence the parent triazolotriazine (123) from the triazolylhydrazone carboxylic acid (121) requires Dimroth rearrangement prior to cyclisation [(121) $\rightleftharpoons$ (124)] or before [(125) $\rightleftharpoons$ (122)] or after [(127) $\rightleftharpoons$ (123)] decarboxylation.

Having achieved the synthesis of the triazolotriazine carboxylic acid (122) and the parent triazolotriazine (123) it was decided at this stage as a preliminary to annulation of the pyrimidine ring (see Scheme 29) to investigate the behaviour of the triazolotriazine derivatives (122) and (123) towards acid-catalysed triazole scission. Initially the reaction (Scheme 33) of the triazolotriazine carboxylic acid (122) with acetyl chloride in glacial acetic acid was studied in the expectation that the preliminary decarboxylation would be followed by triazole scission to give the chloromethyltriazine derivative (128). In practice, despite its apparent ready decarboxylation as discussed before, the triazolotriazine carboxylic acid (122) was largely unchanged by heating under reflux with acetyl chloride in glacial acetic acid. However, this reaction did
give a low yield of a product which analysed correctly and
showed mass spectral, i.r. and $^1$H n.m.r. properties in
accord with the expected chloromethyltriazine structure
(128). Heating the parent triazolotriazine (123) under
reflux with acetyl chloride in glacial acetic acid also
afforded the chloromethyltriazine (128) but in only
marginally improved yield compared with the carboxylic acid
(122). This result indicates that ease of preliminary
decarboxylation of the carboxylic acid (122) is not the
predominant reason for its inefficient scission to the
chloromethyltriazine (128). That this inefficiency was
primarily due to the reagent (i.e. acetyl chloride) employed
was demonstrated by the efficient conversion of the
triazolotriazine (123) to the chloromethyltriazine (128) in
high yield (86%) by heating under reflux with hydrogen
chloride in glacial acetic acid. Heating under reflux with
glacial acetic acid alone also caused triazole cleavage of
the triazolotriazine (123) to the acetoxy methyltriazine
(129) in good yield (77%). The acetoxy methyl derivative
(129) analysed correctly and showed spectroscopic properties
consistent with its assigned structure. In particular, its
i.r. spectrum showed high frequency i.r. carbonyl absorption
at 1745 cm$^{-1}$ consistent with the presence of an
acetoxy methyl substituent.

The transformations (Scheme 33) [(123) → (128)] and
[(123) → (129)] clearly demonstrate the efficiency of
acid-catalysed scission as a route from 5-amino-1,2,3-
\[
\begin{align*}
\text{(130)} & \quad + \quad \begin{align*}
\text{O}_2\text{Me} & \quad \text{CH}_2 \\
\text{N} & \quad \text{C} \quad \text{N}\end{align*}
\rightarrow \quad \begin{align*}
\text{H}_2\text{C} & \quad \text{N}_2\text{Me} \\
\text{N}_2\text{Me} & \quad \text{CH}_2 \\
\text{N} & \quad \text{C} \quad \text{N}\end{align*}
\text{(131)}
\end{align*}
\]

\[
\text{(i)} \quad \text{NaOMe, MeOH, reflux.}
\]

\[
\text{(ii)} \quad \text{CF}_3\text{CO}_2\text{H, 60 - 65°.}
\]

\[
\text{(iii)} \quad \text{MeOH, H}_2\text{SO}_4 (\text{conc.}), \text{reflux.}
\]

\[
\text{(iv)} \quad \text{MeOH, HCl (gas), reflux.}
\]

\text{Scheme 34}
triazolo[1,5-b]-1,2,4-triazine-6-carboxamide derivatives to 3-substituted 5-amino-1,2,4-triazine-6-carboxamides. However, because of the relative difficulty of working with carboxylic acid intermediates prone to salt formation and thermal decarboxylation such as (121) and (122), it was decided at this stage to investigate (Scheme 34) the use of the known amino-1,2,3-triazole methyl ester (133) as an alternative to the carboxylic acid (119) for elaboration (see scheme 29) via the corresponding 1,2,3-triazolediazonium derivative (108; R1=Me) to 6-azapteridine derivatives (113).

Initially it was decided to develop an alternative more convenient method (Scheme 34) for the synthesis of the aminotriazole ester (133) to that described in the literature. This involved the synthesis and de(methoxybenzylation) of the 4-methoxybenzyltriazole ester (132). The latter compound was readily prepared, though in disappointingly low yield (13%) by the sodium methoxide catalysed condensation of the known compound 4-methoxybenzyl azide (130) with methyl cyanoacetate (131). Heating the methoxybenzyltriazole (132) with trifluoroacetic acid under conditions known to effect the de(methoxybenzylation) of other N-(4-methoxybenzyl)triazoles afforded the required aminotriazole methyl ester (133) though only in low yield (29%). The inefficiency of the synthesis and de(methoxybenzylation) of the 4-
Scheme 35

(i) NaNO₂, 2M HNO₃, H₂O, 0°.

(ii) NaOAc, MeOH, H₂O, room temp.

(iii) 2M NaOH, H₂O, reflux.
methoxybenzyltriazole methyl ester (132) as a route to the required aminotriazole methyl ester (133) promoted the synthesis of this compound by the more orthodox esterification of the already available aminotriazole carboxylic acid (119). However the attempted esterification of the latter compound by heating with methanol in the presence of concentrated sulphuric acid also gave only a low yield of the required methyl ester (133). In contrast, heating the aminotriazole carboxylic acid (119) with methanol in the presence of hydrogen chloride afforded the aminotriazole methyl ester hydrochloride (134) in excellent yield (86%).

Initially the aminotriazole ester (133) was diazotatively coupled as the free base (135) (Scheme 35) with cyanoacetamide (115) to afford a moderate yield of the triazolotriazine (137) whose combustion analysis and spectroscopic properties were consistent with its assigned structure. In particular, the $^1$H n.m.r. spectrum of the compound showed resonances for a total of four exchangeable NH protons and also a singlet at δ3.84 assignable to the methyl proton resonances of the ester group. An improved yield (82%) of the triazolotriazine derivative (137) was obtained when cyanoacetamide (115) was diazotatively coupled with the aminotriazole ester hydrochloride (134) rather than the free aminotriazole ester (133). The formation of the triazolotriazine (137) in the diazotative base-catalysed coupling reactions of cyanoacetamide (115) with either the
aminotriazole ester (133) or its hydrochloride (134) presumably involves the intermediacy of the triazolylhydrazone (136) but in neither case was any of this product detected in the reaction mixture.

At this stage it was decided, prior to the annulation of the pyrimidine ring, to determine the feasibility of selectively hydrolysing the ester group in the triazolotriazine (137) (Scheme 35) in the presence of the 5-amino and 6-carboxamido substituents which it was anticipated might also be prone to hydrolysis. In practice, heating the triazolotriazine derivative (137) with dilute sodium hydroxide afforded a moderate yield (61%) of an acidic product which gave analytical and mass spectral data and showed i.r. absorption consistent with either of the triazolotriazinone structures (138) or (139). However, its $^1$H n.m.r. spectrum contained a one-proton resonance at $\delta 7.68$ close to the chemical shift ($\delta 7.70$) of the triazole proton at the 3-position in the triazolotriazine derivative (123) (see before). On this basis and the previously observed ready decarboxylation of the triazolotriazine carboxylic acid (122) (see before), the triazolotriazinone product derived by hydrolysis of the ester (137) is tentatively formulated as the 6-carboxylic acid (138) rather than the 3-carboxylic acid.

Because of the apparent difficulty of selectively hydrolysing the ester group without also hydrolysing the
(i) \( (\text{EtO})_2\text{C}=\text{O}, \text{NaOEt, EtOH, heat} \).
(ii) \( \text{HC(OEt)}_3, \text{heat} \).
(iii) \( (\text{EtO})_2\text{CHO(C}=\text{O}\text{)Me, heat} \).
(iv) \( \text{H}_2\text{NCH}=\text{O, NaOEt, EtOH, heat} \).

\text{Scheme 36}
amino and carboxamide substituents in the triazolotriazine derivative (137), attention was next turned to the attempted annulation of the latter (Scheme 36) to the triazolopyrimidotriazine derivatives (140) and (141) which it was hoped would be susceptible to hydrolysis to carboxylic acids (142) and (143), potentially convertible by decarboxylation and acid-catalysed triazole scission into 6-azapteridine derivatives (144) and (145). However, the attempted reaction of the amino-amide (137) with diethyl carbonate in the presence of sodium ethoxide under conditions known\(^{50}\) to effect the annulation of amino-1,2,4-triazine carboxamides to pyrimido-1,2,4-triazines afforded only some unreacted starting-material (137) and a complex mixture, with no evidence for the formation of the expected triazolopyrimidotriazinedione derivative (140). Heating the amino-amide (137) with triethyl orthoformate in an attempt to achieve annulation\(^{51}\) to the triazolopyrimidotriazinone derivative (141) gave a high yield of a product (isomer B) which differed in m.p. and i.r. spectrum from the starting triazolotriazine derivative (137) (isomer A) but otherwise showed identical \(^1\)H and \(^{13}\)C n.m.r. absorption to the latter. Heating the amino-amide (137) (isomer A) in diglyme also converted it in good yield (68\%) into the isomer B. In view of their identical \(^1\)H and \(^{13}\)C n.m.r. absorption the two forms (isomers A and B) of the aminotriazolotriazine carboxamide (137) are suggested to be simply different crystal modifications of the same molecule.
(i) NaNO₂, 2M HNO₃, H₂O, 0°.

(ii) NaOAc, MeOH, H₂O, room temp.

(iii) AcOH, reflux.

(iv) 1, 4-dioxane, reflux.

(v) H₂NCH=O, 170°.

Scheme 37
The attempted annulation of the aminotriazolotriazine carboxamide (137) to the triazolopyrimidotriazine derivative (141) by heating with diethoxymethyl acetate or with formamide in ethanolic sodium ethoxide (reagents known\textsuperscript{52,53} to effect heterocyclisations of this type) were also unsuccessful. In both cases complex mixtures were obtained which yielded none of the expected triazolopyrimidotriazine derivative (141).

Since the failure of the aminotriazolotriazine carboxamide (137) to undergo heterocyclisation to the triazolopyrimidotriazine derivatives (140) and (141) under a variety of conditions could be attributed to the lack of reactivity of the carboxamide substituent in the initial condensation with reagents such as diethyl carbonate etc., attention was next directed to the synthesis (Scheme 37) and annulation of the aminotriazolotriazine ester (147) in the hope that the 6-methoxycarbonyl group of the latter would prove a more reactive substituent in initial condensations leading to heterocyclisation. Diazotative coupling of the aminotriazole ester (133) with methyl cyanoacetate (131) in contrast to the similar reaction with cyanoacetamide (see before) afforded only a poor yield (10\%) of the expected triazolotriazine derivative (147) which analysed correctly and showed spectroscopic properties in accord with its assigned structure.
On the other hand, the similar diazotative coupling of the aminotriazole ester hydrochloride (134) with methyl cyanoacetate (131) afforded a readily separable mixture of the triazolotriazine derivative (147) (yield 9%) and a second product formed in high yield (75%). Since the latter compound was converted into the triazolotriazine derivative (147) on attempted crystallisation it had to be purified by repeated dissolution in dilute aqueous sodium hydroxide and reprecipitation with dilute aqueous hydrochloric acid. It then analysed correctly as a monohydrate and gave mass, i.r. and $^1$H n.m.r. spectra allowing its formulation as the triazolylhydrazone (146) and explaining its conversion into the triazolotriazine derivative (147) simply on crystallisation. In particular, the major product of the diazotative coupling of the aminotriazole ester hydrochloride (134) with methyl cyanoacetate (131) showed i.r. cyano absorption at 2240 cm$^{-1}$ consistent with its triazolylhydrazone structure (146).

Unexpectedly, heating the triazolylhydrazone (146) in glacial acetic acid in an effort to obtain the triazolotriazine derivative (147) in sufficient quantity to investigate its annulation to triazolopyrimidotriazine derivatives afforded a readily separable mixture of two isomeric products in moderate total yield. The minor product (isomer A) (yield 8%) was identical in all respects to the aminotriazolotriazine ester (147) obtained before. However, though the major isomer (isomer B) differed in m.p.
and i.r. spectrum from the isomer A particularly in exhibiting a single high frequency i.r. carbonyl absorption at 1720 cm\(^{-1}\), it gave the same analytical and mass spectroscopic data and both isomers showed identical \(^1\)H and \(^{13}\)C n.m.r. absorption.

It is proposed therefore that as in the case of the isomeric forms of the aminotriazolotriazine carboxamide (137) (see before) the A and B isomers of the aminotriazolotriazine ester (147) are simply different crystal modifications of the same molecule. Heating the triazolylhydrazone (146) in dioxane resulted in the exclusive formation, albeit in low yield (50%), of the isomer B of the aminotriazolotriazine ester (147).

In an attempt to effect the annulation (Scheme 37) of the aminotriazolotriazine ester (147) to the triazolopyrimidotriazine derivative (141), the isomer A was heated with formamide under conditions described in the literature\(^5^3\) for the related heterocyclisations of anthranilate esters. However, in the case of the aminotriazolotriazine ester (147) only a complex mixture, which yielded no identifiable material, was obtained.
(i) NaNO₂, 2M HNO₃, H₂O, 0°C.
(ii) NaOAc, MeOH, H₂O, room temp.
(iii) POCl₃, PhNEt₂, heat.
(iv) POCl₃, Cl(CH₂)₂Cl, reflux.
(v) POCl₃, Me₂NCH=O, 80°C.
(vi) POCl₃, PhNEt₂, Me₂NCH=O, reflux.
(vii) SOCl₂, reflux.
(viii) Ac₂O, reflux.

Scheme 38
2.3 The Investigation of Pyrimidine-2,4,6-(1H,3H,5H)-trione 5-(1H-1,2,3-triazol-5-yl)hydrazones as Synthetic Precursors of Pyrimido[4,5-e]-1,2,4-triazine (6-Azapteridine) Derivatives

The initial lack of success encountered in developing the original strategy for the general synthesis of pyrimido[4,5-e]-1,2,4-triazine (6-azapteridine) derivatives outlined in Scheme 29 before, promoted the evaluation of the alternative general approach outlined in Scheme 38. This was based on the assumption that 5-(1H-1,2,3-triazol-5-yl)hydrazones (149) derived from barbituric acid derivatives (148) would undergo formal cyclodehydration providing an alternative route to 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine derivatives (150) appropriate for subsequent hydrolysis, decarboxylation, and acid-catalysed triazole scission to the corresponding pyrimido[4,5-e]-1,2,4-triazine derivatives. In practice, (Scheme 38) diazotative coupling of barbituric acid (148a) with the aminotriazole ester hydrochloride (134) afforded a product in high yield (79%) with analytical and spectroscopic properties consistent with a dihydrate of the anticipated hydrazone product (149a). Disappointingly, heating the hydrazone (149a) with phosphoryl chloride in the presence of N,N-diethylaniline in the expectation of effecting its chlorinative/dehydrochlorinative cyclisation to the triazolopyrimidotriazinedione (150a), or a chloro
derivative, afforded only a complex mixture which yielded no identifiable material.

Since it was possible that the complex mixture obtained in the attempted phosphoryl chloride promoted cyclisation of the hydrazone (149a) was due to the presence of free lactam substituents in the latter, it was decided to investigate the analogous cyclisation of the N,N-dimethyl derivative (149b). This compound was readily synthesised in good yield (75%) by the diazotative coupling of the aminotriazole ester hydrochloride (134) with 1,3-dimethylbarbituric acid (148b) and gave analytical and spectroscopic data entirely consistent with its assigned structure. This was further verified by its conversion on heating with acetic anhydride into a monoacetyl derivative which showed i.r. carbonyl absorption at 1780 cm\(^{-1}\) and a three proton singlet at \(\delta 2.80\) characteristic of a ring N-acetyl substituent as in the structure (151). However, it should be noted that this structure has been assigned for convenience and that the acetyl group could be sited on any one of the three triazole nitrogen atoms.

Unfortunately, as in the case of the triazolylhydrazone (149a), the N,N-dimethyl derivative (149b) failed to undergo chlorinative/dehydrochlorinative cyclisation under a variety of conditions to afford the hoped for triazolopyrimidotriazinedione derivative (150b). Initially, heating the triazolylhydrazone (149b) with phosphoryl
chloride in 1,2-dichloroethane for different lengths of time afforded only high recoveries (84-86%) of the unreacted starting material (149b). The hydrazone (149b) was also recovered unchanged in high yield (70-100%) after heating with phosphoryl chloride in the presence or absence of N,N-diethylaniline and/or dimethylformamide or with thionyl chloride in the absence of catalyst or solvent. In view of these results, investigations of the synthesis of triazolopyrimidotriazinedione derivatives (150) by cyclisation of 5-triazolylhydrazones of barbituric acid derivatives (149) were terminated at this point.
Scheme 39
(i) NaNO₂, 2M HNO₃, H₂O, 0°C

(ii) NaOAc, MeOH or 1,2-dimethoxyethane or 1,4-dioxane, H₂O, room temp.

(iii) 2M HCl, H₂O, room temp.

(iv) 1,4-dioxane, reflux.

(v) p-tsa, 1,4-dioxane, reflux.

(vi) AcOH, H₂O, reflux.

(vii) AcOH, reflux.

(viii) Ac₂O, reflux.

Scheme 40
2.4 The Investigation of 5-Amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine 6-N-Acyl- and 6-N-Cyanocarboxamides as Synthetic Precursors of Pyrimido[4,5-e]-1,2,4-triazine (6-Azapteridine) Derivatives

 Having failed to develop general synthetic routes to pyrimido[4,5-e]-1,2,4-triazine derivatives using the 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide derivatives or pyrimidine-2,4,6(1H,3H,5H)-trione 5-(1H-1,2,3-triazol-5-yl)hydrazones as the key precursors, attention was next turned to a general approach (Scheme 39) based on 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine 6-N-acyl and 6-N-cyanocarboxamides (152) as starting materials. It was anticipated that the conversion of these substrates into the 1,2,3-triazolopyrimido-1,2,4-triazines [(153)-(156)] required for triazole scission to the corresponding pyrimido[4,5-e]-1,2,4-triazine derivatives would be favoured by the intramolecular (as opposed to intermolecular) nature of the cyclisations.

 The general synthetic approach to pyrimido[4,5-e]-1,2,4-triazine derivatives outlined in Scheme 29 was initially investigated in the case of the attempted synthesis and cyclisation (Scheme 40) of the aminotriazolotriazine N-formylcarboxamide derivative (160). In practice, the known compound, N-cyanoacetylformamide\(^{55}\) (157) coupled with the diazonium cation (135) generated in situ from the aminotriazole ester hydrochloride (134), in
(i) NaOAc, MeOH, H₂O, room temp.

(ii) 2M NaOH, H₂O, room temp.

\textbf{Scheme 41}
methanol in the presence of sodium acetate to afford a separable mixture of the triazolotriazine diester (147) and the triazolotriazine carboxamide (137) in yields of 14\% and 29\% respectively, together with a low yield (15\%) of a product whose analytical and spectroscopic properties were consistent with its formulation as the expected hydrazone (159). The low yield of the latter can be attributed to its solvolytic breakdown under the reaction conditions as indicated by the formation of the triazolotriazine products (147) and (137) (Scheme 41). In accord with its hydrolytic instability, the triazolylhydrazone (159) was converted by brief treatment with 2M aqueous sodium hydroxide, into 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (136). The coupling of N-cyanoacetylformamide (157) with the triazolediazonium cation (135) was therefore repeated in aqueous 1,2-dimethoxyethane in the presence of sodium acetate and under these conditions afforded a yellow salt (158) brief treatment of which with aqueous hydrochloric acid afforded the required triazolylhydrazone (159) in good yield (65\%). In an attempt to increase the yield of the triazolylhydrazone (159) still further, N-cyanoacetylformamide (157) was coupled with the triazolediazonium cation (135) in the presence of sodium acetate in the new solvent system of aqueous 1,4-dioxane. However, these conditions resulted in essentially the same yield (66\%) of the triazolylhydrazone (159).
In an initial attempt to effect cyclisation (Scheme 40) of the triazolylhydrazone derivative (159) to the triazolotriazine derivative (160) it was heated under reflux in 1,4-dioxane. Under these conditions a product was obtained in moderate yield (62%) which gave analytical and mass spectral data consistent with the expected triazolotriazine structure (160). This was further supported by the product's i.r. spectrum which lacked absorption due to a cyano group but contained bands attributable to a primary amino group. The $^1$H n.m.r. spectrum of the triazolotriazine derivative (160) was also consistent with its assigned structure but unlike the triazolylhydrazone derivative (159) did not exhibit coupling between the formyl and NH protons of the formamide substituent. In an attempt to improve the yield of the triazolotriazine derivative (160), the triazolylhydrazone (159) was heated under reflux in 1,4-dioxane containing a trace of toluene-4-sulphonic acid as acid catalyst. However, these conditions gave a much reduced yield of the triazolotriazine derivative (160). In view of the greater nucleophilicity of the negatively charged triazole nitrogen centre in the triazolylhydrazone sodium salt (158) it was anticipated that this compound might undergo more efficient cyclisation to the triazolotriazine derivative (160) compared with the free triazolylhydrazone (159). However, heating the triazolylhydrazone sodium salt (158) in water afforded only the aminotriazolotriazinecarboxamid (137) in
high yield (72%). This product can be explained in terms of the formation and \textit{in situ} hydrolysis of the triazolotriazine derivative (160).

With the aminotriazolotriazine N-formylcarboxamide (160) readily available, attention was directed to the cyclisation (Scheme 40) to the corresponding triazolopyrimidotriazine derivative (141). Initially this was attempted by heating in aqueous acetic acid. However, under these conditions the triazolotriazine derivative (160) was recovered unchanged in 50\% yield together with the aminotriazolotriazinocarboxamide (137) in an amount corresponding to the remaining starting-material. Heating the triazolotriazine derivative (160) in glacial acetic acid also afforded the aminoamide (137) though only in low yield (19\%) together with a complex mixture with no evidence for the formation of the hoped for triazolopyrimidotriazine derivative (141). The triazolotriazine derivative (160) was also unchanged to a large extent after heating with acetic anhydride, these conditions also resulting in the additional formation of a complex mixture. In a final attempt to achieve the cyclisation [(160)-(141)], the triazolotriazine derivative (160) was heated under reflux in 1,4-dioxane in the presence of toluene-4-sulphonic acid as acid catalyst. However, under these conditions the triazolotriazine (160) was recovered unchanged in high yield (96\%).

Since the failure of the aminotriazolotriazine
(i) NaNO₂, 2M HNO₃, H₂O, 0°.

(ii) NaOAc, MeOH, H₂O.

(iii) AcOH, heat.

(iv) 2M HNO₃, H₂O, room temp.

Scheme 42
N-formylcarboxamide (160) to undergo cyclisation to the triazolopyrimidotriazine (141) could be attributed to its ease of hydrolysis, it was next decided to investigate the synthesis and cyclisation (Scheme 42) of the aminotriazolotriazine N-acetylcarboxamide (163). It was hoped that the N-acetyl substituent in the latter would be less prone to hydrolysis and hence more likely to undergo cyclisation to the corresponding triazolopyrimidotriazine derivative (164).

The triazolodiazonium cation (135), generated in situ from the aminotriazole (134), coupled in neutral solution with the known compound N-cyanoacetylacetamide (161) to afford a readily separable mixture of two products. The product isolated in lower yield (31%) analysed correctly and gave mass spectral data consistent with its formation as a hydrate of the sodium salt of the triazolylhydrazone derivative (162). This structure was also supported by the product's $^1$H n.m.r. absorption and in particular by the presence of cyano absorption in its i.r. spectrum. The product formed in larger amount (60%) gave analytical and mass spectral data in accord with its formulation as the triazolotriazine derivative (163). In further support of this structure the compound's i.r. spectrum lacked cyano absorption but contained bands attributable to a primary amino group.

Disappointingly, various attempts to achieve the cyclisation of the aminotriazolotriazine N-acetylcarboxamide
\[ \text{HN} \overset{(i)}{\text{COM}} \text{HN} \]
\[ \text{HN} \overset{(ii)}{\text{COM}} \text{HN} \]
\[ \text{HN} \overset{(iii)}{\text{COM}} \text{HN} \]

(i) \( \text{NaNO}_2, 2\text{M HNO}_3, \text{H}_2\text{O}, \text{O}^\circ \).

(ii) \( \text{NaOAc, MeOH, H}_2\text{O, room temp.} \).

(iii) \( \text{AcOH, heat.} \)

\textbf{Scheme 43}
(163) to the triazolopyrimidotriazine (164) were unsuccessful. Thus heating the triazolotriazine derivative (163) in glacial acetic acid afforded only a moderate recovery of the unreacted starting material (163) and no other identifiable material. In contrast, the attempted ring-closure of the triazolotriazine (163) in cold aqueous alkali afforded only a low yield of the sodium salt of the triazolylhydrazone derivative (162) obtained before. The unexpected formation of this product indicates that opening of the triazine ring in the triazolotriazine (163) occurs in preference to its cyclisation to the triazolopyrimidotriazine (164).

Despite the failure of the aminotriazolotriazine N-acylcarboxamides (160) and (163) to undergo cyclisation to the corresponding triazolopyrimidotriazine derivatives (141) and (164), attention was next turned to the study of the synthesis and cyclisation (Scheme 43) of the aminotriazolotriazine N-ethoxycarbonylcarboxamide derivative (169).

To this end the commercially available compound N-cyanoacetylurethane (165) was coupled in neutral solution with the triazolediazonium cation (135) generated in situ by diazotisation of the aminotriazole ester hydrochloride (134). In an initial run this reaction afforded a high yield (85%) of a product which was unstable to attempted purification by crystallisation but could be purified by
<table>
<thead>
<tr>
<th>Compound</th>
<th>max/nm (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(169)</td>
<td>220 (4.23), 261 (4.44), 342 (3.14)</td>
</tr>
<tr>
<td>(167)</td>
<td>221 (4.19), 262 (4.42), 345 (3.19)</td>
</tr>
<tr>
<td>(170)</td>
<td>225 (3.80), 264 (3.94)</td>
</tr>
<tr>
<td>(140)</td>
<td>221 (4.07), 260 (4.43), 275 (sh) (3.32), 344 (3.26)</td>
</tr>
</tbody>
</table>

(Recorded on a Unicam 800A spectrometer in 95% ethanol)
dissolution in dilute aqueous alkali and reprecipitation with aqueous hydrochloric acid. It then analysed correctly as a monohydrate of the expected triazolylhydrazone (166). In further support of this structure the product showed the expected parent ion at m/z 309 in its mass spectrum as well as cyano absorption at 2220 cm\(^{-1}\) in its i.r. spectrum.

The triazolylhydrazone (166) was accompanied by a by-product, isolated in low yield (6%) which analysed correctly and gave mass, i.r. and \(^1\)H n.m.r. spectra consistent with its formulation as the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169). This compound was also formed in quantitative yield when attempts were made to purify the triazolylhydrazone (166) by crystallisation. In a repeated coupling reaction of the triazolediazonium cation (135) with N-cyanoacetylurethane (165) in neutral solution the principal triazolylhydrazone product (166) and the minor 1,2,3-triazolo[1,5-b]-1,2,4-triazine product (169) were accompanied by a third compound. This new by-product was isomeric with, but differed in melting point from the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) and like the latter lacked the i.r. cyano absorption shown by the triazolylhydrazone derivative (166). However, though the new by-product and the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) exhibited virtually identical u.v. absorption (see Table 1) their i.r. and \(^1\)H n.m.r. spectra showed significant differences. Thus, whereas the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) showed i.r.
carbonyl absorption at 1710 and 1640 cm\(^{-1}\), the i.r. spectrum of the isomeric by-product contained carbonyl bands at 1790, 1725 and 1695 cm\(^{-1}\). Also the \(^1\)H n.m.r. spectrum of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) contained two broad exchangeable resonances at \(\delta 11.68\) and 8.60 integrating for one and two protons respectively and attributable to the NH and NH\(_2\) substituents.

In contrast, the \(^1\)H n.m.r. spectrum of the isomeric by-product contained three broad exchangeable resonances at \(\delta 11.77\), 8.95 and 8.30 each integrating for one proton and assignable to three distinct NH groups. On the basis of this and the foregoing evidence, the isomeric by-product is tentatively formulated as the imino tautomeric form (168) of the amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine derivative (167). This compound is the expected product of the initial cyclisation of the triazolylhydrazone intermediate (166). However, as already discussed, the attempted crystallisation of the triazolylhydrazone (166) resulted in its conversion into the amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine N-ethoxycarbonylcarboxamide derivative (169). This result indicates that initial cyclisation of the triazolylhydrazone (166) to the 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivative (167) is followed by rapid rearrangement of the latter to the presumable more thermodynamically stable 1,2,3-triazolo[1,5-b]-1,2,4-triazine isomer (169). In accord with this supposition, heating the triazolylhydrazone (166) in
Scheme 44

(i) 2M NaOH, H₂O, room temp. then 2M HCl, H₂O

Scheme 45

(i) NaH, DMF, room temp., then Mel.
glacial acetic acid afforded the amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine N-ethoxycarbonylcarboxamide derivative (169) in good yield (75%).

In an attempt to define the conditions (Scheme 44) under which this cyclisation would occur and at the same time improve the yield of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine product (169), a solution of the triazolylhydrazone (166) in 2M aqueous alkali was stirred at room temperature for 0.5h. However, subsequent acidification with 2M aqueous hydrochloric acid instead of giving the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) afforded a good yield of a product whose i.r. and $^1$H n.m.r. absorption indicated the presence of cyano and methoxycarbonyl substituents as well as a lactam (-NHC=O) moiety, but the absence of an ethoxycarbonyl group. Moreover, the u.v. absorption of the compound was markedly different from that of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) (see Table 1). The compound analysed correctly for a monohydrate of the molecular formula C$_8$H$_5$N$_7$O$_4$ which was further confirmed by the presence of a parent ion at m/z 263 in the product's mass spectrum.

On the basis of the foregoing analytical and spectroscopic evidence, the product of the sodium hydroxide promoted transformation of the triazolylhydrazone (166) is formulated as the 1,2,3-triazolyl-1,2,4-triazinedione (170). The formation of this product can be viewed as the result of the base-catalysed condensation between the ethoxycarbonyl
substituent and the hydrazone NH group in the triazolylhydrazone (166).

With the amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine N-ethoxycarbonylcarboxamide (169) readily available, attention was turned to the study (Scheme 43) of its cyclisation to the triazolopyrimidotriazinedione derivative (140). Initially thermal cyclisation was attempted by heating in diglyme for 0.5h. Surprisingly, however, these conditions afforded a moderate yield (67%) of the compound tentatively formulated as the tautomeric amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine N-ethoxycarbonylcarboxamide derivative [(167) \(\rightleftharpoons\) (168)], which on attempted crystallisation from glacial acetic acid was reconverted in quantitative yield into the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169). Interestingly, these results indicate that under neutral conditions in diglyme the triazolo[1,5-b]-1,2,4-triazine derivative (169) is thermally unstable relative to the triazolo[5,1-c]-1,2,4-triazine derivative [(167) \(\rightleftharpoons\) (168)] but under weakly acidic conditions in glacial acetic acid the reverse of this relative thermal stability applies. In accord with this supposition, prolonged heating of the triazolo[1,5-b]-1,2,4-triazine derivative (169) in diglyme resulted only in an intractable mixture demonstrating that initial thermal rearrangement to the triazolo[5,1-c]-1,2,4-triazine derivative [(167) \(\rightleftharpoons\) (168)] precludes, as would be expected, cyclisation to the triazolopyrimidotriazinedione.
derivative (140). Conversely, as expected from its thermal stability in glacial acetic acid, heating the triazolo[1,5-b]-1,2,4-triazine derivative (169) in this solvent afforded a high yield (75%) of a product which showed u.v. absorption markedly different from that of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) (see Table 1) and analysed correctly as a monohydrate of the required triazolopyrimidotriazinedione derivative (140). In accord with this structure the compound showed a parent ion at m/z 263 in its mass spectrum and contained absorption at 3500-2500 and 1770-1700 cm\(^{-1}\) in its i.r. spectrum assignable to the NH and carbonyl moieties of a pyrimidine-2,4(1H,3H-dione) nucleus. The \(^1\)H and \(^{13}\)C n.m.r. absorption of the compound was also fully consistent with its formation as the triazolopyrimidotriazinedione derivative (140). This compound was also formed in a quantitative yield by briefly warming the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169) with dilute aqueous alkali and then acidifying the resulting alkaline solution. The triazolopyrimido-triazinedione (140) was also formed in essentially quantitative yield by treating the tautomeric 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivative [(167) \(\rightleftharpoons\) (168)] with warm aqueous alkali followed by acidification. Since the 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivative [(167) \(\rightleftharpoons\) (168)] shows no apparent tendency to cyclise thermally to the triazolopyrimidotriazinedione derivative (140) (see before), formation of the latter from the former in aqueous
alkali requires initial rearrangement of the 1,2,3-
triazolo[1,5-b]-1,2,4-triazine derivative (169). This in
turn demonstrates the close structural relationship between
the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (169)
and the tautomeric 1,2,3-triazolo[5,1-c]-1,2,4-triazine
derivative [(167) ⇌ (168)] and hence the structure
assigned to the latter.

The triazolopyrimidotriazinedione (140) was also formed
in low yield (26%), together with unreacted starting-
material (yield 48%) when the 1,2,3-triazolo[5,1-c]-1,2,4-
triazine derivative [(167) ⇌ (168)] was briefly treated
with aqueous sodium hydrogen carbonate at room temperature.

By way of further verifying the structure of the
triazolopyrimidotriazinedione (140) its behaviour towards
methylation (Scheme 45) was investigated. Initially
complete methylation of the triazolopyrimidotriazinedione
(140) (as the disodium salt) using two equivalents of methyl
iodide was investigated. Under these conditions a readily
separated mixture of the two products was obtained, together
with a low recovery (10%) of the unreacted starting-material
(140). The major product (yield 42%) analysed correctly and
gave mass, i.r. and ¹H n.m.r. spectra entirely consistent
with its formulation as the expected di-N-methyl derivative
(171). The minor product (yield 12%) gave analytical and
mass spectral data consistent with the molecular formula
C₉H₉N₇O₃, corresponding to the formal loss of a carbonyl
moiety from the di-N-methyltriazolopyrimidotriazinedione (171). The formulation of this product as the ring-contracted triazoloimidazotriazinone derivative (174) followed from its i.r. and $^1$H and $^{13}$C n.m.r. absorption. The compound's i.r. spectrum contained only carbonyl absorption at 1770 and 1725 cm$^{-1}$ attributable to the carbonyl moieties of an imidazolone nucleus and a methoxycarbonyl substituent respectively. Correspondingly the compound's $^1$H n.m.r. spectrum showed only three three-proton singlets at 83.91, 3.40 and 3.39 attributable to the protons of the methoxycarbonyl and two N-methyl substituents in the structure (174). This was further substantiated by the compound's $^{13}$C n.m.r. spectrum which in addition to absorption due to three methyl carbons also contained absorption due to the six quaternary carbon atoms in the structure (174). The known$^57$ base-catalysed ring contraction of a pyrimido[5,4-e]-1,2,4-triazine derivative to an imidazo[4,5-e]-1,2,4-triazine product suggested analogous ring contraction of the triazolopyrimidotriazinedione (140) followed by methylation, or initial formation of the di-N-methyl derivative (171) then ring contraction as the mode of formation of the triazoloimidazotriazinone derivative (174). However, the recovery of the triazolopyrimidotriazinedione (140) unchanged in high yield after treatment with sodium hydride in dimethylformamide in the absence of methyl iodide excludes ring contraction prior to methylation. In
contrast, similar treatment of the di-N-methyl triazolopyrimidotriazinedione (171) with sodium hydride in dimethylformamide in the absence of methyl iodide gave the ring-contracted product (174) albeit only in low yield. This result, though not entirely conclusive, indicates that the triazoloimidazotriazinone (174) can be derived by ring contraction of the di-N-methyl triazolopyrimidotriazinedione derivative (171). The pathway for this transformation is not entirely clear but a possible mechanism is outlined in Scheme 45. This proposes hydrolytic opening of the pyrimidinedione ring by a hydroxide ion (derived by hydrolysis of the sodium hydride by trace amounts of moisture) as the first step [(171) → (172)]. Subsequent ring-closure followed by oxidative decarboxylation in the presence of atmospheric oxygen then accounts for the observed product [(172) → (173) → (174)]. In an attempt to effect the monomethylation of the triazolopyrimidotriazinedione (140) it was treated with one equivalent of methyl iodide in dimethylformamide in the presence of sodium hydride. However, this reaction gave in addition to unreacted starting-material (140) (yield 46%), only a low yield (32%) of the di-N-methyl derivative (171) with no evidence for the formation of a mono-N-methyl derivative.

Having developed a viable method for the synthesis of the 1,2,3-triazolopyrimido-1,2,4-triazine ester (140)
(i) $2M \text{HCl}, \text{H}_2\text{O}, \text{AcOH}$, reflux.

(ii) $2M \text{NaOH}, \text{H}_2\text{O}$, room temp. or reflux.

(iii) LiI, H$_2$O, DMF, reflux.

(iv) NaI, Me$_3$SiCl, N$_2$, reflux.

*Scheme 46*
attention was next turned (Scheme 46) to its hydrolysis to the carboxylic acid (142). It was anticipated that this compound would undergo decarboxylation followed by acid-catalysed triazole scission to provide a new synthetic route to functionalised pyrimido[4,5-e]-1,2,4-triazine derivatives (144). Initially, hydrolysis of the ester (140) was attempted by heating with aqueous hydrochloric acid in acetic acid in the hope of achieving hydrolysis, decarboxylation and acid-catalysed triazole scission in one step to afford the chloromethyl- and/or the acetoxymethyl pyrimido[4,5-e]-1,2,4-triazine derivatives (144; X=Cl) and/or (144; X=OAc). However, briefly heating the ester (140) under reflux with aqueous hydrochloric acid in acetic acid afforded only a low recovery (39%) of the unreacted starting material (140) together with an intractable mixture. Conversely, prolonged heating under these conditions gave after work-up no identifiable material. Hydrolysis under alkaline conditions was no more successful. Thus heating the ester (140) under reflux with aqueous alkali afforded only a complex mixture which yielded no identifiable material. Alternatively, attempted hydrolysis of the ester (140) with aqueous alkali at room temperature afforded only unreacted starting material (140) (42%) and no other identifiable product. The attempted hydrolysis of the di-N-methyl derivative (171) using aqueous alkali also afforded an intractable mixture which yielded no identifiable material. Heating the ester (140) with lithium
Scheme 47

140 + NH₄OH, 100° → 175

142
(i) NaNO₂, 2M HNO₃, H₂O, 0°.
(ii) NaOAc, MeOH, H₂O, room temp.
(iii) AcOH, reflux.
(iv) diglyme, reflux.
(v) 2M NaOH, H₂O, warm, 2M HCl, H₂O.
(vi) NaNO₂, H₂SO₄ < 30°.
(vii) NO⁺BF₄⁻, MeCN, 50°.
(viii) NaH, DMF, room temp., then Mel or Me₂SO₄.

Scheme 48
iodide monohydrate in dimethylformamide under conditions known\textsuperscript{58} to effect the conversion of methyl esters to carboxylic acids also yielded no characterisable material. Methyl esters are also specifically converted into carboxylic acids by treatment with sodium iodide in acetonitrile in the presence of trimethylsilyl chloride\textsuperscript{59}. However, under these conditions the ester (140) gave only an intractable brown solid which could not be characterised.

The lack of success encountered in attempts to convert the ester (140) into the acid (142) under various conditions prompted the investigation of the synthesis and deamination (Scheme 47) of the triazolopyrimidotriazinedione carboxamide (175) as an alternative route to the acid (142). Initially the direct conversion of the ester (140) into the amide (175) by reaction with concentrated ammonia was attempted but gave only a quantitative recovery of the unreacted starting-material (140). However, the required carboxamide (175) was readily prepared in good overall yield as outlined in Scheme 48.

Thus the triazolecarboxamide diazonium cation (176) [prepared \textit{in situ} from the aminotriazole carboxamide (117)] coupled readily with \textit{N}-cyanoacetylurethane (165) to afford a high yield (76\%) of a product whose infrared spectrum indicated it to be the expected triazolylhydrazone (177). However on attempted purification by crystallisation, the triazolylhydrazone (177) underwent ring-closure to the
1,2,3-triazolo[1,5-b]-1,2,4-triazine carboxamide (178). This compound was also obtained in high yield (82%) by heating the triazolylhydrazone (177) under reflux in acetic acid and had analytical and spectroscopic properties fully in accord with its assigned structure (178).

Initially cyclisation of the triazolotriazine carboxamide (178) to the required triazolopyrimidotriazinedione carboxamide (175) was attempted by heating in glacial acetic acid. However under these conditions the amide (178) was recovered unchanged in high yield (90%). The attempted cyclisation of the amide (178) in refluxing diglyme was no better, but in addition to unreacted triazolotriazine carboxamide (178) (yield 73%) did afford a low yield (16%) of product whose analytical and spectroscopic properties were in accord with its formulation as the triazolopyrimidotriazinedione carboxamide (175). In contrast this compound was isolated in quantitative yield when the triazolotriazine carboxamide (178) was warmed briefly with 2M aqueous sodium hydroxide and the resulting solution then acidified with 2M aqueous hydrochloric acid. The structure of the triazolopyrimidotriazinedione carboxamide (175) was verified by its conversion on methylation into the dimethyl derivative (179). This product was isolated in yields of 20% and 58% by reaction of the disodium salt of the triazolopyrimidotriazinedione carboxamide (175) with methyl iodide or dimethyl sulphate respectively.
(i) NaNO₂, 2M HNO₃, H₂O, 0°.

(ii) NaOAc, MeOH, H₂O, room temp.

(iii) EtOH or 1,4-dioxane, reflux.

(iv) AcOH, reflux.

Scheme 49
Disappointingly attempts to deaminate the amide (175) to the required triazolopyrimidotriazinedione carboxylic acid (142) were unsuccessful. Thus attempted reaction with sodium nitrite in sulphuric acid at < 30° afforded only a low recovery (42%) of the unreacted amide (175). Correspondingly reaction of the triazolopyrimidotriazinedione derivative (175) with nitrosonium tetrafluoroborate in acetonitrile under conditions known to effect the conversion of primary amides into carboxylic acids, gave only unreacted starting material (175) (yield 51%) together with a complex mixture.

Having failed to obtain the triazolopyrimidotriazinedione carboxylic acid (142) required for conversion by triazole scission into pyrimido[4,5-e]-1,2,4-triazine derivatives by the approaches described before, attention was turned to an alternative route (Scheme 49) involving the coupling of the triazole carboxylic acid diazonium cation (180) with N-cyanoacetylurethane (165) as the initial step. In practice, diazotisation of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119), followed by coupling of the resulting diazonium salt (180) with N-cyanoacetylurethane (165) afforded a high yield (93%) of a product which analysed correctly as a monohydrate of the expected triazolylhydrazone derivative (181). This structure was confirmed by the compound's FAB mass spectrum which contained the expected (M+H)^+ peak at m/z 296 and also by
its i.r. spectrum which showed absorption due to the presence of cyano, N-ethoxycarbonylcarboxamide and carboxyl substituents. The $^1$H n.m.r. spectrum of the triazolylhydrazone (181) was also consistent with its assigned structure.

Unfortunately, attempts to cyclise the triazolylhydrazone (181) to the 1,2,3-triazolo[1,5-b]-1,2,4-triazine carboxylic acid (182) precursor of the triazolopyrimidotriazinedione carboxylic acid (142) were unsuccessful. Thus, heating the triazolylhydrazone carboxylic acid (181) in 1,4-dioxane or even in ethanol afforded only intractable multicomponent mixtures which yielded no identifiable material. The failure of these attempts to thermally cyclise the triazolylhydrazone carboxylic acid (181) to the triazolotriazine carboxylic acid (182) prompted the use of glacial acetic acid as the solvent in this context. Heating the triazolylhydrazone carboxylic acid (181) under reflux in glacial acetic acid gave a complex mixture, dry flash-chromatography of which gave a low yield (14%) of a product which analysed correctly and gave mass, i.r. and $^1$H n.m.r. spectra consistent with its identity as the acetoxymethyl-1,2,4-triazine derivative (183). In particular, its i.r. spectrum in addition to containing carbonyl absorption due to an N-ethoxycarbonylcarboxamide group also had a band at 1735 cm$^{-1}$ assignable to the carbonyl moiety of an acetoxymethyl substituent. The presence of the latter was
further verified by two- and three-proton singlet resonances at 64.19 and 2.11 attributable to the protons of a methylene group and an acetyl methyl group respectively. The formation of the acetoxy methyl-1,2,4-triazine derivative (183) when the triazolylhydrazone (181) is heated in glacial acetic acid can be explained in terms of cyclisation to the originally expected triazolotriazine carboxylic acid (182) and its simultaneous decarboxylation and acid-catalysed triazole scission (see before). Consequently in an attempt to isolate the triazolotriazine carboxylic acid (182) the triazolylhydrazone derivative (181) was reacted with glacial acetic acid at the lower reaction temperature of 50°. Under these conditions chromatographic separation of the resulting reaction mixture afforded, in addition to a moderate yield (50%) of the acetoxy methyl-1,2,4-triazine derivative (183) obtained before, a low yield of a second product. The mass spectrum of this compound demonstrated the presence of a single chlorine substituent and its combustion analysis and i.r. and $^1$H n.m.r. absorption were clearly consistent with its identity as the chloromethyl-1,2,4-triazine derivative (185). The origin of this product is not at all obvious but it may be an artefact produced in the original preparation of the triazolylhydrazone carboxylic acid (181), which was isolated by acidification of the initially formed sodium salt with hydrochloric acid.

In view of the failure of the triazolylhydrazone
(i) 2M NaOH, room temp.

(ii) AcOH, heat.

(iii) Ac₂O, heat.

Scheme 50
carboxylic acid (181) to undergo thermal cyclisation to the triazolotriazine derivative (182) it was decided to attempt the base-catalysis of this process (Scheme 50). However treatment of the triazolylhydrazone carboxylic acid (181) with aqueous alkali at room temperature followed by acidification afforded a good yield (68\%) of a product which analysed correctly and gave mass spectral data consistent with a monohydrate of the molecular formula C7H3N7O4. This corresponded to the elimination of the elements of ethanol from the carboxylic acid (181) and indicated that the product had the triazolyltriazinone structure (186). This was fully in accord with the product's i.r. and 1H spectra. Thus, it showed i.r. absorption due to a cyano group but lacked i.r. absorption assignable to an ethoxycarbonyl substituent. The absence of the latter was further substantiated by the lack of signals due to the presence of an ethyl group in the product's 1H n.m.r. spectrum. In accord with the triazolyltriazinone structure (186), the product, though stable in acetic acid at 100°, underwent decarboxylation when heated under reflux affording the parent triazolyltriazinone (187) in quantitative yield. This compound analysed correctly and gave mass, i.r. and 1H n.m.r. spectra consistent with its structure. However, its further characterisation by conversion into the triazole N-acetyl derivative (188) was unsuccessful. Thus, heating the triazolyltriazinone (187) with acetic anhydride afforded only a complex gum which yielded no identifiable material.
(i) 2M NaOH, H₂O, room temp. 1h.

(ii) 2M NaOH, H₂O, room temp., few min.

(iii) Ac₂O, 100°.

Scheme 51
Failure to achieve the synthesis of pyrimido[4,5-e]-1,2,4-triazine derivatives using the triazolylhydrazone carboxylic acid (181) prompted the investigation of an alternative route (Scheme 51) involving the cyclisation of the readily available amino-1,2,4-triazine-N-ethoxycarbonylcarboxamide derivative (183). This was initially attempted by heating in acetic acid and in dioxane. However, in both cases the starting material (183) was recovered unchanged in moderate yield together with mixtures which yielded no identifiable material. In contrast, brief treatment of the triazine derivative (183) with dilute aqueous sodium hydroxide at room temperature followed by acidification afforded in addition to unreacted starting-material (183) (yield 42%), a low yield (40%) of a product which analysed correctly and had spectroscopic properties in accord with its formulation as the expected pyrimido[4,5-e]-1,2,4-triazinedione derivative (190). Prolonged treatment of the triazine derivative (183) with dilute aqueous sodium hydroxide followed by acidification afforded a high yield (78%) of a product which gave a combustion analysis consistent with its formation as a dihydrate of the hydroxymethyl pyrimido[4,5-e]-1,2,4-triazinedione derivative (189). This structure was further verified by the product's mass, i.r. and $^1$H n.m.r. spectra and by its conversion on acetylation with acetic anhydride to give the acetoxyethyl derivative (190) obtained before.
\[(134)\] \rightarrow \text{[135]} \quad (191)

\text{(i) NaNO}_2, 2\text{M HNO}_3, \text{H}_2\text{O}, 0^\circ.

\text{(ii) NaOAc, MeOH, H}_2\text{O, room temp.}

\text{Scheme 52}
The conversion of the amino-1,2,4-triazine N-ethoxycarbonylcarboxamide (183) in aqueous sodium hydroxide in high yield into the pyrimido[4,5-e]-1,2,4-triazinedione derivative (189) illustrates the viability of this new approach for the efficient synthesis of 6-azapteridine derivatives.

In parallel with the studies (Scheme 43) which culminated in the successful synthesis of the triazolopyrimidotriazinedione (140) the related synthesis (Scheme 52) of the triazolopyrimidotriazinone (194) was investigated with the intention of converting the latter compound into the corresponding pyrimido[4,5-e]-1,2,4-triazine derivatives (195). Thus, coupling of the known\textsuperscript{61,62} compound N-cyanoacetylcyanamide (191) with the triazole ester diazonium cation (135) under the usual conditions afforded a good yield (70%) of a product which analysed correctly as a dihydrate of the expected triazolylhydrazone (192). The structure of this compound was further substantiated by its mass spectrum and its i.r. and \textsuperscript{1}H n.m.r. absorption. Initially the cyclisation of the triazolylhydrazone (192) to the triazolotriazine derivative (193) was attempted by heating under reflux in glacial acetic acid. However these conditions afforded only an intractable mixture which yielded no identifiable material. Heating the triazolylhydrazone (192) under reflux in 1,4-dioxane had the same result. On the other hand heating the triazolylhydrazone (192) under reflux in ethanol afforded a
low yield (24%) of a solid product which, though it did not give an intelligible mass spectrum, analysed correctly for the molecular formula C₈H₆N₈O₃. The formulation of this product as the 1,2,3-triazolo[1,5-quinazoline]-1,2,4-triazine derivative (194) is based on its i.r. absorption. Thus its i.r. spectrum showed bands at 3550 and 3360 cm⁻¹ consistent with the presence of a primary amino group while i.r. absorption at 3100 - 2200 and 1660 cm⁻¹ can be attributed to the NH and carbonyl moieties respectively of a lactam group. The formation of the triazolopyrimidotriazine derivative (194) when the triazolylhydrazone (192) is heated in ethanol presumably involves the initial formation and spontaneous thermal cyclisation of the triazolotriazine derivative (193). Because of the low yield obtained in the transformation [(192) → (194)] as well as a lack of time, no attempt was made to investigate the further conversion of the aminotriazolopyrimidotriazine (194) into the corresponding aminopyrimido[4,5-quinazoline]-1,2,4-triazinone derivatives (195). Investigation of the latter transformations will depend on the result of future studies designed to improve the efficiency of the cyclisation [(192) → (194)].
2.5 EXPERIMENTAL

Benzyl Azide (114)

Benzyl azide (114) was prepared by the reaction of benzyl chloride with sodium azide as described by Curtius and Ehrhart\textsuperscript{63}, as an oil, yield 67\%, $\nu_{\text{max}}$ 2100 cm$^{-1}$, and was used without further purification.

5-Amino-1-benzyl-1H-1,2,3-triazole-4-carboxamide (116)

5-Amino-1-benzyl-1H-1,2,3-triazole-4-carboxamide (116) was prepared by the reaction of benzyl azide with cyanoacetamide as described by Hoover and Day\textsuperscript{45} yield 90\% and had m.p. 225-229° (lit.\textsuperscript{45} 230-232°), $\nu_{\text{max}}$ 3430, 3300, 3210 and 3160 (NH) and 1655 (CO) cm$^{-1}$, and was used without further purification.

5-Amino-1H-1,2,3-triazole-4-carboxamide (117)

5-Amino-1H-1,2,3-triazole-4-carboxamide (117) was prepared by the debenzylation of 5-amino-1-benzyl-1H-1,2,3-triazole-4-carboxamide (116) using sodium in liquid ammonia as described by Hoover and Day\textsuperscript{45} yield quant., m.p. 223-225° (lit.\textsuperscript{45} 224-225°), $\nu_{\text{max}}$ 3570, 3420 and 3300 - 3190 (NH) and 1670 (CO) cm$^{-1}$, and was used without further purification.
5-Amino-1H-1,2,3-triazole-4-carboxylic Acid (119)

A solution of 5-amino-1H-1,2,3-triazole-4-carboxamide (117) (50.8 g, 0.4 mol) in 10M aqueous sodium hydroxide (240 ml) was heated at 100° (steam bath) for 8 h.

The solution obtained was cooled and acidified dropwise with concentrated hydrochloric acid to pH 6.5 then allowed to stand overnight in a fridge. The mixture was then filtered and the solid dissolved in water (550 ml) with warming (water bath) and the solution acidified by dropwise addition of 2M aqueous sulphuric acid to pH 1.5 and the solid collected to yield 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (45.6 g; 89%), m.p. 164 - 166°, \[\text{lit.}^{44} 153° \text{ (decomp.)}\], \(v_{\text{max}}\) 3450, 3320 and 3210 (NH) and 1670 (CO) cm\(^{-1}\), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.\(^{46}\)

4-Carboxy-1H-1,2,3-triazole-5-diazonium Betaine (120)

A solution of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (2.6 g, 0.02 mol) in 2M aqueous sulphuric acid (40.0 ml) was stirred at 0° (ice-salt bath) and treated dropwise with a solution of sodium nitrite (1.5 g, 0.02 mol) in water (6.0 ml). The mixture was stirred at 0° for a further 15 min then filtered to give 4-carboxy-1H-1,2,3-triazole-5-diazonium betaine (120) (2.6 g; 94%), m.p. 109 - 111° (explosive decomp.), \(v_{\text{max}}\) 3450 - 2300 br (NH,OH), 2240 (N=N) and 1730 (CO) cm\(^{-1}\), identified by comparison (i.r. spectrum).
The Attempted Diazotisation of 5-Amino-1H-1,2,3-triazole-4-carboxamide (117)

A solution of 5-amino-1H-1,2,3-triazole-4-carboxamide (117) (1.3 g, 0.01 mol) in 2M aqueous sulphuric acid (35.0 ml) was stirred at 0 - 5° (ice-salt bath) and treated dropwise with a solution of sodium nitrite (0.8 g, 0.011 mol) in water (5.0 ml). The mixture was stirred for 15 min at 0 - 5° then filtered to yield 4-carbamoyl-1H-1,2,3-triazole-5-diazonium betaine (118) (0.80 g, 58%), m.p. 225° (decomp.), which decomposed on attempted purification by crystallisation, \( \nu_{\text{max}} \) 3400 - 2500 br (NH), 2200 (N=N) and 1700 (CO) cm\(^{-1}\), and was identified by comparison (i.r. spectrum) with an authentic sample\(^4\).

Neutralisation of the acidic mother liquor and extraction with methylene chloride yielded no further material.

2-Cyano-2-oxoacetamide-2-(4-carboxy-1H-1,2,3-triazol-5-yl)-hydrazone (121)

(a) A solution of cyanoacetamide (0.17 g, 0.002 mol) and anhydrous sodium acetate (0.25 g, 0.003 mol) in ethanol (10.0 ml) and water (5.0 ml) was treated dropwise with stirring at 0 - 5° (ice-salt bath) with a solution of 4-carboxy-1H-1,2,3-triazole-5-diazonium betaine (120) (0.28 g, 0.002 mol)
in ethanol (5.0 ml) and water (5.0 ml) and the mixture was stirred in the melting ice-bath for 2.5 h.

Filtration afforded the sodium salt of the 2-cyano-2-oxoacetamide-2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (121) (0.4 g; 82%), m.p. 260 - 265°, $v_{\text{max}}$ 3350 br and 3150 br (NH) and 1635 and 1625 (CO) cm$^{-1}$, which was slurried with 2M aqueous hydrochloric acid to give the free triazolylhydrazone carboxylic acid (121) (0.32 g; 72%), m.p. 212 - 215° (decomp.), $v_{\text{max}}$ 3420, 3280 and 3170 (NH), 2700 - 2300 br (OH), 2210 (C=N), and 1680 and 1650 (CO) cm$^{-1}$, which was converted by crystallisation from dimethylsulphoxide-water into 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123), m.p. 240 - 244°, identical (m.p. and i.r. spectrum) to a sample prepared later.

Evaporation of the ethanolic mother liquor and treatment of the residue with 2M aqueous hydrochloric acid gave only a negligible quantity of yellow solid.

(b) A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (5.1 g, 0.04 mol) in 2M aqueous nitric acid (80.0 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (3.0 g, 0.044 mol) in water (10.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with a solution of cyanoacetamide (3.4 g, 0.04 mol) and anhydrous sodium acetate (23.0 g, 0.28 mol) in methanol (120 ml) and water (60.0 ml) and the mixture was stirred in the melting ice-bath for 2 h.
Filtration afforded an orange solid which was collected to give the sodium salt of 2-cyano-2-oxoacetamide-2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (121) which was slurried with 2M aqueous hydrochloric acid to afford the free triazolylhydrazone carboxylic acid (121) (3.7 g; 42%), m.p. 214 - 215° (decomp.) which was identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

The original methanolic mother liquor was concentrated to remove the methanol and the orange solid which precipitated was collected to give the sodium salt of 5-amino-6-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (122) $\nu_{\text{max}}$ 3360 and 3150 - 2500 br (NH and OH) and 1700 and 1655 (CO) cm$^{-1}$. This was slurried with 2M aqueous hydrochloric acid to give the free triazolotriazine carboxylic acid (3.4g; 39%) m.p. 210 - 214°, $\nu_{\text{max}}$ 3480, 3340 and 3180 - 2500 br (NH and OH) and 1700 br (CO) cm$^{-1}$, which underwent decarboxylation on attempted purification by crystallisation to afford 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123), m.p. 240 - 244°, identical (m.p. and i.r. spectrum) to a sample prepared later.

5-Amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123)

(a) A solution of 5-amino-6-carbamoyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (122) (0.89 g, 0.004 mol) in dimethylformamide (10.0 ml) and water (5.0 ml) was heated under reflux for 2h.

The mixture was evaporated to give an orange residue which was triturated with methylene chloride to yield 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123) (0.50 g; 70%) which formed orange crystals, m.p. 244 - 246° (from dimethylformamide-water), $\nu_{\text{max}}$ 3340, 3240 and 3170 - 3140 (NH) and 1695 (CO) cm$^{-1}$, $\delta_{\text{H}}$ [(CD$_3$)$_2$SO] 8.67 (1H, brs, NH) (exch.), 8.33 - 8.17 (3H, brs, NH) (exch.) and 7.70 (1H, s, CH).

Found: C,33.1; H,2.8; N,54.0 %; m/z (EI ms), 179.0556 (M$^+$).
C$_5$H$_5$N$_7$O requires: C,33.5; H,2.8; N,54.8 %; M, 179.0549.

(b) A suspension of the sodium salt of 5-amino-6-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (122) (0.98 g, 0.004 mol) in dimethylformamide (10.0 ml) was heated at 100° (oil-bath) for 1 h. The mixture was treated with water (5.0 ml) and then heated under reflux for 2 h.

The mixture was filtered and the solid combined with further material which precipitated from the mother liquor on standing to give 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123) (0.28 g; 39%), m.p. 225 - 226° identified by comparison (i.r. spectrum) with a sample prepared in (a) before.
Work-up of the aqueous dimethylformamide mother liquor yielded no other identifiable material.

(c) A solution of 2-cyano-2-oxoacetamide 2-(4-carboxy-\textit{1H}-1,2,3-triazol-5-yl)hydrazone (121) (0.80 g, 0.0036 mol) in dimethylformamide (10.0 ml) was heated at 100° (steam-bath) for 10 min.

The mixture was diluted with water (5.0 ml) and heating under reflux continued for a further 20 min. The solid which precipitated on cooling was combined with further material obtained by evaporating the filtrate and subjecting the residue to flash-chromatography in ethyl acetate-methanol (1:5) over silica to afford 5-amino-1,2,3-triazolo[1,5-\textit{b}]-1,2,4-triazine-6-carboxamide (123) (0.46 g; 71%), m.p. 240 – 243°, which was identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

(d) A suspension of the sodium salt of 2-cyano-2-oxoacetamide 2-(4-carboxy-\textit{1H}-1,2,3-triazol-5-yl)hydrazone (121) (0.89 g, 0.0036 mol) in dimethylformamide (10.0 ml) was heated at 100° (steam-bath) for 0.5 h. Water (5.0 ml) was then added and heating at 100° continued for a further 1.5 h. The suspension was further diluted with water (5.0 ml) and the resulting solution then heated under reflux for 2.5 h.

The orange solid which precipitated from the mixture on cooling was collected to yield
5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123) (0.24 g; 37%), m.p. 225 - 227°, which was identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Further workup of the aqueous dimethylformamide mother liquor gave no further identifiable material.

5-Amino-3-chloromethyl-1,2,4-triazine-6-carboxamide (128)

(a) A suspension of 5-amino-6-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (122) (0.45 g, 0.002 mol) in glacial acetic acid (2.5 ml) and acetyl chloride (7.5 ml) was heated under reflux for 3 h.

The mixture was hot-filtered to afford the unreacted triazolotriazine (122) (0.41 g; 91%), m.p. 210 - 215°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Evaporation of the filtrate and treatment of the residue with 10% w/v aqueous sodium hydrogen carbonate solution afforded 5-amino-3-chloromethyl-1,2,4-triazine-6-carboxamide (128) (0.04 g; 11%), identified by comparison (i.r. spectrum) with a sample prepared in (c) later.

(b) A suspension of 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123) (0.30 g, 0.002 mol) in glacial acetic acid (2.5 ml) and acetyl chloride (7.5 ml) was heated under reflux for 3 h.
The mixture was hot-filtered to give a tan solid (0.12 g) which was stirred with 10% w/v aqueous sodium hydrogen carbonate solution to afford 5-amino-3-chloromethyl-1,2,4-triazine-6-carboxamide (128) (0.07 g; 22%), m.p. 185° (decomp.) identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (c) later.

Workup of the acetic acid-acetyl chloride mother liquor gave no other identifiable material.

(c) A solution of 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123) (0.70 g, 0.004 mol) in glacial acetic acid (15.0 ml) saturated with dry hydrogen chloride gas was heated under reflux for 3 h.

Evaporation of the mixture gave a brown residue which was treated with 10% w/v aqueous sodium hydrogen carbonate solution to yield 5-amino-3-chloromethyl-1,2,4-triazine-6-carboxamide (128) (0.63 g; 86%), which formed brown crystals, m.p. 200 - 203° (decomp.) (from dimethylformamide-water), 

\[ \nu_{\text{max}} \] 3355, 3250 and 3180 - 3160 (NH) and 1680 (CO) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\)_2SO] 8.46 (3H, brs, NH), 7.88 (1H, brs, NH) and 4.68 (2H, s, CH\(_2\)).

Found: C, 31.7; H, 3.2; N, 37.1%; m/z (EI ms) 189, 187 (M\(^+\)).

\( \text{C}_5\text{H}_6\text{ClN}_5\text{O} \) requires: C, 32.0; H, 3.2; N, 37.3%; M, 189; 187.
3-Acetoxymethyl-5-amino-1,2,4-triazine-6-carboxamide (129)

A solution of 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (123) (0.36 g, 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 3 h.

The mixture was evaporated to give a brown residue which was triturated with toluene and the insoluble solid (0.4 g) obtained heated under reflux in ethyl acetate for 2.5 h. Hot-filtration of the mixture gave unreacted triazolotriazine (123) (0.06 g; 16%), m.p. 197 – 202°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the ethyl acetate mother liquor afforded 3-acetoxymethyl-5-amino-1,2,4-triazine-6-carboxamide (129) (0.27 g; 77%), which formed yellow crystals, m.p. 176 – 178° (from ethyl acetate), $\nu_{\text{max}}$ 3440, 3370, 3320 and 3180 – 3160 (NH) and 1745 and 1695 (CO) cm$^{-1}$, $\delta_H$ [($\text{CD}_3$)$_2$SO] 8.50 – 8.36 (3H, brs, NH), 7.86 (1H, brs, NH), 5.12 (2H, s, CH$_2$) and 2.12 (3H, s, CH$_3$).

Found: C, 40.1; H, 4.2; N, 32.7%; m/z (EI ms) 211 (M$^+$).

C$_7$H$_9$N$_5$O$_3$ requires: C, 39.8; H, 4.3; N, 33.2%; M, 211.

Evaporation of the original toluene mother liquor gave only a negligible quantity of a colourless solid which was not further investigated.
4-Methoxybenzyl Chloride

4-Methoxybenzyl chloride was prepared by the reaction of 4-methoxybenzyl alcohol with anhydrous hydrogen chloride in sodium-dried ether as described by Buckle and Rockell,\textsuperscript{49} as an oil, yield 97\%, and was used without further purification.

4-Methoxybenzyl Azide (130)

4-Methoxybenzyl azide (130) was prepared by the reaction of 4-methoxybenzyl chloride with sodium azide in anhydrous dimethylformamide as described by Buckle and Rockell,\textsuperscript{49} as an oil, yield 83\%, $\nu_{\text{max}}$ 2100 (N=N) cm$^{-1}$, and was used without further purification.

Methyl 5-Amino-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate (132)

A solution of sodium (2.3 g, 0.01 g.atom) in methanol (40.0 ml) was added to a mixture of 4-methoxybenzyl azide (130) (16.3 g, 0.10 mol) and methyl cyanoacetate (9.9 g, 0.10 mol) and the mixture was heated under reflux for 3 h.

The cooled mixture was filtered to remove some insoluble material and on standing slowly deposited a yellow solid which was collected to afford methyl 5-amino-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate (132) (3.4 g; 13\%) which formed colourless needles, m.p. 189 - 190° (from
ethanol), $\nu_{\text{max}}$ 3480, 3290, 3250, 3180 and 3120 (NH) and 1690 (CO) cm$^{-1}$, $\delta_H ([\text{CD}_3]_2\text{SO})$ 7.25 - 6.80 (4H, m, ArH), 6.57 (2H, brs, NH), 5.34 (2H, s, CH$_2$), 3.76 (3H, s, CH$_3$) and 3.72 (3H, s, CH$_3$).

**Found:** C, 54.1; H, 5.3; N, 21.0%; m/z (EI ms) 262.1066. (M$^+$).  
C$_{12}$H$_{14}$N$_4$O$_3$ requires: C, 55.0; H, 5.3; N, 21.4%; M, 262.1066.

The methanolic mother liquor was evaporated and the residue was treated with water (70.0 ml) and extracted with methylene chloride to afford an orange-red gum whose t.l.c. in methylene chloride over silica showed it to be a multi-component mixture which was not further investigated.
Methyl 5-Amino-1H-1,2,3-triazole-4-carboxylate (133)

(a) A solution of methyl 5-amino-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate (132) (2.6 g, 0.01 mol) in trifluoroacetic acid (10.0 ml) was stirred at 60 - 65° (oil bath) for 3 h.

The mixture was evaporated and the residue was treated with water to give a gummy solid which was triturated with ether to afford the unreacted 4-methoxybenzyltriazole (132) (1.8 g; 70%), m.p. 189 - 190°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

On standing, the aqueous mother liquor deposited methyl 5-amino-1H-1,2,3-triazole-4-carboxylate (133) (0.41 g; 29%) which formed tan plates, m.p. 199 - 203° (from water) (lit44, 199°), $v_{max}$ 3480 and 3300 - 2500 br (NH), 1680 (CO) and 1640 (C=N) cm$^{-1}$, $\delta_H [(CD_3)_2SO]$ 7.60 (1H, brs, NH), 6.57 (2H, brs, NH) and 3.80 (3H, s, CH$_3$).

Found: C, 34.0; H, 4.0; N, 39.6%; m/z (EI ms) 142 (M$^+$$)$. Calc. for C$_4$H$_6$N$_4$O$_2$: C, 33.8; H, 4.2; N, 39.4%; M, 142.

(b) A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (1.3 g, 0.01 mol) in methanol (10.0 ml) was treated with concentrated sulphuric acid (1.0 ml) and the mixture was heated under reflux for 6 h.

The solution was concentrated, cooled (ice-bath) and treated with water (10.0 ml). The resulting acidic solution was neutralised with concentrated aqueous ammonia and the yellow solid which gradually precipitated was collected to
give methyl 5-amino-1H-1,2,3-triazole-4-carboxylate (133) (0.15 g; 10%) which formed tan plates, m.p. 198 – 200° (from water) and was identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Extraction of the aqueous mother liquor with ethyl acetate gave no further material.

Methyl 5-Amino-1H-1,2,3-triazole-4-carboxylate Hydrochloride (134)

A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (9.8 g, 0.08 mol) in methanol (150 ml) was heated under reflux for 0.5 h, then the suspension was saturated with dry hydrogen chloride and heated under reflux for a further 2 h.

The orange solution was evaporated and the residue was triturated with anhydrous ether and filtered to yield methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (12.3 g; 86%) which formed tan needles, m.p. 195 – 200° (from glacial acetic acid - toluene) (phase change at 119°), \( \nu_{\text{max}} \) 3500 – 2000 br (NH) and 1710 (CO) cm\(^{-1}\), \( \delta_{\text{H}} \) [(CD\(_3\)]\(_2\)SO] 4.52 (4H, brs, NH) and 3.81 (3H, s, CH\(_3\)).

**Found:** m/z (EI ms), 181.0306 and 179.0336 (M\(^+\)).

**C\(_4\)H\(_7\)ClN\(_4\)O\(_2\)** requires: M, 181.0306 and 179.0336.

Evaporation of the ethereal mother liquor afforded no further identifiable material.
5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137)

(a) A suspension of methyl-5-amino-1H-1,2,3-triazole-4-carboxylate (133) (0.57 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated at 0-5°C (ice-salt bath) with a solution of sodium nitrite (0.30 g, 0.0044 mol) in water (5.0 ml). The mixture was stirred at 0-5°C for 15 min then treated with a solution of cyanoacetamide (0.34 g, 0.004 mol) and sodium acetate (2.3 g, 0.028 mol) in methanol (12.0 ml) and water (6.0 ml) and the mixture then stirred in the melting ice-bath for 2 h.

Filtration afforded an orange solid which was combined with further material obtained by allowing the filtrate to stand to yield 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (isomer A) (0.48 g; 51%), m.p. 235°C (decomp.) identified by comparison (m.p. and i.r. spectrum) to a sample prepared in (b) later.

The methanolic mother liquor was concentrated and extracted with ethyl acetate to give only a small amount of a yellow solid (0.03 g) which was not further investigated.

Acidification of the aqueous mother liquor with aqueous 2M hydrochloric acid afforded no further material.

(b) A suspension of methyl 5-amino-1H-1,2,3-triazole-4
-carboxylate hydrochloride (134) (7.1 g, 0.04 mol) in 2M aqueous nitric acid (80.0 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (3.0 g, 0.04 mol) in water (10.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with a solution of cyanoacetamide (3.4 g, 0.04 mol) and sodium acetate (23.0 g, 0.28 mol) in methanol (100 ml) and water (50.0 ml).

Stirring was continued for 2 h in the melting ice-bath and the mixture was then filtered to give a yellow solid. This was combined with further material deposited by the filtrate on standing to yield 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (isomer A) which formed yellow prisms (7.8 g; 82%), m.p. 268 - 270° (from dimethylformamide - water), \( \nu_{\text{max}} \) 3340, 3260 and 3200 (NH) and 1720 and 1660 (CO) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\))\(_2\)SO] 8.95 - 8.70 (3H, brs, NH) (exch.), 8.25 (1H, brs, NH) (exch.) and 3.84 (3H, s, CH\(_3\)), \( \delta_C \) [CD\(_3\)]\(_2\)SO] 164.0 (quat.), 160.5 (quat.), 152.6 (quat.), 139.3 (quat.), 131.7 (quat.), 121.2 (quat.) and 51.2 (CH\(_3\)).

Found: C, 35.3 ; H, 2.9 ; N, 41.7 %; m/z (EI ms), 237 (M\(^+\)).

C\(_7\)H\(_7\)N\(_7\)O\(_3\) requires: C, 35.4 ; H, 2.9 ; N, 41.4 %; M, 237.

Extraction of the aqueous mother liquor with methylene chloride yielded no further material.
The Reaction of 5-Amino-3-methoxycarbonyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) with
Aqueous Sodium Hydroxide

A solution of 5-amino-3-methoxycarbonyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (isomer A)
(137) (0.47 g, 0.002 mol) in aqueous 2M sodium hydroxide was
heated under reflux for 1 h.

The mixture was cooled and acidified with aqueous 2M
hydrochloric acid to yield a yellow solid which was combined
with further material obtained from the acidic mother liquor
on standing and reslurried with aqueous 2M hydrochloric acid
to afford 1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one-6-
carboxylic acid (138) (0.22 g; 61%), which formed yellow
crystals of a trihydrate, m.p. 166 - 169° (from water), $\nu_{\text{max}}$
3600 - 3100 br (OH) and 1710 (CO) cm$^{-1}$, $\delta_{H}$ [(CD$_3$)$_2$SO] 11.48
(2H, brs, OH) (exch.) and 7.68 (1H, s, CH).

Found: C, 25.0; H, 3.5; N, 29.8%; m/z (EI ms), 181 (M$^+$-3H$_2$O).
C$_5$H$_3$N$_5$O$_3$.3H$_2$O requires: C, 25.5; H, 3.8; N, 29.8%; M, 235.

The Attempted Reaction of 5-Amino-3-methoxycarbonyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) with
Diethyl Carbonate in the Presence of Sodium Ethoxide

5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-
triazine-6-carboxamide (isomer A) (137) (0.47 g, 0.002 mol)
was added to a solution of sodium (0.23 g, 0.01 g.atom) in
anhydrous ethanol (15.0 ml) then diethyl carbonate (0.94 g, 0.008 mol) was added and the mixture was heated under reflux for 5 h.

The mixture (containing a solid) was evaporated and the residue then treated with water (5.0 ml) and filtered to afford the unreacted triazolotriazine (0.07 g; 15%), m.p. 235° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The aqueous filtrate was acidified with glacial acetic acid and filtered to afford an orange solid (0.23 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not therefore further investigated.

The Attempted Reaction of 5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) with Diethoxymethyl Acetate

A solution of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.95 g, 0.004 mol) in diethoxymethyl acetate (10.0 ml) was heated under reflux for 6 h.

The mixture was evaporated to afford a brown oil. This was triturated with ether to give a brown solid (0.93 g) which was dry flash-chromatographed over silica.

Elution with methylene chloride - ethyl acetate through to methanol afforded only a series of intractable solids (total 0.52 g) whose t.l.c. in ethyl acetate over silica
showed them to be complex mixtures which were therefore not further investigated.

The Attempted Reaction of 5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) with Triethyl Orthoformate

A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (isomer A) (137) (0.47 g, 0.002 mol) in triethyl orthoformate (10.0 ml) was heated under reflux for 3 h.

The mixture was hot-filtered to afford isomer B of the unreacted triazolotriazine (137) (0.43 g; 92%), m.p. 258 - 260°, which was identified by comparison with a sample prepared later.

Evaporation of the triethyl orthoformate mother liquor gave only a negligible amount of yellow solid which was not further investigated.

The Conversion of 5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) Isomer A into Isomer B in Diglyme

A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (isomer A) (0.47 g, 0.002 mol), \( v_{\text{max}} \) 3340, 3260 and 3200 (NH) and 1720 and 1640 (CO) cm\(^{-1}\), in anhydrous diglyme (10.0 ml) was heated under reflux for 3 h.
The mixture was hot-filtered to afford isomer B of the triazolotriazine (137) (0.32 g; 68%), m.p. 255°, $\nu_{\text{max}}$ 3480, 3430 and 3260 - 3200 br (NH) and 1710 - 1680 br (CO) cm$^{-1}$, $\delta_{\text{H}}$ [(CD$_3$)$_2$SO] 8.95 - 8.70 (3H, brs, NH) (exch.), 8.25 (1H, brs, NH) (exch.), 3.84 (3H, s, CH$_3$), $\delta_{\text{C}}$ [(CD$_3$)$_2$SO] 164.2 (quat.), 160.6 (quat.), 152.7 (quat.), 139.4 (quat.), 131.8 (quat.), 121.2 (quat.) and 51.4 (CH$_3$) identified by comparison (m.p. and t.l.c.) with a sample prepared before.

Evaporation of the diglyme mother liquor gave an intractable brown gum (0.18 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which was not further investigated.

The Attempted Reaction of 5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) with Formamide in the Presence of Sodium Ethoxide

5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.47 g, 0.002 mol) was added to a solution of sodium (0.23 g, 0.01 g. atom) in anhydrous ethanol (20.0 ml) then formamide (0.8 ml) was added and the mixture was heated under reflux for 3 h.

The mixture was cooled and filtered to yield a brown solid which was treated with water and the solution acidified at 5 - 10° (ice-bath) with glacial acetic acid.

The precipitated solid was washed with ethanol to yield an intractable orange solid (0.29 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture from
which no identifiable material could be obtained.

Evaporation of the ethanolic mother liquor afforded only a negligible amount of material.

The original ethanolic mother liquor was evaporated to give a yellow residue which was treated with water (4.0 ml) and the resulting solution combined with the aqueous acetic acid mother liquor and filtered to yield the unreacted triazolotriazine (137) (0.05 g), m.p. 215° (decomp.) identified by comparison (i.r. spectrum) with a sample prepared before. Extraction of the aqueous acidic mother liquor with methylene chloride yielded no further material.

Methyl 2-Cyano-2-oxoacetate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone(146)

A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (7.1 g; 0.04 mol) in aqueous 2M nitric acid (80.0 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (3.0 g, 0.04 mol) in water (12.0 ml). The mixture was stirred for 15 min at 0-5° then treated in one portion with a solution of methyl cyanoacetate (4.0 g, 0.04 mol) and sodium acetate (23.0 g, 0.28 mol) in methanol (130 ml) and water (65.0 ml) and stirred in the melting ice-bath for a further 2 h.

The precipitated yellow solid was collected and
slurried with 2M aqueous hydrochloric acid to give methyl 2-cyano-2-oxoacetate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-4-yl)hydrazone (146) (7.6 g; 75%), which was purified by repeated dissolution in 2M aqueous sodium hydroxide and reprecipitation with 2M aqueous hydrochloric acid to give cream crystals of a monohydrate, m.p. 200-203° (with melting at 112-114° and resolidification at 135°), $\nu_{\text{max}}$ 3620 and 3370 br (NH), 2200 (C≡N) and 1730 and 1660 (CO) cm$^{-1}$, $\delta_H[(CD_3)\text{SO}]$ 3.89 (3H, s, CH$_3$) and 3.84 (3H, s, CH$_3$). Found: C, 35.0; H, 3.7; N, 31.4%; m/z (EI ms), 252 (M$^+$-H$_2$O).

$C_8H_8N_6O_4.H_2O$ requires: C, 35.5; H, 3.7; N, 31.1%; M, 270.

Concentration of the filtrate afforded dimethyl 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) (isomer A) (0.94 g; 9%), which formed orange prisms, m.p. 220-223° (from dimethylformamide-water), identical (m.p. and i.r. spectrum) to a sample prepared later.

Extraction of the aqueous mother liquor before and after acidification with 2M aqueous hydrochloric acid yielded no further material.

**Dimethyl 5-Amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147)**

(a) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate (133) (0.57 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.30 g,
0.0044 mol) in water (5.0 ml) and the mixture was stirred at 0-5° for 15 min then treated in one portion with a solution of methyl cyanoacetate (0.40 g, 0.004 mol) and sodium acetate (2.3 g, 0.028 mol) in methanol (10.0 ml) and water (5.0 ml). The mixture was then stirred in the melting ice-bath for 2 h.

Filtration afforded a yellow solid (0.92 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture from which no identifiable material could be obtained.

The aqueous methanolic mother liquor was concentrated and filtered to afford dimethyl 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) (isomer A) which formed orange prisms, m.p. 220-225° (from dimethylformamide-water), νmax 3440 and 3280 br (NH) and 1730 and 1710 (CO) cm⁻¹, δH[(CD₃)₂SO] 9.10 (1H, brs, NH), 8.12 (1H, brs, NH), 3.98 (3H, s, CH₃) and 3.85 (3H, s, CH₃), δC [(CD₃)₂SO] 162.2 (quat.), 160.4 (quat.), 152.0 (quat.), 139.2 (quat.), 130.9 (quat.), 121.2 (quat.), 53.7 (CH₃) and 51.3 (CH₃).

Found: C,38.2; H,3.1; N,33.1%; m/z (EI ms), 252 (M⁺).
C₈H₈N₆O₄ requires: C,38.1; H,3.2; N,33.3%; M,252.

Extraction of the aqueous mother liquor with ethyl acetate afforded no further material.
(b) A solution of 2-cyano-2-oxoacetate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl) hydrazone (146) (0.50 g, 0.002 mol) in anhydrous dioxane (10.0 ml) was heated under reflux for 19 h.

The mixture was hot-filtered to give a yellow solid which was combined with further material obtained by cooling the filtrate to yield dimethyl 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) (isomer B) (m.p. 211-213°, $\nu_{\text{max}}$ 3400, 3280 and 3180 br (NH) and 1720 br (CO) cm$^{-1}$, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (c) later.

Evaporation of the dioxane filtrate gave no further identifiable material.

(c) A solution of 2-cyano-2-oxoacetate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (146) (7.5 g, 0.03 mol) in glacial acetic acid (50.0 ml) was heated under reflux for 17 h.

The mixture was hot-filtered to afford one isomer of dimethyl 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) (isomer A) (0.57 g; 8%), m.p. 220-225°, $\nu_{\text{max}}$ 3440 and 3280 br (NH) and 1730 and 1710 (CO) cm$^{-1}$, identical (m.p. and i.r. spectrum) to a sample prepared before.

The acetic acid filtrate was evaporated and the residue was washed with methanol to afford the other isomer of dimethyl 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-
dicarboxylate (147) (isomer B) (3.3 g; 45%), m.p. 226-228° (from acetic acid), $\nu_{\text{max}}$ 3400, 3280 and 3180 br (NH) and 1720 (CO) cm$^{-1}$, $^1$H and $^{13}$C n.m.r. identical to isomer A before.

Found: C,38.2; H,3.1; N,33.1 %; m/z (EI ms), 252 (M$^+$).

$\text{C}_8\text{H}_8\text{N}_6\text{O}_4$ requires: C,38.1; H,3.2; N,33.3 %; M, 252.

The methanol mother liquor was evaporated to afford a red oil whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not therefore further investigated.

The Attempted Reaction of Dimethyl 5-Amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) with Formamide

A solution of dimethyl 5-Amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) (isomer A) (0.50 g, 0.002 mol) in formamide (5.0 ml) was heated at 170° (oil-bath) for 1 h.

The mixture was evaporated to give a brown solid (0.40 g), whose t.l.c. in ethyl acetate showed it to be an unresolvable multicomponent mixture which was not further investigated.

Evaporation of the ethanol mother liquor afforded no further material.
**4,5-Dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149a)**

A suspension of methyl 5-amino-1,2,3-triazole-4-carboxylate hydrochloride (134) (0.71 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0-5°C (ice-salt bath) with a solution of sodium nitrite (0.30 g, 0.0044 mol) in water (5.0 ml). The mixture was stirred in the ice-salt bath for 15 min, then treated in small portions with a suspension of barbituric acid (0.51 g, 0.004 mol) and anhydrous sodium acetate (2.3 g, 0.028 mol) in methanol (5.0 ml) and water (10.0 ml) and the resulting mixture stirred in the melting ice-bath for 2 h.

The mixture was filtered and the yellow solid obtained washed with methanol to afford 4,5-dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149a) (1.0 g; 79%), which formed yellow crystals, m.p. 230-233°C (from dimethylformamide-water), ν\text{max} 3570, 3500 and 3420 (NH), 3100 - 2500 br (OH, NH), 1780 and 1670 (CO) and 1620 (C=N) cm\(^{-1}\), δ\text{H} [(CD\text{3})\text{2}SO]\n14.50 (1H, s, NH or OH)(exch.), 11.65 (1H, s, NH)(exch.), 11.40 (1H, s, NH)(exch.), 5.10 (1H, brs, NH or OH) and 3.91 (3H, s, CH\text{3}).

Found: C, 29.8; H, 3.4; N, 30.7%; m/z (EI ms), 281 (M\text{+}-2H\text{2}O). C\text{8}H\text{7}N\text{7}O\text{5}.2H\text{2}O requires: C, 30.3; H, 3.5; N, 30.9%; M, 317.

The methanol filtrate was evaporated to give only a small amount of solid (0.08 g) which was not further
investigated.

Extraction of the original aqueous mother liquor yielded no further material.

The Attempted Phosphoryl Chloride Catalysed Cyclisation of 4,5-Dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149a)

A suspension of 4,5-dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)-hydrazone (149a) (0.56 g, 0.002 mol) in phosphoryl chloride (2.0 ml) containing N,N-diethyl aniline (0.5 ml) was heated under reflux for 1.5 h.

The mixture was concentrated under reduced pressure to remove the excess of phosphoryl chloride and the oily residue was treated with ice. The mixture was filtered to give only an intractible brown solid (0.22 g) from which no identifiable material could be obtained.

Extraction of the aqueous mother liquor with ethyl acetate gave an intractible red gum (0.15 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which was not further investigated.

1,3-Dimethyl-4,5-dihydropyrimidine-2,4,5,6-(1H,3H)-tetraone 5-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149b)

A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylate
hydrochloride (134) (0.71 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.30 g, 0.0044 mol) in water (5.0 ml). The mixture was stirred at 0-5° for a further 15 min then treated in small portions with a solution of 1,3-dimethylbarbituric acid (0.62 g, 0.004 mol) and anhydrous sodium acetate (2.3 g, 0.028 mol) in methanol (15.0 ml) and water (7.0 ml) and the mixture then stirred in the melting ice-bath for 2 h.

The mixture was filtered and the yellow solid obtained was combined with further material which precipitated from the aqueous mother liquor on standing and slurried with 2M aqueous hydrochloric acid to yield 1,3-dimethyl-4,5-dihydropyrimidine-2,4,5,6-(1H,3H)-tetraone 5-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149b) (1.0 g; 76%) which formed yellow crystals (from dimethylformamide-water), m.p. 226-228°, $\nu_{\text{max}}$ 3360 (NH), 3100 - 2200 br (OH, NH) 1740, 1715, 1670 and 1650 (CO) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 14.55 (1H, s, NH or OH), 4.25 (1H, brs, NH or OH), 3.93 (3H, s, CH$_3$), 3.22 (3H, s, CH$_3$) and 3.21 (3H, s, CH$_3$).

Found: C,36.7; H,3.9; N,30.1 %; m/z (EI ms), 309 (M$^+$-H$_2$O).
C$_{10}$H$_{11}$N$_7$O$_5$.H$_2$O requires: C,36.7; H,4.0; N,30.0%; M,327.

Concentration of the original methanolic mother liquor and extraction of the resulting aqueous residue both before and after acidification with 2M aqueous hydrochloric acid
afforded no further material.

1,3-Dimethyl-4,5-dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(1-Acetyl-4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)-hydrazone (151b)

A solution of 1,3-dimethyl-4,5-dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149b) (0.62 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h.

The mixture was evaporated to afford 1,3-dimethyl-4,5-dihydropyrimidine-2,4,5,6(1H,3H)-tetraone 5-(1-Acetyl-4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (151b) as a yellow solid (0.70 g; quant.) which formed yellow needles, m.p. 214-217° (from dimethylformamide-toluene), \( \nu_{\text{max}} \) 1780, 1710, 1690 and 1650 (CO) \( \text{cm}^{-1} \), \( \delta_{\text{H}} \) [(CD\(_3\)\(_2\)S\(_0\)] 4.01 (3H, s, CH\(_3\)), 3.25 (6H, s, CH\(_3\)) and 2.80 (3H, s, CH\(_3\)).

**Found**: C, 40.2; H, 3.6; N, 27.2%; m/z (FAB ms), 352.1005 [(M+H\(^+\)].

**C\(_{12}\)H\(_{14}\)N\(_7\)O\(_6\) requires**: C, 40.9; H, 4.0; N, 27.8%; M, 352.1005.

**Attempted Dehydrative Cyclisation Reactions of**

1,3-Dimethyl-4,5-dihydropyrimidine-2,4,5,6-(1H,3H)-tetraone 5-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (149b)

(a) A suspension of 1,3-dimethyl-4,5-dihydropyrimidine-2,4,5,6-(1H,3H)-tetraone 5-(4-methoxycarbonyl-1H-1,2,3-
triazol-5-yl)hydrazone (149b) (0.62 g, 0.002 mol) in anhydrous 1,2-dichloroethane (15.0 ml) was treated with a single portion of phosphoryl chloride (1.5 g, 0.01 mol) and the mixture was heated under reflux with the exclusion of atmospheric moisture for 1 h 45 min.

The mixture was hot-filtered and the yellow solid was collected and combined with further material obtained by evaporation of the organic filtrate and washed with 10% w/v aqueous sodium hydrogen carbonate solution then slurried with aqueous 2M hydrochloric acid to afford the unreacted pyrimidinyl hydrazone (149b) (0.49 g; 84%), m.p. 239-241°, which was identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(b) Repetition of the reaction described in (a) before but with heating under reflux for 8 h followed by hot filtration gave only the unreacted pyrimidinyl hydrazone (149b) (0.53 g; 86%), m.p. 226-228° which was identified by comparison (i.r. spectrum) with a sample prepared previously.

Workup of the dichloroethane mother liquor afforded no other identifiable material.

(c) A suspension of the pyrimidinyl hydrazone (149b) (0.62 g, 0.002 mol) in phosphoryl chloride (2.0 ml) containing N,N-diethylaniline (0.5 ml) was heated (oil-bath) until an exothermic reaction occurred. When this subsided,
the mixture was heated under reflux for 1.5 h.

The mixture was concentrated to remove the excess of phosphoryl chloride and the residue was treated with ice (10.0 g). Filtration afforded an orange solid which was washed with water to give the unreacted pyrimidinyl hydrazone (149b) (0.45 g; 73%), m.p. 240-244°, which was identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Workup of the aqueous mother liquor gave no other identifiable material.

(d) A suspension of the pyrimidinyl hydrazone (149b) (0.62 g, 0.002 mol) in anhydrous dimethylformamide (15.0 ml) was stirred and treated dropwise with phosphoryl chloride (0.30 g, 0.004 mol), then the mixture was heated at 80° (oil-bath) for 1 h.

The mixture was evaporated and the residue treated with water to give an orange solid which was washed with water and methylene chloride to give the unreacted pyrimidinyl hydrazone (149b) (0.62 g; quant.), m.p. 229-233°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(e) Repetition of the reaction described in (d) before but with heating under reflux for 2 h in the presence of N,N-diethylaniline gave after evaporation of the mixture a black gum which was treated with ice and extracted with
methylene chloride to give a purple oil (0.44 g) which was dry flash-chromatographed over silica.

Elution with ethyl acetate - methylene chloride (4:1) afforded an intractible brown solid (0.10 g) from which no identifiable material could be obtained.

(f) A suspension of the pyrimidinyl hydrazone (149b) (0.28 g, 0.0009 mol) in thionyl chloride (5.0 ml) was heated under reflux for 1 h.

The mixture was evaporated to give a yellow solid (0.28 g) which was crystallised from dimethylformamide to afford the unreacted starting-material (149b) (quant.) which was identified by comparison (i.r. spectrum) with a sample prepared before.

N-Cyanoacetylformamide (157)

N-Cyanoacetylformamide (157) was prepared by the reaction of cyanoacetic acid with formamide in the presence of acetic anhydride as described by Hildick and Shaw\textsuperscript{55}, yield 13\%, m.p. 125-129° (lit.\textsuperscript{55}, 139°) and was used without further purification.

N-Formyl 2-Cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (159)

(a) A suspension of methyl 5-amino-1\textsubscript{H}-1,2,3-triazol-4-carboxylate hydrochloride (134) (1.8 g, 0.01 mol) in 2M aqueous nitric acid (20.0 ml) was stirred and treated
dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.76 g, 0.011 mol) in water (5.0 ml). The mixture was stirred at 0-5° for 15 min then treated in one portion with a solution of N-cyanoacetylfomamide (157) (1.1 g, 0.01 mol) and sodium acetate (5.7 g, 0.07 mol) in methanol (40.0 ml) and water (20.0 ml) and the mixture stirred in the melting ice-bath for 2 h.

Filtration afforded the yellow salt of the hydrazone (158) which was slurried with 2M aqueous hydrochloric acid to yield N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (159) (0.43 g; 15%), m.p. 192-200° (decomp.), identical (i.r. spectrum) to a sample prepared later.

The original mother liquor was concentrated to remove the methanol and filtered to yield 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.69 g; 29%), m.p. 218-221°, identified by comparison (i.r. spectrum) with a sample prepared later.

The aqueous mother liquor was extracted with methylene chloride to give a yellow solid which was combined with further material obtained by acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride to yield dimethyl 5-amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3,6-dicarboxylate (147) (0.31 g; 14%), m.p. 208-212°, identified by comparison (i.r. spectrum) with a sample prepared before.
(b) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (1.8 g, 0.01 mol) in 2M aqueous nitric acid (20.0 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.76 g, 0.011 mol) in water (5.0 ml). The mixture was stirred at 0-5° for 15 min then treated with solutions of N-cyanoacetylformamide (157) (1.1 g, 0.01 mol) in 1,2-diethoxyethane (40.0 ml) and sodium acetate (5.7 g, 0.07 mol) in water (20.0 ml) and the mixture stirred in the melting ice-bath for 1 h.

Filtration afforded the yellow sodium salt of N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (158) which was slurried briefly with 2M aqueous hydrochloric acid to give the free hydrazone (159) (1.8 g; 65%), which formed colourless needles, m.p. 175-180° [with resolidification and remelting at 230° (decomp.)] (from methanol), $\nu_{\text{max}}$ 3560, 3440 and 3240 (NH), 2240 (C=O) and 1730, 1710 and 1680 (CO) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 11.0 (1H, d, J=9Hz, NH), 9.10 (1H, d, J=9Hz, CH), 7.40 (brs, NH + H$_2$O) and 3.86 (3H, s, CH$_3$).

*Found:* C, 33.7; H, 3.1; N, 34.1%; m/z (FAB ms), 266 [(M+H)$^+$-H$_2$O].

C$_8$H$_7$N$_7$O$_4$.H$_2$O requires: C, 33.9; H, 3.2; N, 34.6%; M, 283.

Extraction of the original aqueous mother liquor with methylene chloride before and after acidification with 2M
aqueous hydrochloric acid yielded no further material.

(c) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (1.8 g, 0.01 mol) in 2M aqueous nitric acid (20.0 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.76 g, 0.011 mol) in water (5.0 ml).

The mixture was stirred at 0-5° for 15 min then treated in one portion with solutions of N-cyanoacetylformamide (157) (1.1 g, 0.01 mol) in dioxane (40.0 ml) and sodium acetate (5.7 g, 0.07 mol) in water (20.0 ml) and the mixture stirred in the melting ice-bath for 1 h.

Filtration of the mixture afforded a gummy, yellow solid which was washed with methanol and slurried briefly with 2M aqueous hydrochloric acid to yield \( \text{N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)-hydrazone} \) (159) (1.9 g; 66%), m.p. 215 - 219°, identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

The original aqueous mother liquor was evaporated and the residue was treated with water (30.0 ml) and filtered to yield 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.20 g; 8%), m.p. 221 - 224°, identified by comparison (i.r. spectrum) with a sample prepared before.

Workup of the original aqueous methanolic mother liquor yielded no further material.
2-Cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (136)

A sample of N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (159) was treated with 2M aqueous sodium hydroxide and the resulting orange solution was left at room temperature for a few min, then acidified with 2M aqueous hydrochloric acid to yield 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (136) which formed colourless crystals, m.p. 276 - 278° (decomp.), \( \nu_{\text{max}} \) 3500, 3310, 3230 and 3160 (NH) and 1700 and 1675 (CO) cm\(^{-1}\), \( \delta_H[(CD_3)_2SO] \) 7.74 (4H, brs, NH) and 3.88 (3H, s, CH\(_3\)).

Found: C, 31.8; H, 3.2; N, 37.8%; \( m/z \) (EI ms), 237.0610.
C\(_7\)H\(_7\)N\(_7\)O\(_3\).H\(_2\)O requires: C, 32.9; H, 3.5; N, 38.4%; (M-H\(_2\)O), 237.0610.

5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160)
(a) A suspension of N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (159) (2.6 g, 0.01 mol) in anhydrous dioxane (15.0 ml) was heated under reflux for 3 h.

The mixture was hot-filtered to afford an orange solid which was combined with material obtained by cooling the filtrate to yield 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160) (1.8 g; 62%), which formed orange crystals, m.p. 225°
(decomp.) (from toluene-dimethylformamide), $\nu_{\text{max}}$ 3380 and 3160 - 2500 br (NH), 1740, 1720 and 1675 br (CO) and 1635 (C=N) cm$^{-1}$, $\delta_H[(\text{CD}_3)_2\text{SO}]$ 12.15 (1H, brs, NH), 9.21 (1H, s, CH) and 3.85 (3H, s, CH$_3$).

**Found:** C, 35.2; H, 2.5; N, 36.4%; m/z (EI ms), 265 (M$^+)$.

**C$_8$H$_7$N$_7$O$_4$ requires:** C, 36.2; H, 2.6; N, 37.0%; M, 265.

The dioxane mother liquor was evaporated and the residue was triturated with methylene chloride to yield a yellow solid (0.27 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated. The methylene chloride mother liquor afforded no other identifiable material.

(b) A suspension of N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (159) (0.53 g, 0.002 mol) and toluene-4-sulphonic acid (0.05 g) in anhydrous dioxane (10.0 ml) was heated under reflux for 17 h.

The mixture was hot-filtered to afford 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160) (0.05 g; 9%), m.p. 220° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Evaporation of the dioxane mother liquor gave only an intractible brown gum (0.35 g), whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which was not therefore further investigated.
Cyclisation of the Sodium Salt of N-Formyl 2-Cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)-hydrazone (158)

A suspension of the sodium salt of N-formyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)-hydrazone (158) (0.58 g, 0.002 mol) in water (10.0 ml) was heated under reflux for 15 min.

The mixture was hot-filtered to give a yellow solid which was combined with further material obtained by acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid to give 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.34 g; 72%), m.p. 259° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Extraction of the aqueous acidic mother liquor with methylene chloride gave no further material.

Attempted Cyclisation of 5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160)

(a) A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160) (0.53 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1 h.

The mixture was hot-filtered to yield the unreacted triazolotriazine (160) (0.28 g; 53%), m.p. 225° (decomp.)
identical (m.p. and i.r. spectrum) to a sample prepared before.

Evaporation of the filtrate gave a red brown gum which was triturated with methanol to yield an intractible brown solid (0.20 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

(b) A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160) (0.53 g, 0.002 mol) in glacial acetic acid (5.0 ml) and water (5.0 ml) was heated under reflux for 0.5 h.

The mixture was hot-filtered to give the unreacted triazolotriazine (160) (0.27 g; 51%), m.p. 225° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.

The filtrate on cooling was filtered to afford a yellow solid which was combined with further solid obtained by evaporation of the filtrate to yield 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.22 g; 46%), m.p. 225° (decomp.) identified by comparison (i.r. spectrum) with a sample prepared before.

(c) A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide
(160) (0.53 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 19 h.

The mixture was hot-filtered to remove a small amount of insoluble solid and the filtrate was cooled and filtered to afford 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxamide (137) (0.09 g; 19%), m.p. 257°, identified by comparison (i.r. spectrum) with a sample prepared before.

Evaporation of the acetic acid mother liquor gave a brown gum which was triturated with ethanol to afford an orange solid (0.33 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresoluble, multicomponent mixture which was not therefore further investigated.

(d) A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-formyl)carboxamide (160) (0.53 g, 0.002 mol) and toluene-4-sulphonic acid (0.05 g) in anhydrous dioxane (20.0 ml) was heated under reflux for 6 h.

The mixture was hot-filtered and the yellow solid obtained was combined with further solid obtained by evaporating the filtrate and triturating the residue with ether-ethanol to yield the unreacted triazolotriazine (160) (0.51 g; 96%), m.p. 228° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.
N-Cyanoacetylacetamide (161)

A suspension of cyanoacetic acid (34.0 g, 0.4 mol) in acetic anhydride (30.0 ml) was heated at 70° (oil-bath) for 15 min. The resulting solution was treated with acetamide (11.8 g, 0.2 mol) and the mixture heated at 70° for 3 h.

The mixture was evaporated to give a red oil which was triturated with ether-ethyl acetate to yield the known \textsuperscript{56} N-cyanoacetylacetamide (161) (10.3 g; 41%), which formed tan plates, m.p. 155 - 158° (from ethanol), \( \nu_{\text{max}} \) 3270 and 3190 (NH), 2260 (C=\text{N}) and 1745 br (CO) cm\(^{-1}\), \( \delta_H[(CD_3)_2SO] \) 11.00 (1H, brs, NH) (exch.), 4.06 (2H, s, CH\(_2\)) (exch.) and 2.12 (3H, s, CH\(_3\)).

Found: C, 47.7; H, 4.9; N, 22.2%; m/z (EI ms), 126 (M\(^+\)).

Calc for C\(_5\)H\(_6\)N\(_2\)O\(_2\): C, 47.6; H, 4.8; N, 22.2%; m, 126.

Evaporation of the ether-ethyl acetate mother liquor yielded no further identifiable material.

The Diazotative Coupling of Methyl 5-Amino-1H-1,2,3-triazole-4-carboxylate Hydrochloride (134) with N-Cyanoacetylacetamide (161)

A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (1.8 g, 0.01 mol) in 2M aqueous nitric acid (20.0 ml) was stirred at 0 - 5° (ice-salt bath) and treated dropwise with a solution of sodium nitrite (0.76 g, 0.011 mol) in water (5.0 ml). The mixture was stirred at 0
- 5° for 15 min then treated in one portion with a solution of N-cyanoacetylacetamide (161) (1.3 g, 0.01 mol) and sodium acetate (5.7 g, 0.07 mol) in methanol (40.0 ml) and water (20.0 ml). The mixture was stirred in the melting ice-bath for 2 h then filtered to yield an orange solid which when slurried with 2M aqueous hydrochloric acid gave the monosodium salt of N-acetyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (162) (1.0 g; 31%), which was purified by repeated dissolution in 2M aqueous sodium hydroxide and reprecipitation with 2M aqueous hydrochloric acid to give a monohydrate, m.p. 122 - 125°, ν_{max} 3640, 3580, 3420 and 3200 br (NH), 2220 and 2170 br (C=O) and 1770 and 1700 (CO) cm⁻¹, δ_H[(CD₃)₂SO] 10.45 (1H, s, NH)(exch.), 6.03 (1H, brs, NH)(exch.) 3.86 (3H, s, CH₃) and 2.35 (3H, s, CH₃).

Found: C, 32.2; H, 3.5; N, 30.1 %; m/z (FAB ms), 302[(M+H)⁺-2H₂O]. C₉H₈O₄Na.2H₂O requires: C, 32.0; H, 3.6; N, 29.1%; M, 337.

The solid which separated from the aqueous methanolic mother liquor on standing was collected to afford 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-acetyl)carboxamide (163) (1.7 g; 60%), which formed yellow needles, m.p. 239 - 241° (decomp.) (from glacial acetic acid), ν_{max} 3390, 3280 and 3140 (NH), 1700 (CO) and 1640 (C=N) cm⁻¹, δ_H[(CD₃)₂SO] 11.78 (1H, s, NH), 9.06 (1H, brs, NH), 8.30 (1H, brs, NH), 3.89 (3H, s, CH₃) and 2.31 (3H, s, CH₃).
Attempted Cyclisation Reactions of 5-Amino-3-
methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-
acetyl)carboxamide (163)

(a) A solution of 5-amino-3-methoxycarbonyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-(N-acetyl)carboxamide
(163) (0.56 g, 0.002 mol) in glacial acetic acid (10.0 ml)
was heated under reflux for 1 h.

The mixture was evaporated and the residue was tritutrated
with methylene chloride to afford the unreacted
triazolotriazine (163) (0.24 g; 43%), m.p. 150° (decomp.),
which was identified by comparison (i.r. spectrum) to a
sample prepared before.

Evaporation of the methylene chloride mother liquor
afforded only an intractable residue which yielded no
identifiable material.

(b) A solution of 5-amino-3-methoxycarbonyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-(N-acetyl)carboxamide
(163) (0.56 g, 0.002 mol) in 2M aqueous sodium hydroxide (3.0
ml) was stirred at room temperature for 3 min then acidified
with 2M aqueous hydrochloric acid to pH 1. The mixture was
filtered to yield a brown solid (0.33 g), which was slurried
in 2M aqueous hydrochloric acid to yield the monosodium salt
of N-acetyl 2-cyano-2-oxoacetamide 2-(4 methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (162) (0.18 g; 32%), m.p. 115° (decomp.) identified by comparison (i.r. spectrum) with a sample prepared before.

Workup of the aqueous acidic mother liquor yielded no further identifiable material.

N-Ethoxycarbonyl 2-Cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (166)

(a) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (10.7 g, 0.06 mol) in 2M aqueous nitric acid (120 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (4.6 g, 0.066 mol) in water (10.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with a suspension of N-cyanoacetylurethane (9.4 g, 0.06 mol) and sodium acetate (34.4 g, 0.42 mol) in methanol (160 ml) and water (80.0 ml) and the mixture was stirred in the melting ice-bath for 2 h.

The mixture was filtered to afford N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (166) (16.7 g; 85%), which was purified by repeated dissolution in 2M aqueous sodium hydroxide and reprecipitation with 2M aqueous hydrochloric acid to give a monohydrate, m.p. 197 - 200° (with melting and resolidification at 135 - 137°), $\nu_{max}$ 3650, 3450, 3250 - 2600 br (NH), 2220 (C≡N), and 1750 and 1700 (CO) cm$^{-1}$, $\delta_H[(CD_3)_2SO]$ 10.27 (1H, s, NH),
5.10 (brs, NH+H2O), 4.20 (2H, q, J7Hz, CH2), 3.87 (3H, s, CH3), and 1.27 (3H, t, J7Hz, CH3).

Found: C, 37.0; H, 3.8; N, 30.3%; m/z (El ms), 309 (M+-H2O).

C10H11N7O5·H2O requires: C, 36.7; H, 3.9; N, 30.0%; m, 327.

The aqueous mother liquor on standing deposited 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (169) (1.1 g; 6%), which formed yellow needles, m.p. 206 - 211° (from dimethylformamide-water), \( \nu_{max} \) 3400, 3260, and 3180 br(NH), 1710 (CO), and 1640 (C=N) cm\(^{-1}\), \( \delta \)H[(CD\(_3\)]2SO] 11.68 (1H, s, NH), 8.60 (2H, brs, NH), 4.18 (2H, q, J7Hz, CH\(_2\)), 3.85 (3H, s, CH\(_3\)), 1.23 (3H, t, J7Hz, CH\(_3\)), \( \delta \)C[(CD\(_3\)]2SO], 161.6 (quat.), 160.4 (quat.), 151.6 (quat.), 150.7 (quat.), 138.7 (quat.), 136.3 (quat.), 121.4 (quat.), 62.1 (CH\(_2\)), 51.3 (CH\(_3\)) and 13.9 (CH\(_3\)) (For U.V. data see Table 1).

Found: C, 39.1; H, 3.5; N, 31.1%; m/z (El ms), (M\(^+\)), 309.0823

C_{10}H_{11}N_{7}O_{5} requires: C, 38.8; H, 3.6; N, 31.7%; M, 309.0822.

(b) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (14.2 g, 0.08 mol) in 2M aqueous nitric acid (160 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (6.1 g, 0.088 mol) in water (20.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with a suspension of N-cyanoacetylmurethane (12.5 g, 0.08 mol) and sodium acetate
(45.9 g, 0.56 mol) in methanol (160 ml) and water (80.0 ml) and the mixture was stirred in the melting ice-bath for 2 h.

The mixture was filtered to afford N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazolo-5-yl)hydrazone (166) (21.3 g; 81%), m.p. 199° (decomp.), identical (m.p. and i.r. spectrum) to a sample obtained in (a) before.

The filtrate was concentrated to remove the methanol and filtered to give an unstable product, tentatively formulated as 7-amino-3-methoxycarbonyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (167) (2.2 g; 9%) which formed yellow needles, m.p. 215 - 218° (from dimethylformamide-toluene), $\nu_{\text{max}}$ 3360, 3270 and 3150 br (NH), 1790, 1725 and 1695 (CO), and 1635 (C=N) cm$^{-1}$, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 11.77 (1H, s, NH)(exch.), 8.95 (1H, brs, NH)(exch.), 8.30 (1H, brs, NH)(exch.), 4.17 (2H, q, J7Hz, CH$_2$), 3.84(3H, s, CH$_3$), 1.22 (3H, t, J7Hz, CH$_3$), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 161.6 (quat.), 160.4 (quat.), 151.7 (quat.), 150.7 (quat.), 138.7 (quat.), 136.3 (quat.), 121.4 (quat.), 62.1 (CH$_2$), 51.3 (CH$_3$), and 13.9 (CH$_3$), (for U.V. data see Table 1).

Found: C,38.7; H,3.5; N,31.3%; m/z (EI ms), 309 (M$^+$).

C$_{10}$H$_{11}$N$_7$O$_5$ requires: C,38.8; H,3.6; N,31.7%; M, 309.

The aqueous mother liquor was extracted with methylene chloride to give a brown solid which was washed with ether to afford 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (169) (0.35 g; 1%), m.p. 175-181°, identified by comparison (i.r. spectrum) with a sample prepared previously.
Evaporation of the ether mother liquor afforded no further material.

5-Amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (169)

A suspension of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (166) (9.4 g, 0.30 mol) in glacial acetic acid (50.0 ml) was heated under reflux for 1.75 h.

The mixture was hot-filtered to give a yellow solid which was combined with further material obtained by cooling the filtrate to afford 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (169) (7.1 g; 75%), m.p. 214-216°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the acetic acid mother liquor gave no further identifiable material.

6-Cyano-2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (170)

A solution of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (166) (0.62 g, 0.002 mol) in 2M aqueous sodium hydroxide (2.0 ml) was stirred at room temperature for 0.5 h.

The solution was acidified with 2M aqueous hydrochloric
acid and filtered to afford a pale yellow solid which was
combined with further material obtained by extracting the
filtrate with ethyl acetate and tritivating the oil obtained
with toluene to give 6-cyano-2-(4-methoxycarbonyl-1H-1,2,3-
triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (170) (0.39 g;
69%), which formed colourless plates of the monohydrate, m.p.
136-138° (with resolidification and remelting at 214-216°) (from
water), $\nu_{\text{max}}$ 3500, 3420, 3180 and 3110 (NH), 3060-2300 br
(NH,OH), 2250 (C=\text{N}), and 1750, 1730 and 1710 (CO) cm$^{-1}$,
$\delta_H[\text{(CD}_3\text{)}_2\text{SO}]$ 6.0 - 3.0 (brs, NH) and 3.83 (3H, s, \text{CH}_3), (for
u.v. data see Table 1).

Found: C,34.0; H,2.2; N,35.2%;, m/z (EI ms), 263 (M$^+$-H$_2$O).
C$_8$H$_5$N$_7$O$_4$H$_2$O requires: C,34.2; H,2.5; N,35.3%; M,281.

Evaporation of the toluene mother liquor afforded no
further material.

Methyl 1,2,3-Triazolo[1,5-\text{b}]pyrimido[4,5-e]-1,2,4-triazine-
6,8(5H,7H)-dione-3-carboxylate (140)
(a) A solution of 5-amino-3-methoxycarbonyl-1,2,3-
triazolo[1,5-\text{b}]-1,2,4-triazine-6-(N-ethoxycarbonyl)
carboxamide (169) (0.62 g; 0.002 mol) in glacial acetic acid
(20.0 ml) was heated under reflux for 18 h.

The resulting solution was cooled to give a yellow
solid which was combined with further material obtained by
evaporating the filtrate and crystallisation of the residue
to afford methyl 1,2,3-triazolo[1,5-\text{b}]pyrimido[4,5-e]-1,2,4-
triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.41 g; 75%),
which formed yellow crystals of the monohydrate, m.p. 235-236\degree (from dimethylformamide-water), $\nu_{\text{max}}$ 3500 and 3100-2500 br(NH,OH) and 1770, 1740 and 1700 (CO) cm$^{-1}$, $\delta_H[(CD_3)_2SO]$ 12.96 (1H, s, NH)(exch.), 12.35 (1H, s, NH)(exch.), and 3.92 (3H, s, CH$_3$), $\delta_C[(CD_3)_2SO]$ 159.9 (quat.), 157.4 (quat.), 149.2 (quat.), 148.8 (quat.), 137.9 (quat.), 131.6 (quat.), 124.3 (quat.), and 51.9 (CH$_3$) (for u.v. data see Table 1).

**Found:** C,34.6; H,2.2; N,35.0%; m/z (EI ms), 263 (M$^+$/H$_2$O).

**C$_8$H$_5$N$_7$O$_4$H$_2$O requires:** C,34.2; H,2.5; N,34.9%; M,281.

(b) A solution of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)-carboxamide (169) (0.60 g, 0.002 mol) in anhydrous diglyme (10.0 ml) was heated under reflux for 0.5 h.

The mixture was evaporated and the residue was triturated with methylene chloride to afford the compound tentatively identified as 7-amino-3-methoxycarbonyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (167) as a yellow solid (0.40 g; 67%), m.p. 199-202\degree, identified by comparison (i.r. spectrum) with an authentic sample obtained before. The attempted crystallisation of this product from glacial acetic acid resulted in the quantitative conversion into the triazolo[1,5-b]-1,2,4-triazine derivative (169) identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Evaporation of the dioxane mother liquor gave a brown oil
(0.45 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which was therefore not further investigated.

(c) A solution of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)-carboxamide (169) (0.62 g, 0.002 mol) in anhydrous diglyme (10.0 ml) was heated under reflux for 4 h.

The mixture was evaporated and the residue was triturated with ether-methylene chloride to give an intractible brown solid (0.22 g) which yielded no identifiable material.

Evaporation of the ether-methylene chloride mother liquor gave an intractible black oil (0.30 g) which was not further investigated.

(d) A suspension of 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)-carboxamide (169) (0.62 g, 0.002 mol) in 2M aqueous sodium hydroxide (2.0 ml) and water (3.0 ml) was warmed gently at 100° (water-bath) for 2-3 min.

The solution was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected and washed with water to afford methyl 1,2,3-triazolo[1,5-b]-pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.60 g; quant.), m.p. 217° (decomp.), identified by comparison (i.r. spectrum) with a sample prepared in (a) before.
(e) The compound tentatively formulated as 7-amino-3-methoxycarbonyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (167) (0.62 g, 0.002 mol) was dissolved in 2M aqueous sodium hydroxide (2.0 ml) and water (5.0 ml) and the solution then immediately acidified with 2M aqueous hydrochloric acid (2.0 ml). Filtration afforded methyl 1,2,3-triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.55 g; 98%), m.p. 230° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Extraction of the acidic aqueous mother liquor with ethyl acetate yielded 5-amino-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (169) (0.02 g; 2%), m.p. 198-200°, identical (m.p. and i.r. spectrum) with a sample prepared before.

(f) A suspension of the compound tentatively formulated as 7-amino-3-methoxycarbonyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (167) (0.31 g, 0.001 mol) in 10% w/v aqueous sodium hydrogen carbonate (5.0 ml) was stirred at room temperature for 5 min.

The mixture was filtered to give an orange solid which was slurried with 2M aqueous hydrochloric acid to yield the unreacted triazolotriazine (167) (0.15 g; 48%), m.p. 196-200°, identified by comparison (m.p. and i.r. spectrum) with
Acidification of the original aqueous mother liquor precipitated a solid which was collected and washed with water to give methyl 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.07 g; 26%), m.p. 240° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample obtained in (a) before.

Methylation Reactions of Methyl 1,2,3-Triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140)

(a) A suspension of methyl 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (1.1 g, 0.004 mol) in anhydrous dimethylformamide (15.0 ml) was treated with a suspension of sodium hydride (0.19 g, 0.008 mol) in anhydrous dimethylformamide (10.0 ml). The mixture was stirred at room temperature for 15 min then treated with methyl iodide (1.1 g, 0.008 mol) and stirred at room temperature with the exclusion of atmospheric moisture for 24 h.

The mixture was diluted with water (15.0 ml) and the precipitated green solid was collected and combined with further material obtained by evaporating the aqueous mother liquor and treating the residue with water to afford methyl 5,7-dimethyl-1,2,3-triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (171) (0.49 g; 42%) which formed green prisms, m.p. 221-223° (from
dimethylformamide-water), $\nu_{\text{max}}$ 1720 and 1680 (CO) cm$^{-1}$, 
$\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 3.96 (3H, s, OCH$_3$), 3.61 (3H, s, NCH$_3$), 3.27 (3H, s, NCH$_3$).

**Found:** C, 40.9; H, 2.8; N, 34.0%; m/z (EI ms), 291 (M$^+$).

**C$_{10}$H$_9$N$_7$O$_4$ requires:** C, 41.2; H, 3.1; N, 33.7%; M, 291.

Extraction of the aqueous mother liquor with methylene chloride afforded methyl 5,7-dimethyl-1,2,3-triazolo[1,5-$b$]-5H-imidazo[4,5-$e$]-1,2,4-triazin-6(7H)-one-3-carboxylate (174) (0.12 g; 12%), which formed colourless needles, m.p. 249-252° (from glacial acetic acid), $\nu_{\text{max}}$ 1770 and 1725 (CO) cm$^{-1}$, 
$\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 3.91 (3H, s, OCH$_3$), 3.40 (3H, s, NCH$_3$), 3.39 (3H, s, NCH$_3$), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 160.2 (quat.), 153.9 (quat.), 144.5 (quat.), 141.6 (quat.), 136.3 (quat.), 124.9 (quat.), 51.6 (CH$_3$), 26.2 (CH$_3$), 26.1 (CH$_3$).

**Found:** C, 40.8; H, 3.5; N, 37.3%; m/z (EI ms), 263 (M$^+$).

**C$_9$H$_9$N$_7$O$_3$ requires:** C, 41.1; H, 3.4; N, 37.3%; M, 263.

Acidification of the aqueous mother liquor with concentrated hydrochloric acid gave the unreacted triazolopyrimidotriazine (140) (0.11 g; 10%), m.p. 250° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Extraction of the acidic aqueous mother liquor with methylene chloride gave no further identifiable material.

(b) A suspension of methyl 1,2,3-triazolo[1,5-$b$]pyrimido[4,5-$e$]-1,2,4-triazine-6,8(5H,7H)-dione-3-
carboxylate (140) (2.6 g, 0.01 mol) in anhydrous dimethylformamide (20.0 ml) was treated with a suspension of sodium hydride (0.24 g, 0.01 mol) in anhydrous dimethylformamide (5.0 ml). The mixture was stirred at room temperature for 15 min then treated with methyl iodide (1.4 g, 0.01 mol) and the mixture stirred at room temperature with the exclusion of atmospheric moisture for 24 h.

The mixture was diluted with water (30.0 ml) and the precipitated solid was collected to give methyl 5,7-dimethyl-1,2,3-triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (171) (0.93 g; 32%), m.p. 222-224°, identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

Evaporation of the aqueous mother liquor and treatment of the residue with water (25.0 ml) gave an orange solid (1.0 g) which was slurried with 2M aqueous hydrochloric acid and combined with further material obtained by acidification of the aqueous filtrate with concentrated hydrochloric acid to yield the unreacted triazolopyrimidotriazine derivative (140) (1.2 g; 46%), m.p. 228-230°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Extraction of the acidic aqueous mother liquor with methylene chloride afforded no further material.

The Attempted Reaction of Methyl 1,2,3-Triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) with Sodium Hydride in Dimethylformamide
A suspension of methyl 1,2,3-triazolo[1,5-b]pyrimido-
[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140)
(0.53 g, 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was
stirred and treated with a suspension of sodium hydride (0.096 g,
0.004 mol) in anhydrous dimethylformamide (10.0 ml) and the
mixture was stirred at room temperature for 19 h.

The mixture was diluted with water (10.0 ml) and the
precipitated red solid was collected and slurried with 2M
aqueous hydrochloric acid and combined with further material
obtained by evaporating the original aqueous mother liquor
and treatment of the residue obtained with 2M aqueous
hydrochloric acid to give the unreacted
triazolopyrimidotriazine (140) (0.44 g; 83%), m.p. 219°
(decomp.) identified by comparison (i.r. spectrum) with an
authentic sample obtained before.

Extraction of the acidic aqueous mother liquor with
methylen chloride yielded no further material.

The Reaction of Methyl 5,7-Dimethyl-1,2,3-triazolo[1,5-
b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-
carboxylate (171) with Sodium Hydride in Dimethylformamide

A solution of methyl 5,7-dimethyl-1,2,3-triazolo[1,5-
b]pyrimido[4,5-e]1,2,4-triazine-6,8(5H,7H)-dione-3-
carboxylate (171) (0.29 g, 0.001 mol) in anhydrous
dimethylformamide (15.0 ml) was stirred and treated with a
suspension of sodium hydride (0.048 g, 0.002 mol) in
anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 19 h.

The mixture was diluted with water (10.0 ml), filtered to remove some insoluble material and the filtrate evaporated. The resulting residue was dissolved in water (10.0 ml) and the solution extracted with methylene chloride to afford methyl 5,7-dimethyl-1,2,3-triazolo[1,5-b]-5H-imidazo[4,5-e]-1,2,4-triazin-6(7H)-one-3-carboxylate (174) (0.01 g; 4%), m.p. 234-237\degree, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride gave a brown oil (0.07 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

Attempted Hydrolysis Reactions of Methyl 1,2,3-Triazolo[1,5-b]pyrimido[4,5-e]1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140)

(a) A suspension of methyl 1,2,3-triazolo[1,5-b]pyrimido[4,5-e]1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (1.0 g, 0.004 mol) in glacial acetic acid (20.0 ml) was heated under reflux and treated dropwise with 2M aqueous hydrochloric acid (5.0 ml) and the mixture was heated under reflux for a further 10 min after the addition was complete.

The mixture was evaporated and the residue treated with
water (10.0 ml) to afford a gummy solid (0.78 g) which was heated in ethanol (20.0 ml) and filtered to yield the unreacted triazolopyrimidotriazine derivative (140) (0.41 g; 39%), m.p. 238° (decomp.) identical (m.p. and i.r. spectrum) to an authentic sample prepared previously.

Evaporation of the ethanol mother liquor afforded only intractable material which yielded no identifiable product.

(b) A solution of methyl 1,2,3-triazolo[1,5-\textbf{b}]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.52 g, 0.002 mol) in glacial acetic acid (10.0 ml) and 2M aqueous hydrochloric acid (2.5 ml) was heated under reflux for 3 h.

The mixture was evaporated and the residue triturated with ethanol to give an intractible solid (0.52 g) which yielded no identifiable material.

(c) A solution of methyl 1,2,3-triazolo[1,5-\textbf{b}]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.53 g, 0.002 mol) in 2M aqueous sodium hydroxide (5.0 ml) was heated under reflux for 1 h.

The mixture was cooled and acidified to pH 6 with 2M aqueous hydrochloric acid to give a low yield of an intractable solid (0.25 g) which defied characterisation.

Extraction of the acidic aqueous mother liquor with methylene chloride gave no further material.
(d) A solution of methyl 1,2,3-triazolo[1,5-\(b\)]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.26 g, 0.002 mol) in 2M aqueous sodium hydroxide (2.0 ml) was stirred at room temperature for 5 min. The mixture was then diluted with water (1.0 ml) and stirred at room temperature for a further 0.5 h.

The mixture was filtered to remove some insoluble material and the filtrate acidified with 2M aqueous hydrochloric acid to give the unreacted triazolopyrimidotriazine derivative (0.11 g; 42%), m.p. 220° (decomp.), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The Attempted Hydrolysis of Methyl 5,7-Dimethyl-1,2,3-triazolo[1,5-\(b\)]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (171)

Methyl 5,7-dimethyl-1,2,3-triazolo[1,5-\(b\)]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (171) (0.58 g; 0.002 mol) was dissolved in 2M aqueous sodium hydroxide (5.0 ml). The resulting solution was immediately acidified with 2M aqueous hydrochloric acid to afford a low yield of an intractible solid (0.14 g) which defied characterisation.

Extraction of the acidic aqueous mother liquor with methylene chloride afforded no further material.

The acidic aqueous mother liquor was neutralised by the addition of 2M aqueous sodium hydroxide and extracted with
methylen chloride to afford no further material.

The Attempted Reaction of Methyl 1,2,3-Triazo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) with Lithium Iodide in Dimethylformamide

A suspension of methyl 1,2,3-triazolo[1,5-b]pyrimido-[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.53 g, 0.002 mol) in anhydrous dimethylformamide (8.0 ml) was treated with lithium iodide monohydrate (1.5 g, 0.01 mol) and the mixture was heated under reflux for 2 h.

The mixture was evaporated to give an oil which was treated with 2M aqueous hydrochloric acid (15.0 ml) to afford only a small amount of a solid which was not further investigated.

Extraction of the acidic mother liquor with methylene chloride gave only an intractible red oil.

The Attempted Reaction of Methyl 1,2,3-Triazo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) with Sodium Iodide and Trimethylsilyl chloride in Acetonitrile

A suspension of methyl 1,2,3-triazolo[1,5-b]-pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.53 g, 0.002 mol) and sodium iodide (0.60 g, 0.004 mol) in anhydrous acetonitrile (40.0 ml) was stirred under a
nitrogen atmosphere and treated with trimethylsilyl chloride (0.43 g, 0.004 mol). The mixture was then heated under reflux under nitrogen for 40 h.

The mixture was evaporated and the residue was treated with water (2.5 ml) and 10% w/v aqueous sodium thiosulphate (2.5 ml) then filtered to afford an intractible brown solid (0.28 g) which could not be characterised.

Extraction of the aqueous mother liquor with methylene chloride afforded no further material.

The Attempted Reaction of Methyl 1,2,3-Triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) with Concentrated Aqueous Ammonia

A suspension of methyl 1,2,3-triazolo[1,5-g]-pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxylate (140) (0.26 g, 0.002 mol) in concentrated aqueous ammonia (S.G. 0.88) (2.5 ml) was warmed gently at 100° (water-bath) for 2-3 h.

The mixture was treated with water (2.0 ml) then cooled and acidified with concentrated hydrochloric acid to yield the unreacted triazolopyrimidotriazine derivative (140) (0.26 g, quant.), m.p. 207-213°, identified by comparison (i.r. spectrum) with an authentic sample prepared previously.
N-Ethoxycarbonyl 2-Cyano-2-oxoacetamide 2-(4-Carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (177).

A suspension of 5-amino-1H-1,2,3-triazole-4-carboxamide (117) (0.51 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.30 g, 0.0044 mol) in water (5.0 ml). The mixture was stirred at 0-5° for 15 min the treated with a suspension of N-cyanoacetylurethane (0.62 g, 0.004 mol) and sodium acetate (2.30 g, 0.028 mol) in methanol (15.0 ml) and water (7.0 ml) and the mixture stirred in the melting ice-bath for 2 h.

The precipitated solid was collected and washed with methanol and ether to yield N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (177) (0.90 g; 76%), m.p. 240° (decomp.), \( \nu_{\text{max}} \) 3640, 3460, 3350 and 3150 (NH), 2220 (C≡N) and 1740 br and 1670 br (CO) cm\(^{-1}\), which was converted by cyclisation from dimethylformamide-water into 5-amino-3-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)-carboxamide (178), m.p. 234-237° (decomp.), \( \nu_{\text{max}} \) 3440 and 3150 br (NH), and 1770, 1680, and 1640 (CO) cm\(^{-1}\), \( \delta \)\textsubscript{H}[\text{CD}_{3}]\textsubscript{2}SO 11.65 (1H, s, NH), 8.44 (2H, s, NH), 7.41 (2H, s, NH), 4.19 (2H, q, J7Hz, CH\(_2\)), and 1.24 (3H, t, J7Hz, CH\(_3\)).

Found: C,36.6; H,3.3; N,38.4%; m/z (EI ms), 294 (M\(^+\)).

C\(_9\)H\(_{10}\)N\(_8\)O\(_4\) requires: C,36.7; H,3.4; N,38.1 %; M, 294.

Evaporation of the ether-methanol mother liquor gave only
a negligible amount of solid.

Extraction of the concentrated aqueous mother liquor before and after acidification with concentrated hydrochloric acid yielded no further material.

5-Amino-3-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (178)

A suspension of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carbamoyl-1H-1,2,3-triazol-5-yl)hydrazone (177) (8.5 g, 0.029 mol) in glacial acetic acid (60.0 ml) was heated under reflux for 1.5 h.

The mixture was hot-filtered to give a yellow solid which was combined with further material obtained by cooling the filtrate to afford 5-amino-3-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (178) (7.0 g; 82%), m.p. 247° (decomp.) identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the acetic acid mother liquor gave no further identifiable material.

1,2,3-Triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175).

(a) 5-Amino-3-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (178) (0.59 g, 0.02 mol) was added to 2M aqueous sodium hydroxide (2.0 ml). A solution was formed but after 3-4 min an orange solid
separated and the suspension was then warmed gently to dissolve the solid.

The solution was cooled and acidified with 2M aqueous hydrochloric acid (2.0 ml) and the yellow solid which precipitated was collected to yield 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175) (0.58 g; quant.) which formed orange crystals of a dihydrate, m.p. 255° (decomp.) (from dimethylformamide-water), \( \nu_{\text{max}} \) 3480, 3400, 3280 and 3200 br (NH), 3100 - 2500 br (NH, OH), and 1770-1660 br (CO) cm\(^{-1}\), \( \delta_H[(CD_3)_2SO] \) 12.30 - 12.00 (2H, brs, NH or OH) (exch.) 7.84 (1H, brs, NH) and 7.61 (1H, brs, NH).

Found: C, 29.7; H, 2.9; N, 39.2%; m/z(FAB ms), 249\([(M+H)^+\)-2H\(_2\)O\].

C\(_7\)H\(_4\)N\(_8\)O\(_3\).2H\(_2\)O requires: C, 29.6; H, 2.8; N, 39.4%; M, 284.

(b) A suspension of 5-amino-3-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-\(N\)-ethoxycarbonyl)carboxamide (178) (0.59 g, 0.002 mol) in glacial acetic acid (25.0 ml) was heated under reflux for 24 h.

The mixture was hot-filtered to afford a yellow solid which was combined with further material which precipitated from the filtrate on cooling to give the unreacted triazolotriazine derivative (178) (0.53 g; 90%), m.p. 247° (decomp.) identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the glacial acetic acid mother liquor gave
only a small quantity of a yellow solid (0.06 g) which was not further investigated.

(c) A suspension of 5-amino-3-carbamoyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (178) (0.59 g, 0.002 mol) in anhydrous diglyme (15.0 ml) was heated under reflux for 2 h.

The mixture was hot-filtered to yield a yellow solid which was combined with a further crop obtained by cooling the filtrate to give the unreacted triazolotriazine (178) (0.43 g; 73%), m.p. 245° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The diglyme mother liquor was evaporated and the residue was triturated with ethanol to afford 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175) (0.09 g; 16%), m.p. 245-250°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

5,7-Dimethyl-1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (179)

(a) A suspension of the dihydrate of 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175) (1.1 g, 0.004 mol) in anhydrous dimethylformamide (20.0 ml) was treated with a suspension of sodium hydride (0.21 g, 0.0088 mol) in anhydrous dimethylformamide (10.0 ml). The mixture was stirred at
room temperature for 15 min then treated with a single portion of dimethyl sulphate (1.0 g, 0.008 mol) and stirring continued at room temperature with the exclusion of atmospheric moisture for 22 h.

The mixture was diluted with water (10.0 ml) and the precipitated green solid was stirred with 2M aqueous hydrochloric acid, collected, and combined with further material obtained by evaporating the aqueous dimethylformamide mother liquor and treating the residue with water to give the dimethyl derivative (179) (0.55 g; 58%), which formed yellow needles, m.p. 256-258° (from dimethylformamide-glacial acetic acid), $\nu_{\text{max}}$ 3460 and 3360 (NH), and 1740 and 1720 - 1650 br (CO) cm$^{-1}$, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.86 (1H, brs, NH), 7.73 (1H, brs, NH), 3.61 (3H, s, CH$_3$), 3.40 (3H, s, CH$_3$).

Found: C, 39.2; H, 2.9; N, 40.7%; m/z (EI ms), 276 (M$^+$).

C$_9$H$_8$N$_8$O$_3$ requires: C, 39.1; H, 2.9; N, 40.6%; M, 276.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid and the solid was collected to afford the unreacted starting material (0.17 g; 15%), m.p. 200° (decomp.), identified by comparison (i.r. spectrum) with a sample prepared before.

Extraction of the aqueous mother liquor before and after acidification with 2M aqueous hydrochloric acid afforded no further material.
(b) A suspension of the dihydrate of 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175) (0.56 g, 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was treated with a suspension of sodium hydride (0.095 g, 0.004 mol) in anhydrous dimethylformamide (10.0 ml). The mixture was stirred at room temperature for 15 min then treated with a single portion of methyl iodide (0.57 g, 0.004 mol) and stirring continued at room temperature with the exclusion of atmospheric moisture for 19 h.

The mixture was diluted with water (10.0 ml) and the precipitated solid was slurried with 2M aqueous hydrochloric acid and the solid collected to afford the dimethyl derivative (179) (0.11 g; 20%), m.p. 220° (decomp.) identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

Workup of the aqueous dimethylformamide mother liquor yielded no identifiable material.

**Attempted Deamination Reactions of 1,2,3-Triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175)**

(a) A solution of 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175) (0.50 g; 0.002 mol) in 90% w/v sulphuric acid (4.0 ml) was stirred and treated under the surface of the solution with a solution of sodium nitrite (0.14 g, 0.002 mol) in water (4.0
ml) at such a rate that the reaction temperature was < 30°. Gas evolution occurred and the mixture was stirred for a further 5 min at < 30° after the addition was complete then diluted with water (8.0 ml) and stirred at room temperature for 1 h.

The mixture was filtered to give the unreacted triazolopyrimidotriazine derivative (175) (0.21 g; 42%), m.p. 235° (decomp.), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Extraction of the aqueous acidic mother liquor before and after neutralisation with aqueous potassium hydroxide solution yielded no other identifiable material.

(b) A suspension of 1,2,3-triazolo[1,5-g]pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione-3-carboxamide (175) (0.57 g, 0.002 mol) in acetonitrile (5.0 ml) was stirred and treated at 0-10° (ice-bath) in one portion with a suspension of nitrosonium tetrafluoroborate (0.26 g, 0.0022 mol) in acetonitrile (5.0 ml). The temperature of the mixture was increased to 50° (water-bath) at which point gas evolution occurred and the mixture was stirred at 50° for 25 min until gas evolution had ceased.

The mixture was treated with water (0.1 ml) and hot-filtered to afford a yellow solid which was combined with further material obtained from the organic filtrate on cooling to yield the unreacted triazolopyrimidotriazine
derivative (0.29 g; 51%), m.p. 240° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.

The acetonitrile mother liquor was evaporated to give an orange oil which was triturated with ethanol-light petroleum (40 - 60°) to afford an orange solid (0.13 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was therefore not further investigated.

Evaporation of the ethanol-light petroleum mother liquor afforded a red oil (0.22 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

N-Ethoxycarbonyl 2-Cyano-2-oxoacetamide 2-(4-Carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181)

A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (5.1 g, 0.04 mol) in 2M aqueous nitric acid (80.0 ml) was stirred and treated at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (3.1 g, 0.044 mol) in water (10.0 ml). The mixture was stirred for a further 15 min at 0 - 5° then treated with a suspension of N-cyanoacetylurethane (6.2 g, 0.04 mol) and sodium acetate (23.0 g, 0.28 mol) in methanol (140 ml) and water (70 ml) and the mixture stirred in the melting ice-bath for 2 h.

Filtration gave a yellow solid which was collected and immediately slurried with 2M aqueous hydrochloric acid to afford N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181) as a
monohydrate (11.6 g; 93%), which formed colourless crystals, m.p. 170 - 173°C (decomp.) from methanol, \( v_{\text{max}} \) 3640 and 3480 (NH), 3200 - 2500 br (OH), 2220 (C≡N), and 1750 br and 1665 br (CO) cm\(^{-1}\), \( \delta_H[(CD_3)_2SO] \) 10.26 (1H, s, NH or OH) (exch.), 9.20 - 7.20 (3H, brs, NH and/or OH) (exch.), 4.20 (2H, q, J7Hz, CH\(_2\)), and 1.31 (3H, t, J7Hz, CH\(_3\)).

Found: C, 34.5; H, 3.4; N, 31.4%; m/z (FAB ms), 296 [(M+H') - H\(_2\)O].

C\(_9\)H\(_9\)N\(_7\)O\(_5\).H\(_2\)O requires: C, 34.5; H, 3.5; N, 31.3%; M, 313.

Attempted Cyclisation Reactions of N-Ethoxycarbonyl 2-Cyano-2-oxoacetamide 2-(4-Carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181)

(a) A suspension of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181) (1.2 g, 0.004 mol) in anhydrous ethanol (10.0 ml) was heated under reflux for 1 h.

The mixture was hot-filtered to remove some insoluble material and the filtrate was evaporated to afford a brown intractible solid (1.1 g) from which no identifiable material could be obtained.

(b) A solution of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181) (1.2 g, 0.004 mol) in anhydrous dioxane (10.0 ml) was heated under reflux for 0.5 h.

The mixture was cooled, filtered to remove a small amount
of insoluble material and the filtrate evaporated to give a brown intractible solid (0.87 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which therefore was not further investigated.

3-(α-Acetoxymethyl)-5-amino-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (183)

(a) A solution of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181) (2.4 g, 0.008 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 0.5 h.

The mixture was evaporated to give a brown gum which was triturated with ethanol to afford a brown solid (1.1 g) which could not be purified directly and was therefore dry flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (1:1) afforded 3-(α-acetoxymethyl)-5-amino-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (183) (0.32 g; 14%), which formed yellow crystals, m.p. 130-131° (from ethanol-b.p. 40-60° light petroleum), v max 3400, 3290 and 3210 (NH), 1780, 1735 and 1710 (CO), and 1615 (C=N) cm⁻¹, δH[(CD3)2SO] 10.71, (1H, s, NH), 8.39 - 8.16 (2H, brs, NH) (exch.), 5.14 (2H, s, CH2), 4.19 (2H, q, J7Hz, CH2), 2.11 (3H, s, CH3) and 1.24 (3H, t, J7Hz, CH3).

Found: C, 42.2; H, 4.5; N, 24.6%; m/z (EI ms), 283 (M⁺).

C10H13N5O5 requires: C, 42.4; H, 4.6; N, 24.7%; M, 283.

Further elution with ethyl acetate through to methanol
gave only a series of solids (total 0.56 g) whose t.l.c. in ethyl acetate over silica showed them to be complex mixtures which therefore were not further investigated.

(b) A solution of \( N \)-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (181) (5.9 g, 0.02 mol) in glacial acetic acid (30.0 ml) was stirred at 100° (oil-bath) for 50 min.

The mixture was evaporated to give a brown gum (5.4 g) which was flash-chromatographed over silica.

Elution with methylene-chloride - ethyl acetate (8:1) afforded 5-amino-3-(\( \alpha \)-chloromethyl)-1,2,4-triazine-6-(\( N \)-ethoxycarbonyl)carboxamide (185) (0.08 g; 2%), which formed tan plates, m.p. 140-142° (from ethanol-light petroleum), \( \nu_{\text{max}} \) 3470 and 3340 (NH), 1785 and 1765 (CO) and 1630 br (C=N) cm\(^{-1}\), \( \delta_{\text{H}}[(\text{CD}_3)_2\text{SO}] \) 10.75 (1H, s, NH)(exch.), 8.30 (2H, brs, NH)(exch.), 4.71 (2H, s, CH\(_2\)), 4.19 (2H, q, J7Hz, CH\(_2\)) and 1.25 (3H, t, J7Hz, CH\(_3\)).

Found: C, 36.9; H, 3.7; N, 26.8%; m/z (EI ms) 261 and 259 (M\(^+\)).

\( \text{C}_8\text{H}_{10}\text{ClN}_5\text{O}_3 \) requires: C, 37.0; H, 3.8; N, 27.0%; M, 261 and 259.

Elution with methylene chloride - ethyl acetate (4:1) followed by methylene chloride - ethyl acetate (7:3) afforded 3-(\( \alpha \)-acetoxymethyl)-5-amino-1,2,4-triazine-6-(\( N \)-ethoxycarbonyl)carboxamide (183) (2.9 g; 50%), m.p. 123-127°, identical (m.p. and i.r. spectrum) to a sample obtained in (a) before.
Further elution with ethyl acetate through to methanol gave only a series of solids (total 1.3 g) whose t.l.c. in ethyl acetate showed them to be complex mixtures which therefore were not further investigated.

6-Cyano-2-(4-carboxy-1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (186)

A solution of N-ethoxycarbonyl 2-cyano-2-oxoacetamide 2-(4-carboxy-1H-1,2,3-triazol-5-yl) hydrazone (181) (2.4 g, 0.008 mol) in 2M aqueous sodium hydroxide (12.0 ml) was stirred at room temperature for 0.5 h.

The mixture was then acidified with 2M aqueous hydrochloric acid (5.0 ml) and extracted with ethyl acetate to afford 6-cyano-2-(4-carboxy-1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (186) (1.4 g; 68%), which formed colourless prisms, m.p. 207-210° (from benzene-ethanol), $\nu_{\text{max}}$ 3400-2300 br (OH, NH) and 1800-1650 br (CO) cm$^{-1}$, $\delta_{(\text{CD}_3)\text{SO}}$ 159.8 (quat.), 154.2 (quat.), 146.7 (quat.), 143.3 (quat.), 132.2 (quat.), 124.5 (quat.), 112.0 (quat.).

Found: C,33.1; H,1.3; N,38.3%; m/z (FAB ms) 250[(M+H)$^+$].

$\text{C}_7\text{H}_3\text{N}_7\text{O}_4$ requires: C,33.7; H,1.2; N,39.4%

Found: 250.0325 (M+H)$^+$. $\text{C}_7\text{H}_3\text{N}_7\text{O}_4$ requires: (M+H)$^+$, 250.0325.
6-Cyano-2-(1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (187)

(a) A solution of 6-cyano-2-(4-carboxy-1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (186) (0.99 g, 0.004 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 19 h.

The mixture was evaporated to give 6-cyano-2-(1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (187) (0.83 g; quant.), which formed colourless crystals, m.p. 209-211° (from ethyl acetate-light petroleum), v_max 3180 (NH), 3100 - 2400 (NH, OH), 2250 (CN) and 1790 - 1620 br (CO) cm⁻¹, δ_H[(CD₃)₂SO] 15.50 (1H, brs, NH or OH)(exch.), 13.10 (1H, brs, NH or OH)(exch.), and 8.14 (1H, s, CH).

Found: C,34.0; H,2.3; N,43.0%; m/z (EI ms), 205 (M⁺-H₂O).
C₆H₄N₇O₂·H₂O requires: C,32.3; H,2.2; N,43.9%; mM 223.

(b) A suspension of 6-cyano-2-(4-carboxy-1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (186) (0.50 g, 0.002 mol) in glacial acetic acid (5.0 ml) was stirred and heated at 100° (oil-bath) for 2.5 h, then heated under reflux for 1.5 h.

Evaporation of the mixture afforded the unreacted triazolyltriazine (186) (0.52 g; quant.), m.p. 195-199°, identified by comparison (i.r. spectrum) with an authentic sample prepared previously.
The Attempted Acetylation of 6-Cyano-2-(1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (187)

A solution of 6-cyano-2-(1H-1,2,3-triazol-5-yl)-1,2,4-triazine-3,5(2H,4H)-dione (187) (0.26 g, 0.001 mol) in acetic anhydride (1.0 ml) was heated at 100° (steam bath) for 10 min.

The cooled solution was treated dropwise with ether to give a dark intractable solid (0.02 g) which was not further investigated.

Evaporation of the filtrate gave a gum (0.19 g) from which no characterisable material could be obtained.

Attempted Cyclisation Reactions of 3-(α-Acetoxymethyl)-5-amino-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (183)

(a) A solution of 3-(α-acetoxymethyl)-5-amino-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (183) (0.57 g, 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 2.5 h.

The mixture was evaporated to give a brown oil which was triturated with ethyl acetate to yield an intractable brown solid (0.11 g) from which no identifiable material could be obtained.

The ethyl acetate mother liquor was evaporated to yield a tan solid which was washed with ether to afford the unreacted triazine derivative (183) (0.33 g; 58%), m.p. 103-106°, identified by comparison (i.r. spectrum and t.l.c. in
ethyl acetate over silica) with a sample prepared previously.

The ethereal mother liquor yielded no further material.

(b) A solution of 3-(α-acetoxymethyl)-5-amino-1,2,4-triazine-6-\(N\)-ethoxycarbonyl)carboxamide (183) (0.53 g, 0.0018 mol) in anhydrous dioxane (5.0 ml) was heated under reflux for 19 h.

The mixture was hot-filtered to remove a small amount of insoluble material and the filtrate was evaporated to give a brown solid which was washed with ethanol to afford the unreacted triazine derivative (183) (0.23 g; 43%), m.p. 106-113°, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate over silica) with an authentic sample prepared before.

The ethanolic mother liquor was evaporated to give an intractable brown solid whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which therefore was not further investigated.

\[
3-(α-Acetoxymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione \quad (190)
\]

3-(α-Acetoxymethyl)-5-amino-1,2,4-triazine-6-(\(N\)-ethoxycarbonyl) carboxamide (183) (0.57 g, 0.002 mol) was treated with 2M aqueous sodium hydroxide (1.0 ml) and water (2.0 ml). The mixture was filtered immediately to yield a
cream solid which was combined with further material obtained by acidifying the aqueous filtrate with 2M aqueous hydrochloric acid to give the unreacted triazine derivative (183) (0.24 g; 42%), m.p. 125-130°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Extraction of the aqueous acidic mother liquor with ethyl acetate afforded 3-(a-acetoxymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione (190) (0.11 g; 40%) which formed tan crystals, m.p. 251-253° (from ethanol-methanol), $\nu_{max}$ 3200 - 2500 br (NH, OH) and 1790 - 1630 (CO) cm$^{-1}$, $\delta^H[(CD_3)_2SO]$ 12.45 (1H, brs, NH or OH)(exch.), 11.88 (1H, s, NH or OH)(exch.), 5.37 (2H, s, CH$_2$) and 2.15 (3H, s, CH$_3$).

**Found:** C, 40.6; H, 3.1; N, 29.7%; m/z (EI ms), 237 (M$^+$.)

**C$_8$H$_7$N$_5$O$_4$ requires:** C, 40.5; H, 3.0; N, 29.5%; M, 237.

3-(a-Hydroxymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione (189)

A suspension of 3-(a-acetoxymethyl)-5-amino-1,2,4-triazine-6-(N-ethoxycarbonyl)carboxamide (183) (0.57 g, 0.002 mol) in aqueous 2M sodium hydroxide (4.0 ml) and water (4.0 ml) was stirred at room temperature for 1 h.

The mixture was filtered to give a pale orange solid which was slurried with 2M aqueous hydrochloric acid to afford 3-(a-hydroxymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione (189) (0.36 g; 78%), m.p. 220-225° (decomp.) (from water), $\nu_{max}$ 3550, 3470 and 3400 - 3190 (NH), 3100 - 2500 (NH, OH) and 1750 - 1670 br (CO) cm$^{-1}$, $\delta^H[(CD_3)_2SO]$
11.85 (2H, brs, NH or OH)(exch.), 5.60 (1H, brs, OH)(exch.)
and 4.76 (2H, s, CH₂).

**Found:** C, 31.1; H, 3.9; N, 30.5%; m/z (EI ms), 195 (M⁺).

C₆H₅N₅O₃.2H₂O requires: C, 31.2; H, 3.9; N, 30.3%; M, 195.

Acidification of the alkaline mother liquor with 2M aqueous hydrochloric acid and extraction with ethyl acetate yielded no further material.

**The Acetylation of 3-(α-Hydroxymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione (189)**

A suspension of 3-(α-hydroxymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione (189) (0.32 g, 0.0016 mol) in acetic anhydride (1.0 ml) was heated at 100° (steam bath) for 15 min.

Hot filtration of the mixture gave the unreacted pyrimidotriazine derivative (189) (0.19 g; 59%), m.p. 240° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The acetic anhydride mother liquor was diluted with ether to yield 3-(α-acetoxyymethyl)pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-dione (190) (0.04 g; 25%), m.p. 225-230° (decomp.), identified by comparison (i.r. spectrum) with a sample prepared before.

Evaporation of the ether-acetic anhydride mother liquor yielded no further material.
N-Cyanoacetylcyanamide (191)

N-Cyanoacetylcyanamide (191) was prepared by the reaction of ethyl cyanoacetate with cyanamide in ethanolic sodium ethoxide as described by Dewar and Shaw and the resulting sodium salt passed through an ion exchange resin as described by Hirayama et al to give the free compound, yield 41%, m.p. 88-89° (lit., 84.5-85.5°), which was pure enough for further use.

N-Cyano 2-Cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (192)

A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (1.8 g, 0.01 mol) in 2M aqueous nitric acid (20.0 ml) was stirred and treated dropwise at 0-5°C (ice-salt bath) with a solution of sodium nitrite (0.76 g, 0.011 mol) in water (5.0 ml). The mixture was stirred at 0-5°C for 15 min then treated in one portion with a solution of N-cyanoacetylcyanamide (191) (1.0 g, 0.009 mol) and sodium acetate (5.2 g, 0.63 mol) in methanol (40.0 ml) and water (20.0 ml) and the mixture stirred in the melting ice-bath for 2 h.

Filtration afforded an orange solid which was combined with further material which precipitated from the mother liquor on standing and slurried with 2M aqueous hydrochloric acid to yield N-cyano 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (192) as a dihydrate (2.1 g; 70%) which formed cream plates m.p. 180°
(decomp.) (from ethanol-light petroleum) $v_{\text{max}}$ 3580, 3510, 3370 and 3230 (NH), 3100 - 2500 br (OH), 2260 (C≡N), 1700 br (CO) and 1630 (C=N) cm$^{-1}$, $\delta_H[(\text{CD}_3)_2\text{SO}]$ 6.40 (brs, NH+H$_2$O) and 3.85 (3H, s, CH$_3$).

**Found:** C, 32.2; H, 3.1; N, 37.6%; m/z(FAB ms), 263 [(M+H)$^+$-2H$_2$O].

$\text{C}_8\text{H}_6\text{N}_8\text{O}_3.2\text{H}_2\text{O}$ **requires:** C, 32.2; H, 3.4; N, 37.6%; M, 298.

Extraction of the concentrated aqueous mother liquor with methylene chloride before and after acidification with concentrated hydrochloric acid afforded no further material.

**Attempted Cyclisation Reactions of N-Cyano 2-Cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl) hydrazone (192)**

(a) A solution of N-cyano 2-cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (192) (0.52 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h.

The mixture was hot-filtered to remove a small amount of solid and the filtrate on cooling deposited an intractible brown solid whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

Evaporation of the acetic acid mother liquor gave a brown oil (0.28 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not therefore further investigated.
(b) A solution of N-cyano 2-cyano-2-oxoacetamide 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (192) (0.52 g, 0.002 mol) in anhydrous dioxane (10.0 ml) was heated under reflux for 1 h.

The mixture was hot-filtered to remove a small amount of an insoluble solid and the filtrate was evaporated to give a solid residue. This was trituated with ether to afford an orange solid (0.36 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture from which no identifiable material could be obtained.

Methyl 6-Amino-1,2,3-triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (194) 

A solution of N-cyano 2-cyano-2-oxoacetamide 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl) hydrazone (192) (1.0 g, 0.004 mol) in anhydrous ethanol (10.0 ml) was heated under reflux for 5.5 h.

The mixture was hot-filtered to remove a small amount of solid and the filtrate was evaporated to give a yellow foam (0.90 g) which was treated with aqueous 2M sodium hydroxide and the insoluble yellow solid (0.44 g) was slurried with 2M aqueous hydrochloric acid to afford methyl 6-amino-1,2,3-triazolo[1,5-b]pyrimido[4,5-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (194) (0.25 g; 24%) which formed cream crystals, m.p. 311 - 314° (from dimethylformamide-water), \( v_{\text{max}} \) 3550 and
3360 br (NH), 3100 - 2200 br (NH, OH) and 1740 and 1660 (CO) cm$^{-1}$.

**Found:** C, 36.5; H, 2.1; N, 42.8%; m/z (FAB ms), 245[(M+H)$^+$-H$_2$O].

**C$_8$H$_6$N$_8$O$_3$ requires:** C, 36.6; H, 2.3; N, 42.8%; M, 262.

Acidification of the alkaline mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride gave no further identifiable material.
Chapter 3

New Synthetic Approaches to Pyrido[4,3-e]-1,2,4-triazine (6-Aza-1-deazapteridine) Derivatives Based on Triazole Scission Reactions of 1,2,3-Triazolo[1,5-b]pyrider[4,3-e]-1,2,4-triazine Derivatives
Scheme 53
New Synthetic Approaches to Pyrido[4,3-e]-1,2,4-triazine (6-Aza-1-deazapteridine) Derivatives Based on Triazole Scission Reactions of 1,2,3-Triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazine Derivatives

3.1 Introduction

Many of the known derivatives (Scheme 53) of the four possible pyrido-1,2,4-triazine ring systems (196) - (199) have beneficial biological properties (see chapter 1, pages 14 - 15) e.g. as antibacterial, antifungal and antimicrobial agents. Thus, the biological activity of derivatives of the pyrido[3,2-e]-1,2,4-triazine (196) and pyrido[3,4-e]-1,2,4-triazine (197) ring systems has been extensively investigated. For example, the former have been shown to possess antiinflammatory and antifungal properties and the latter antifungal and antimicrobial properties.

Similarly, derivatives of the pyrido[2,3-e]-1,2,4-triazine ring system (199) exhibit biological properties as antibacterial agents and tranquilisers. In contrast, little is known about the biological activity of derivatives of the pyrido[4,3-e]-1,2,4-triazine (or 6-aza-1-deazapteridine) ring system (198) despite the obvious structural relationship to the biologically significant pyrimido[4,5-e]-1,2,4-triazine (6-azapteridine) ring system (see chapter 2). The lack of information on the biological activity of pyrido[4,3-e]-1,2,4-triazine derivatives can be
Scheme 54
attributed to the lack of suitable general methods for the synthesis of such molecules. It was therefore of interest in the present studies to investigate a potential general strategy for the synthesis of pyrido[4,3-e]-1,2,4-triazine derivatives (Scheme 54) analogous to that studied for pyrimido[4,5-e]-1,2,4-triazine derivatives as already described in chapter 2.

This new synthetic approach to pyrido[4,3-e]-1,2,4-triazine derivatives (Scheme 54) involved the in situ coupling of appropriate 1H-1,2,3-triazol-5-diazonium cations (108) with ethyl 3-ketobutanoate derivatives (200) to afford triazolylhydrazones (201), suitable for dehydrative cyclisation to appropriately functionalised 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives (202) via initial rearrangement of the corresponding 1,2,3-triazolo[5,1-c]-1,2,4-triazines (203) (see chapter 2). Ammonolytic cyclisation of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives (202) so obtained to give the respective 1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazine derivatives (204) and (205) followed by hydrolysis and/or acid-catalysed triazole scission\textsuperscript{41-43} of the latter would then provide a flexible route to pyrido[4,3-e]-1,2,4-triazines (206) and (207). This novel synthetic approach would also allow general access to pyrido[4,3-e]-1,2,4-triazines containing pyridine nuclei with lactam structures and thus having the greatest potential for biological activity.
(i) NaNO₂, 2M HNO₃, H₂O, 0°C.
(ii) NaOAc, MeOH, H₂O, room temp.
(iii) MeCOCl, Et₃N, 1,4-dioxane, room temp.
(iv) EtOH, reflux.
(v) AcOH, reflux.
(v) TSO₃H, benzene, reflux.  [T = 4 - tolyl]

Scheme 55
3.2 The Investigation of 5-Ethoxycarbonylmethyl-6-
ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine
Derivatives as Synthetic Precursors en route to
Pyrido[4,3-e]-1,2,4-triazine (6-Aza-1-deazapteridine) Derivatives

As indicated in the preceding section (Scheme 54), it was anticipated that ethyl 5-ethoxycarbonylmethyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-carboxylate derivatives (202; R^2=CO_2Et) would afford on ammonolysis, 1,2,3-
triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazine derivatives (204) prone to acid-catalysed triazole scission to the corresponding hydroxypyrido[4,3-e]-1,2,4-triazinone derivatives (206). It was also anticipated that the required ethyl 5-ethoxycarbonylmethyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-6-carboxylate derivatives (202; R^2=CO_2Et) would be readily available via triazolylhydrazone intermediates (201; R^2=CO_2Et) by coupling of 1H-1,2,3-triazolediazonium cations (108) with diethyl acetonedicarboxylate (200; R^2=CO_2Et).

In practice (Scheme 55), coupling of the triazole ester diazonium cation (135) generated in situ from methyl 5-
amino-1H-1,2,3-triazole-4-carboxylate (133) with diethyl acetonedicarboxylate (208) afforded a low yield (35%) of a product which analysed correctly for the molecular formula C_{13}H_{17}N_{5}O_{7} and showed a molecular ion at m/z 355 in its mass spectrum also consistent with this molecular formula. The formulation of this product as the expected
triazolylhydrazone derivative (209) followed from this analytical data and from the compound's i.r. and $^1$H n.m.r absorption. In particular, the product showed i.r. NH absorption at 3440 - 3160 cm$^{-1}$ consistent only with the open chain hydrazone structure (209). The non-equivalence of the methylene protons in the structure (209) was demonstrated by the presence in the product's $^1$H n.m.r. spectrum of two one-proton doublets (J 17 Hz) centred at δ4.02 and 3.88. Unexpectedly, coupling of the triazole ester diazonium cation (135) generated in situ from the aminotriazole hydrochloride (134) afforded a much improved yield (73%) of a product which differed significantly in m.p. and i.r. spectrum from the triazolylhydrazone (209) obtained before, but otherwise exhibited identical $^1$H and $^{13}$C n.m.r. absorption to the latter. The new compound (isomer B) was unstable relative to the original triazolylhydrazone (209) (isomer A) and was converted into the latter in good yield on heating in ethanol or merely on attempted purification by crystallisation. The close structural relationship of the unstable isomer B to the stable isomer A of the triazolylhydrazone (209) thus established suggests the two forms are either simply different crystal forms of the triazolylhydrazone (209) or alternatively geometrical isomers resulting from hindered rotation about the carbon-nitrogen double bond in the latter. The gross structure (209) for the isomer B was further substantiated by its
reaction with acetyl chloride in the presence of triethylamine to give a monoacetyl derivative. The formulation of this compound as a triazole N-acetyl derivative [in the absence of more specific evidence arbitrarily assigned the 1-N-acetyl structure (210)] follows from its combustion analysis and mass spectrum and in particular from its i.r. and $^1$H n.m.r. spectra. The former contained carbonyl absorption at 1795 cm$^{-1}$ and the latter a three-proton singlet at 82.77, spectroscopic features characteristic of a 1,2,3-triazole ring N-acetyl substituent. In contrast to the isomer B, the isomer A of the triazolylhydrazone (209) failed to react with acetyl chloride in the presence of triethylamine to give a monoacetyl derivative. Instead this reaction afforded in addition to unreacted starting-material (yield 28%) only a complex mixture which yielded no identifiable material. The differing behaviour of the isomers A and B of the triazolylhydrazone towards acetylation may be indicative of their relationship as geometrical isomers, one of which due to its configuration reacts in complex fashion on attempted acetylation.

In an initial attempt (Scheme 55) to achieve the cyclisation of the triazolylhydrazone (209) (isomer A) to the required triazolotriazine derivative (211), the former compound was heated under reflux in ethanol. These conditions resulted in the recovery of unreacted triazolylhydrazone (209), somewhat surprisingly in the less
Scheme 56
stable isomer B form (yield 31%). Also isolated in low yield (37%) was a product which analysed correctly and had a mass spectrum consistent with its formulation as the expected triazolotriazine derivative (211). However, the i.r. and \(^1\)H n.m.r. absorption of the product clearly indicate (Scheme 56) that it exists as a mixture of the methylene form (211) and one or other of the geometrically isomeric methine tautomers (212a) or (212b). Thus its i.r. spectrum exhibited absorption at 3140 cm\(^{-1}\) assignable to an NH substituent, the presence of which was also indicated by an exchangeable one-proton singlet at 612.00 in the compound's \(^1\)H n.m.r. spectrum. The latter also showed a two-proton singlet at 64.45 and a one-proton singlet at 65.86 attributable to the methylene substituent in the tautomeric form (211) and the methine substituent in one or other of the geometrically isomeric tautomeric forms (212a) or (212b) of the triazolotriazine.

Heating the stable form (isomer A) of the triazolylhydrazone (209) in glacial acetic acid gave an improved yield (65%) of the tautomeric triazolotriazine derivative [(211) \(\Leftrightarrow\) (212)]. In an effort to improve the yield of the triazolotriazine derivative (211) still further, the unstable form (isomer B) of the triazolylhydrazone was heated in benzene with toluene-4-sulphonic acid as cyclodehydration catalyst. However these conditions gave a high yield (96%) of a product identical in
(i) 2M HCl, EtOH, H₂O, heat.
(ii) TSO₃H, benzene reflux.
(iii) NaOAc, MeOH, H₂O, room temp.
(iv) NaN₂O₂, 2M HNO₃, H₂O, 0°.

Scheme 57
melting point, t.l.c. and mass and $^1$H n.m.r. absorption to the triazolotriazine derivative (211) obtained before, but differing significantly in i.r. carbonyl absorption from the latter. Attempted purification of the new compound by crystallisation from ethanol-light petroleum resulted in its conversion in quantitative yield into the triazolotriazine derivative (211) obtained before. Heating the unstable form (isomer B) of the triazolotriazine derivative (211) under reflux in ethanol also resulted in its quantitative conversion into the stable form (isomer A), whereas the latter was unaffected by prolonged heating in ethanol. The obviously close relationship between the stable and unstable forms of the triazolotriazine derivative (211) and the fact that they differ only in i.r. carbonyl absorption suggests that the two species are simply different crystal forms of the latter.

Because of the apparent existence (Scheme 56) of the tautomeric triazolotriazine [(211) ⇌ (212)] in a stable and an unstable form (isomers A and B respectively) it was considered prudent to further establish the simple relationships between the two forms and also the gross structure of the triazolotriazine derivative [(211) ⇌ (212)]. With the latter objective in mind, the acid-catalysed hydrolysis of the stable form (isomer A) of the triazolotriazine derivative [(211) ⇌ (212)] was investigated (Scheme 57). Heating isomer A with dilute hydrochloric acid in ethanol resulted in the formation in
(i) 2M NaOH, H₂O, heat.

(ii) TSO₃H, benzene, heat. \[ T = 4\text{-}tolyl \]

Scheme 58
low yield (19%) of methyl 6-ethoxycarbonyl-5-methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (213) derived by preferential hydrolysis of the 5-ethoxycarbonylmethyl substituent in the triazolotriazine derivative [(211) ⇌ (212)]. The triazolotriazine hydrolysis product (213) gave analytical and spectroscopic data consistent with its assigned structure. This was further firmly established by its unambiguous synthesis (Scheme 57) by in situ coupling of the triazolediazonium cation (135) with ethyl acetoacetate (215) to give a high yield (96%) of the expected triazolylhydrazone (214) followed by cyclodehydration of the latter by heating with toluene-4-sulphonic acid in benzene. The hydrolytic conversion of the stable form (isomer A) of the tautomeric triazolotriazine derivative [(211) ⇌ (212)] into the triazolotriazine diester (213) confirms the gross structure assigned to the former compound.

In contrast to its behaviour towards acid-catalysed hydrolysis, hydrolysis of the stable form (isomer A) of the tautomeric triazolotriazine [(211) ⇌ (212)] by brief heating with dilute aqueous alkali (Scheme 58) afforded a good yield (70%) of a product which analysed correctly and gave mass, i.r. and 1H n.m.r. spectra in accord with a hydrate of the tautomeric triazolotriazinecarboxylic acid structure [(216) ⇌ (217)]. This product is derived by preferential hydrolysis of the 6-ethoxycarbonyl substituent in the tautomeric triazolotriazine derivative [(211) ⇌
(i) Ph₃P, toluene, reflux.

(ii) 10% w/v Na₂CO₃(aq.), room temp.

(iii) NaNO₂, 2M HNO₃, H₂O, 0°.

(iv) NaOAc, MeOH, H₂O, room temp.

Scheme 59
The similar sodium hydroxide catalysed conversion of the unstable form (isomer B) of the triazolotriazine derivative $[(211) \rightleftharpoons (212)]$ into the carboxylic acid $[(216) \rightleftharpoons (217)]$ in good yield (82%) further demonstrates the close structural relationship of this species to the more stable (isomer A) form. In an attempt to obtain the anhydrous tautomeric carboxylic acid $[(216) \rightleftharpoons (217)]$ the hydrated acid was heated under reflux with toluene-4-sulphonic acid in benzene. However, under these conditions the product formed in quantitative yield (Scheme 58) analysed correctly and had mass, i.r. and $^1H$ n.m.r. spectra supporting its identity as the decarboxylated tautomeric triazolotriazine derivative $[(218) \rightleftharpoons (219)]$. However, the product's $^{13}C$ n.m.r. spectrum lacked a signal due to a CH$_2$ group and contained carbon resonances due only to a single species consequently formulated as the alkylidene tautomer of indeterminate configuration (219). Because of the discrepancy between the $^1H$ and $^{13}C$ n.m.r. spectra of the potentially tautomeric triazolotriazine derivative (218) it was decided to firmly establish the identity of the latter by unambiguous synthesis. This was accomplished as indicated in Scheme 59 by reaction of ethyl 4-chloroacetoacetate (220) with triphenylphosphine to afford the phosphonium salt (221) then treatment of the latter with aqueous sodium carbonate to give the known phosphorane (222). Coupling of the latter with the $^{1H}$-1,2,3-triazole ester diazonium cation (135) generated in situ from the
Scheme 60

(i) $\text{NH}_3$ (liq.), $-78^\circ$.

(ii) $\text{NH}_3$, 1,4-dioxane, $\text{H}_2\text{O}$, room temp.

(iii) $\text{NH}_3$, $\text{H}_2\text{O}$, $50^\circ$.

(iv) $\text{NaOEt}$, EtOH, reflux.

(v) $\text{NaNO}_2$, $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}$, $30^\circ$.
aminotriazole ester hydrochloride (134), then yielded the tautomeric triazolotriazine [(218) ⇌ (219)] in moderate yield (34%) via the presumed intermediate formation and subsequent rearrangement of the unstable 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivative (226). The reaction of the triazolediazonium cation (135) with the acylphosphorane (222) to give the tautomeric triazolotriazine derivative [(218) ⇌ (219)] is analogous to similar triazolotriazine syntheses from simpler acylphosphoranes and can be rationalised by the mechanistic pathway outlined in Scheme 59. An attempt to further hydrolyse the triazolotriazine diester [(218) ⇌ (219)] by heating with aqueous ethanolic hydrochloric acid resulted only in the recovery of a large amount of unreacted starting material (58%) and no other identifiable product. The forcing hydrolysis of the triazolotriazine triester [(211) ⇌ (212)] by heating under reflux with aqueous ethanolic sodium hydroxide afforded no identifiable material.

With the tautomeric triazolotriazine triester [(211) ⇌ (212)] now readily available, attention was next turned (Scheme 60) to its aminative cyclisation to the triazolopyridotriazine (229) required for subsequent conversion by hydrolysis and acid-catalysed triazole scission into the desired pyrido[4,3-e]-1,2,4-triazine derivatives (206) (see Scheme 54 before). Initially the
reaction of the stable form (isomer A) of the tautomeric triazolotriazine triester $[(211) \rightleftharpoons (212)]$ with liquid ammonia was investigated and afforded a good yield (81%) of a product which analysed correctly and gave mass, i.r. and $^1$H n.m.r. spectra in accord with its formulation as the tautomeric 6-carbamoyl-5-ethoxycarbonylmethyltriazolotriazine $[(227) \rightleftharpoons (228)]$ or the isomeric 5-carbamoylmethyl-6-ethoxycarbonyl derivative $[(227) \rightleftharpoons (228); \text{CONH}_2 \text{ for CO}_2\text{Et and CO}_2\text{Et for CONH}_2]$. The same product was obtained in somewhat lower yield (61%) by reaction of the less stable form (isomer B) of the tautomeric triazolotriazine triester $[(211) \rightleftharpoons (212)]$ with liquid ammonia. In an attempt to resolve the structural ambiguity of the amide product it was reacted with sodium nitrite in aqueous sulphuric acid at $30^\circ$. It was hoped that under these conditions deamination would occur to afford a carboxylic acid (216) or $[(216); \text{CO}_2\text{H for CO}_2\text{Et and CO}_2\text{Et for CO}_2\text{H}]$ convertible by spontaneous decarboxylation into one or other of the triazolotriazine derivatives (213) or (219) encountered before, thereby establishing the structure of the amide. In fact the attempted deamination of the amide product afforded only a low recovery (19%) of the unreacted starting material and no other identifiable material. In the absence of more definite evidence the amide product is formulated as the tautomeric 6-carboxamidine structure $[(227) \rightleftharpoons (228)]$ on the basis of the absence of a 6-ethoxycarbonyl substituent indicated by the lack of high
frequency ester carbonyl absorption > 1705 cm\(^{-1}\) in its i.r. spectrum. The triazolotriazine derivative (219) of established structure also lacks such high frequency i.r. carbonyl absorption whereas the 6-ethoxycarbonyltriazines (213) and [(211) ⇌ (212)] of confirmed structure exhibit i.r. carbonyl absorption in the range 1750 - 1730 cm\(^{-1}\) attributable to the 6-ethoxycarbonyl substituent.

In an initial attempt to achieve the cyclisation of the triazolotriazine carboxamide [(227) ⇌ (228)] to the desired triazolopyridotriazine derivative (229), it was heated under reflux in glacial acetic acid. However, these conditions were without effect and the starting amide [(227) ⇌ (228)] was recovered unchanged in good yield (76%). In contrast, heating the tautomeric triazolotriazine derivative [(227) ⇌ (228)] under reflux in ethanolic sodium ethoxide afforded in addition to unreacted starting material (27%) a moderate yield (42%) of a product which gave a combustion analysis and showed a parent ion at m/z 276 consistent with it being the ethoxycarbonyltriazolopyridotriazine derivative (229b) formed by concomitant cyclisation and ester exchange. In addition to carbonyl absorption at 1740 - 1715 cm\(^{-1}\) due to the ester function, the i.r. spectrum of the product showed bands at 3300 - 2600 and 1675 cm\(^{-1}\) assignable to hydroxyl and lactam NH and lactam carbonyl absorption respectively in further accord with the triazolopyridotriazine structure (229). However, the
compound's $^1$H n.m.r. spectrum in deuterated dimethyl sulfoxide contained signals assignable to the protons of two ethoxycarbonyl substituents as well as two exchangeable one-proton singlets due to two NH groups and broad exchangeable absorption due to one or more hydroxyl groups. Also present were signals at 65.99 and 5.53 due to two olefinic CH groups both of which appeared as doublets due to coupling with an adjacent OH or NH group as indicated by their collapse to singlets on shaking with D$_2$O. These $^1$H n.m.r. features suggest that in dimethyl sulfoxide at least, the triazolopyridotriazine cyclisation product exists as a tautomeric mixture of the two structures (229b) (A) and (229b) (B) and that the CH proton as the 5- position in both is coupled to the proton of the hydroxyl substituent at the 6- position. The third possible tautomeric form (229b) (C) of the triazolopyridotriazine product is considered unlikely on the basis of the presence in the i.r. spectrum of the latter of only two high frequency i.r. carbonyl bands instead of the three expected for the structure (229b) (C).

Aminative cyclisation of the stable form (isomer A) of the tautomeric triazolotriazine ester [(211)$\Leftrightarrow$ (212)] also occurred on treatment with concentrated aqueous ammonia in 1,4-dioxane at room temperature. Under these conditions two products were obtained, that formed in lower yield (7%) being identical in all respects to an authentic sample of the tautomeric triazolotriazinecarboxamide [(227)$\Leftrightarrow$ (228)] obtained before. The major product isolated in moderate
(i) MeNH₂, NaOEt, EtOH, room temp.

Scheme 61
yield (32%) analysed correctly and gave mass, i.r. and \(^1\)H n.m.r. spectra consistent with its formulation as the tautomeric triazolopyridotriazine methyl ester \([(229)(A) \rightleftharpoons (229)(B)]\). The yield of this product was raised to 63% when the triazolotriazine triester \([(211) \rightleftharpoons (212)]\) was warmed briefly with concentrated aqueous ammonia in the absence of solvent and further, to 77% by heating at 50\(^\circ\) for 0.5 h.

Having shown that the tautomeric triazolotriazine triester \([(211) \rightleftharpoons (212)]\) readily underwent aminative cyclisation to the tautomeric triazolopyridotriazine methyl ester \([(229)(A) \rightleftharpoons (229)(B)]\) on mild treatment with concentrated aqueous ammonia it was decided to investigate analogous aminative cyclisation using methylamine (Scheme 61). However treatment of the triazolotriazine triester \([(211) \rightleftharpoons (212)]\) with ethanolic methylamine at room temperature gave only a good recovery (68%) of the unreacted starting material and no other identifiable product. On the other hand the triazolotriazine triester \([(211) \rightleftharpoons (212)]\) reacted with methylamine in the presence of ethanolic sodium ethoxide at room temperature to afford a readily separated mixture of two products. The major product (yield 27%) analysed correctly and gave mass and i.r. spectra in accord with its formulation as the triazolotriazine bis-N-methylamide (230). Unfortunately, the product was too insoluble to allow its \(^1\)H n.m.r. absorption to be determined. However, by analogy with the triazolotriazine
(i) NaH, Me₂NCH=O, then MeI, room temp.

Scheme 62
triester \([(211) \Leftrightarrow (212)]\) it is assumed to exist as a mixture of tautomers \([(230) \Leftrightarrow (231)]\). The minor product (yield 6%) gave a combustion analysis and mass and i.r. spectra consistent with the 7-N-methyl pyridotriazolotriazine structure (232) which can no longer exhibit tautomerism akin to that shown by the parent pyridotriazolotriazine \([(229a)(A) \Leftrightarrow (229a)(B)]\).

Unfortunately this supposition could not be verified as there was insufficient of the N-methyl triazolopyridotriazine derivative (232) to allow the determination of its $^1$H n.m.r. absorption. However the gross structure of the 7-N-methyl triazolopyridotriazine derivative (232) was verified by its isolation as a methylation product of the tautomeric triazolopyridotriazine derivative \([(229a)(A) \Leftrightarrow (229a)(B)]\) (Scheme 62). Treatment of the latter with two equivalents of sodium hydride in dimethylformamide followed by two equivalents of methyl iodide at room temperature afforded in addition to unreacted starting-material (29%) a moderate total yield of two methylation products. The product isolated in lower yield (13%) was identical in all respects to the monomethyltriazolopyridotriazine derivative obtained in the methylamine-promoted cyclisation of the triazolotriazine triester \([(211) \Leftrightarrow (212)]\) and hence of unambiguous 7-N-methyl structure (232). The major methylation product of the tautomeric triazolopyridotriazine derivative \([(229a)(A) \Leftrightarrow (229a)(B)]\), formed in 34% yield, gave analytical and mass, i.r. and $^1$H n.m.r. spectral data
(i) 2M NaOH, H₂O, heat.

(ii) 2M HCl, H₂O, AcOH, heat.

Scheme 63
consistent with either of the bis-methylated structures (233) or (234) possible on the basis of the probable tautomerism of the starting material. In particular, the $^1$H n.m.r spectrum of the bis- methylation product contained two three-proton singlets at $\delta$4.28 and 3.95 and a three-proton singlet at $\delta$3.24 assignable to the protons of two methoxy groups and one N-methyl substituent. This evidence excludes a bis-N-methyl structure for the compound, which on the basis of an N.O.E. experiment demonstrating significant enhancement of the C(5)- proton resonance on irradiation of the N-methyl protons, is assigned the 4-N-methyl structure (234) rather than the alternative 7-N-methyl structure (233).

Having developed a practical method for the synthesis of the tautomeric triazolopyridotriazine derivative [(229)(A) $\Leftrightarrow$ (229)(B)] attention was next turned (Scheme 63) to its hydrolysis to the corresponding tautomeric carboxylic acid [(235)(A) $\Leftrightarrow$ (235)(B)]. The intention was then to convert the latter, through decarboxylation, with or without the isolation of the parent triazolopyridotriazine [(236)(A) $\Leftrightarrow$ (236)(B)], followed by acid-catalysed triazole scission into the pyridolo[4,3-ε]-1,2,4-triazine derivatives [(237)(A) $\Leftrightarrow$ (237)(B); $X=\text{OCO.Me, Cl}$]. Unfortunately, various attempts to effect the hydrolysis of the ester [(229)(A) $\Leftrightarrow$ (229)(B)] to the carboxylic acid [(235) (A) $\Leftrightarrow$ (235)(B)] were unsuccessful. Thus, heating the ester
[(229)(A) ⇌ (229)(B)] under reflux with dilute aqueous alkali afforded only low recoveries of intractable solids from which no identifiable material could be obtained.

Acid-catalysed hydrolysis was also largely unsuccessful, brief heating of the ester [(229)(A) ⇌ (229)(B)] under reflux with aqueous hydrochloric acid in acetic acid affording only an intractable solid together with unreacted starting-material (yield 25%).

Longer heating of the ester [(229)(A) ⇌ (229)(B)] under reflux with aqueous hydrochloric acid in acetic acid afforded together with an intractable brown solid a low yield (15%) of a product which gave analytical and spectroscopic data consistent with either of the tautomeric chloromethylpyrido[4,3-e]-1,2,4-triazine structures [(237)(A); X=Cl] or [(237)(B); X=Cl]. In particular, its $^1$H n.m.r. spectrum contained two exchangeable one-proton signals assignable to the protons of an OH and NH group as well as a two-proton singlet due to a methylene substituent. Also present was a one-proton doublet at $\delta$5.41 attributable to the CH proton at the 5-position in either of the structures [(237)(A); X=Cl] or [(237)(B); X=Cl]. The observed splitting of this proton resonance can be attributed to coupling with the OH group at the 6-position in the former structure or with the OH group at the 6-position or the NH group at the 4-position in the latter, as indicated by the removal of the splitting on shaking with D$_2$O. The formation of the chloromethylpyridotriazine
Scheme 64

(i) NaNO₂, 2M HNO₃, H₂O, 0°.

(ii) NaOAc, MeOH, H₂O, room temp.

(iii) toluene, heat.

(iv) TSO₃H, benzene, heat.

(v) NH₃, H₂O, 60°.
[(237)(A) or (B); X=Cl] in the hydrochloric acid-catalysed hydrolysis of the tautomeric ester [(229)(A) ⇌ (229)(B)] can be explained by the formation of the acid [(235)(A) ⇌ (235)(B)] followed by spontaneous decarboxylation and acid-catalysed triazole scission [(235)(A) ⇌ (235)(B) → (236)(A) ⇌ (236)(B) → (237)(A) or (B); X=Cl].

Prolonged heating of the triazolopyridotriazine ester [(229)(A) ⇌ (229)(B)] with aqueous hydrochloric acid in acetic acid in an attempt to improve the yield of the chloromethylpyrido[4,3-ĉ]-1,2,4-triazine resulted only in the formation of a complex mixture which yielded no identifiable material.

In the light of the failures to cleanly hydrolyse the tautomeric triazolopyridotriazine ester [(229)(A) ⇌ (229)(B)] to the desired carboxylic acid [(235)(A) ⇌ (235)(B)] it was decided to investigate an alternative route to this compound (Scheme 64). This was based on the coupling of the readily available triazolediazonium carboxylate betaine (120) (see chapter 2) with diethyl acetonedicarboxylate (208) to afford the triazolyhydrazone carboxylic acid (239) which it was anticipated, by analogy with the ester (209), could be readily cyclised to the required triazolotriazine carboxylic acid (241). In practice, the triazolediazonium carboxylate betaine (120) coupled smoothly with diethyl acetonedicarboxylate under neutral conditions to afford a high yield (82%) of the
expected triazolylhydrzone carboxylic acid (239). This compound showed i.r. and $^1$H n.m.r. and $^{13}$C absorption consistent with its structure but on attempted purification by crystallisation from toluene underwent decarboxylation to the parent triazolylhydrzone (238) in quantitative yield. The triazolylhydrzone (238) analysed correctly and gave mass, i.r. and $^1$H n.m.r. spectra consistent with its assigned structure.

Cyclisation of the triazolylhydrzone carboxylic acid (239) occurred smoothly on heating with a catalytic amount of toluene-4-sulphonic acid in benzene to afford the triazolotriazine diester (240) as an oil in quantitative yield. This product analysed correctly and gave mass and i.r. spectra consistent with its assigned structure. However, in contrast to the structurally related tautomeric triazolotriazine triester [(211) $\leftrightarrow$ (212)] (see before), the triazolotriazine diester showed $^1$H n.m.r. absorption consistent with its existence, at least in dimethyl sulfoxide, exclusively as the methylene tautomeric form (240). The existence of the triazolotriazine triester as a tautomeric mixture [(211) $\leftrightarrow$ (212)] may therefore be a consequence of exceptional stabilisation of the alkylidene tautomer [(212a) or (212b)] due to the electron-withdrawing effect of the 3-methoxycarbonyl substituent as well as hydrogen-bonding between the latter and the NH group at the 4-position.

In an initial attempt (Scheme 64) to obtain the
triazolopyridotriazinone derivative (242) required for subsequent acid-catalysed triazole scission to pyrido[4,3-e]-1,2,4-triazine derivatives (see Scheme 54), the triazolotriazine diester (240) was reacted with liquid ammonia. However, aminative cyclisation was unsuccessful under these conditions and the triazolotriazine diester (240) was recovered largely unchanged. On the other hand, aminative cyclisation of the triazolotriazine diester (240) to the triazolopyridotriazinone (242) occurred readily and in moderate yield (49%) by heating with concentrated aqueous ammonia at 60°. The triazolopyridotriazinone derivative (242) analysed correctly and showed mass and i.r. absorption fully consistent with its assigned structure. However, in contrast to the tautomeric triazolopyridotriazinone esters [(229a)(A) ⇄ (229a)(B)] and [(229b)(A) ⇄ (229b)(B)] the 1H n.m.r. spectrum of the product of the aminative cyclisation of the triazolotriazine diester (240) showed the presence of only a single species (242)(A) or (242)(B). The existence of the triazolopyridotriazinone esters [(229a)(A) ⇄ (229a)(B)] and [(229b)(A) ⇄ (229b)(B)] in two tautomeric forms can be attributed to stabilisation of the forms (229a)(B) and (229b)(B) by the electron-withdrawing effect and hydrogen-bonding capability of the 3-alkoxycarbonyl substituent. In the absence of the latter, the triazolopyridotriazinone (242) probably exists largely in the 7-H tautomeric form (242)(A) rather than the 4-H form.
(i) AcOH, heat.

(ii) AcCl, AcOH, heat.

(iii) 20% w/v H₂SO₄, H₂O, 100°.

Scheme 65
With the triazolopyridotriazinone derivative (242) readily available, attention was turned to the study of its acid-catalysed triazole scission to pyrido[4,3-\(e\)]-1,2,4-triazine derivatives (Scheme 65). Heating the triazolopyridotriazinone derivative (242) in glacial acetic acid resulted in its conversion in excellent yield (85\%) into a product which analysed correctly and showed properties allowing its formulation as the acetoxyethyl-pyrido[4,3-\(e\)]-1,2,4-triazinone derivative (243). Thus its FAB mass spectrum showed the expected parent ion at m/z 237 (M+H)\(^+\) and its i.r. spectrum in addition to absorption attributable to a hydroxy group and the amino and carbonyl moieties of a lactam substituent also contained high frequency carbonyl absorption at 1755 cm\(^{-1}\) attributable to an acetoxyethyl group. The \(_1^H\) n.m.r. spectrum of the acetoxyethylpyridotriazinone (243) as well as containing two-proton and three-proton singlets due to the methylene and methyl components of the acetoxyethyl substituents also contained two one-proton exchangeable singlets attributable to the protons of the hydroxyl and NH- groups. In addition, a one-proton doublet at \(\delta 5.35\) which collapses to a singlet and undergoes partial exchange on shaking with D\(_2\)O can be attributed to the proton at the 5-position which appears as a doublet due to coupling with the adjacent hydroxyl group at the 6-position.

Acid-catalysed triazole scission of the
triazolopyridotriazinone derivative (242) also occurred readily on heating under reflux with acetyl chloride in glacial acetic acid. Under these conditions however, the product formed in quantitative yield was identical in all respects to the chloromethylpyridotriazine (244) obtained in low yield in the attempted hydrochloric acid-catalysed hydrolysis of the triazolopyridotriazinone ester (229) as described before. In contrast, the attempted conversion of the triazolopyridotriazinone derivative (242) into the hydroxymethylpyridotriazine (245) by heating with aqueous sulphuric acid gave only a dark intractable product from which no identifiable material could be obtained. However, the conversion of the triazolopyridotriazinone (242) into the pyrido[4,3-e]-1,2,4-triazine derivatives (243) and (244) in high yield clearly demonstrates the viability of this novel synthetic approach for 6-aza-1-deazapteridine derivatives.

3.3 The Investigation of 5-Cyanomethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine Derivatives as Synthetic Precursors en route to Pyrido[4,3-e]-1,2,4-triazine (6-Aza-1-deazapteridine) Derivatives

As demonstrated in the previous section and outlined in general in Scheme 54, aminative cyclisation of 5-ethoxycarbonylmethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives (202; R²=CO₂Et) to 1,2,3-
(i) \( \text{NaNO}_2, 2\text{M HNO}_3, \text{H}_2\text{O}, 0^\circ \) C.

(ii) \( \text{NaOAc, MeOH, H}_2\text{O, room temp.} \)

(iii) \( \text{Ac}_2\text{O, heat.} \)

(iv) \( \text{AcOH, heat.} \)

(v) \( 1,4\text{-dioxane, reflux.} \)

Scheme 66
triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-ones (204) followed by acid-catalysed triazole scission of the latter affords a viable strategy for the synthesis of novel 3-substituted 6-hydroxypyrido[4,3-e]-1,2,4-triazin-8(7H)-ones (206). The success of this strategy prompted the parallel investigation of the corresponding general strategy (see Scheme 54) for the synthesis of the structurally interesting 3-substituted 6-aminopyrido[4,3-e]-1,2,4-triazin-8(7H)-one derivatives (207) based on aminative cyclisation of 5-cyanomethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazines (202; \(R^2=\text{CN}\)) to the corresponding 6-amino-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one derivatives (205) followed by acid-catalysed triazole scission of the latter. Initially it was necessary to develop a practical method for the synthesis of the 5-cyanomethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazines of general type (202; \(R^2=\text{CN}\)). It was anticipated that ready access to these key starting materials would be provided by cyanide displacement of the chloro-substituent in the corresponding 5-chloromethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives (202; \(R^2=\text{Cl}\)). To this end, it was initially decided to investigate the synthesis of methyl 5-chloromethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249) as outlined in Scheme 66. Thus, coupling of the triazole diazonium cation (135), generated \textit{in situ} under standard conditions from the aminotriazole
(i) 2M NaOH, H₂O, room temp.

(ii) Ac₂O, heat.

(iii) 2M NaOH, H₂O, reflux.

Scheme 67
hydrochloride (134), with the commercially available ethyl 4-chloroacetoacetate (220), afforded the expected triazolylhydrazone (246) in high yield (79%). This product analysed correctly and gave mass, i.r. and $^1H$ n.m.r. spectra fully in accord with its assigned structure. This structure was further substantiated by the reaction (Scheme 66) of the triazolylhydrazone (246) with acetic anhydride to afford a monoacetyl derivative (247), which analysed correctly and showed i.r. and $^1H$ n.m.r. absorption consistent with its structure. In particular its i.r. spectrum contained a carbonyl band at 1770 cm$^{-1}$ and its $^1H$ n.m.r. spectrum a three-proton singlet at 62.77 due to a deshielded acetyl group, spectroscopic properties characteristic of a triazole $N$-acetyl substituent (see before).

In a preliminary attempt to effect the cyclisation of the triazolylhydrazone (246) to the required chloromethyltriazolotriazine derivative (249), the former compound was briefly stirred in aqueous alkali at room temperature (Scheme 67). However, contrary to the behaviour expected for the chloromethyltriazolotriazine derivative (249) the product of this reaction had to be isolated by acidification of the reaction mixture, thus demonstrating its acidic character. The absence of chlorine in this acidic compound was demonstrated by its combustion analysis and mass spectrum both of which were in accord with the molecular formula $C_{10}H_{11}N_{5}O_{5}$. This together with the
spectroscopic properties and chemical transformations of the acidic compound allow its formation as the pyrazolyltriazole derivative (250). Thus its i.r. spectrum contained in addition to bands assignable to an NH and OH group, carbonyl absorption due to two ester substituents. The presence of the latter two substituents was also indicated by proton resonances due to an ethyl and a methyl group in the compound's $^1$H n.m.r. spectrum. The latter also contained two exchangeable one-proton resonances and a one-proton singlet assignable to the NH and OH and pyrazole CH protons respectively in the structure (250).

Base-catalysed cyclisation of the triazolylhydrazone (246) involving intramolecular nucleophilic displacement of the chlorine substituent by the NH group in the hydrazone side-chain accounts for the formation of the pyrazolyltriazole (250) whose structure was further verified by its chemical transformations. Thus acetylation with acetic anhydride (Scheme 67) afforded a good yield (68%) of a diacetyl derivative whose analytical and spectroscopic properties were fully in accord with its formulation as the N,O-diacetyl structure (251). Hydrolysis of the pyrazolyltriazole derivative (250) occurred on heating under reflux with aqueous sodium hydroxide giving a separable mixture of the monocarboxylic acid (252) and the dicarboxylic acid (253) in excellent total yield. Both of these products analysed correctly and gave mass, i.r. and $^1$H n.m.r. spectra fully in accord with their assigned
### Table 2  Bond Lengths (Å) with standard deviations

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<th>Bond</th>
<th>Length (Å) ± Standard Deviation</th>
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<td>N(1) - N(2)</td>
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<tr>
<td>N(1) - N(7a)</td>
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</tr>
<tr>
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<tr>
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<td>C(6) - N(7)</td>
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<tr>
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<tr>
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### Table 3  Angles (degrees) and Torsion Angles (degrees) with standard deviations

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<td>N(7) - C(6) - C(61)</td>
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</tr>
<tr>
<td>N(4) - C(3a) - N(7a)</td>
<td>177.2 ± 0.05</td>
</tr>
</tbody>
</table>
structures.

Having failed to convert the triazolylhydrazone derivative (246) into the required chloromethyltriazolotriazine (249) using aqueous alkali as the cyclisation medium attention was turned to other methods for achieving this transformation (Scheme 66). Initially simply heating the triazolylhydrazone (246) in glacial acetic acid was found to give in addition to unreacted starting material (11%) a low yield (26%) of a product which analysed correctly and showed spectroscopic properties fully in accord with its identity as the required methyl 5-chloromethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249). Moreover, this formulation rather than the alternative triazolo[5,1-c]-1,2,4-triazine structure (248) was firmly established by structure determination using x-ray analysis (see Figure 1 and Tables 2 and 3). The cyclisation of the triazolylhydrazone (246) to give the 1,2,3-triazolo[1,5-b]-1,2,4-triazine product (249) most probably involves the initial formation and spontaneous rearrangement of the corresponding 1,2,3-triazolo[5,1-c]-1,2,4-triazine isomer (248). As already discussed (see page 29), on this basis, all of the products derived by cyclisation of triazolylhydrazones of the type (246) are formulated as 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives [e.g. (249)] rather than the 1,2,3-triazolo-[5,1-c]-1,2,4-triazine isomers [e.g. (248)].
(i) KCN, H₂O, room temp.

(ii) KCN, AcOH, H₂O, room temp.

(iii) Et₄N⁺ CN⁻, MeCN, 50°.

(iv) KCN, Me₂NCH=O, room temp.

Scheme 68
In an attempt to obtain an improved method for the preparation of the chloromethyltriazolotriazine derivative (249), the triazolylhydrazone (246) was heated under reflux in 1,4-dioxane with toluene-4-sulphonic acid as cyclodehydration catalyst. However under these conditions the triazolylhydrazone (246) was recovered largely unchanged with no evidence for the formation of the chloromethyltriazolotriazine derivative (249). In contrast simply heating the triazolylhydrazone (246) for a prolonged period in 1,4-dioxane in the absence of any catalyst afforded the required chloromethyltriazolotriazine derivative (249) in excellent yield (92%).

With the chloromethyltriazolotriazine derivative (249) now readily available, effort was directed to its conversion (Scheme 68) into the cyanomethyltriazolotriazine derivative (254) by nucleophilic displacement of the chloro-substituent by cyanide ion. Unfortunately however various conditions (Scheme 68) were ineffective in achieving this transformation. Thus treatment of the chloromethyltriazolotriazine (249) with aqueous potassium cyanide at room temperature resulted in the consumption of the starting material with the formation of no identifiable product. The use of potassium cyanide in aqueous acetic acid as room temperature was no more successful. Under these conditions the chloromethyltriazolotriazine (249) was recovered unchanged in low yield (22%). Surprisingly, also isolated in low yield (16%) from this reaction was the ring-
opened triazolylhydrazone derivative (246). The attempted displacement of the chloro- substituent in the chloromethyltriazolotriazine derivative (249) by cyanide ion under aprotic conditions using tetraethylammonium cyanide in acetonitrile at room temperature afforded only intractable materials which yielded no identifiable product.

In an effort to circumvent the difficulties encountered in the attempted reaction of the chloromethyltriazolotriazine (249) with cyanide ion an alternative approach to the cyanomethyltriazolotriazine (254) was investigated (Scheme 68). This involved the attempted displacement of the chloro- substituent in the triazolylhydrazone (246) by cyanide ion to afford the cyanomethyl compound (255) which it was hoped could then be cyclised to the required cyanomethyltriazolotriazine (254). In practice the attempted reaction of the triazolylhydrazone (246) with potassium cyanide in dimethylformamide at room temperature gave only an intractable oil from which no identifiable material could be obtained. Due to lack of time, investigations of the synthesis of the cyanomethyltriazolotriazine (254) were terminated at this point. The successful synthesis of 3-substituted 6-aminopyrido[4,3-ε]-1,2,4-triazin-8(7H)-one derivatives (207) based on the general strategy outlined in Scheme 54 will therefore require future studies by others.
3.4 EXPERIMENTAL

Diethyl 2,3-Dioxopentanoate 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209)

(a) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate (133) (0.57 g; 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0 - 5°C (ice-salt bath) with a solution of sodium nitrite (0.30 g; 0.0044 mol) in water (5.0 ml). The mixture was stirred at 0 - 5°C for 15 min then treated in one portion with a solution of diethyl acetonedicarboxylate (0.81 g; 0.004 mol) and sodium acetate (2.3 g; 0.028 mol) in methanol (12.0 ml) and water (7.0 ml) and the mixture stirred in the melting ice bath for 2 h.

The mixture was concentrated to remove the methanol, then extracted with ethyl acetate to give a yellow oil which was triturated with ethanol-light petroleum (60 - 80°C) followed by methylene chloride-toluene to afford the stable isomer A of diethyl 2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (0.50 g; 35%), which crystallised from toluene, m.p. 69 - 70°C (with resolidification and remelting at 118 - 120°C), v_max 3440, 3300 - 3160 br (NH) and 1740 and 1715 (CO) cm⁻¹,

δ_H[(CD₃)₂SO] 12.62 (1H, s, NH), 8.28 (1H, s, NH), 4.26 (2H, q, J7Hz, CH₂), 4.02 (1H, d, J17Hz, CH), 3.88 (1H, d, J17Hz, CH), 3.90 (2H, q, J7Hz, CH₂), 1.28 (3H, t, J7Hz, CH₃) and
1.01 (3H, t, J7Hz, CH₃), δC [(CD₃)₂SO] 168.4 (quat.), 162.0 (quat.), 160.2 (quat.), 135.3 (quat.), 131.6 (quat.), 119.0 (quat.), 79.5 (quat.), 61.2 (CH₂), 60.3 (CH₂), 51.5 (CH₃), 41.7 (CH₂), 13.9 (CH₃) and 13.7 (CH₃).

Found: C, 44.4; H, 4.8; N, 19.4%; m/z (EI ms) 355 (M⁺).

C₁₃H₁₇N₅O₇ requires: C, 43.9; H, 4.8; N, 19.7%; M, 355.

Evaporation of the methylene chloride-toluene mother liquor gave only an intractable red oil (0.52 g) which was not further investigated.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and extraction with ethyl acetate afforded no further material.

(b) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (8.9 g; 0.05 mol) in 2M aqueous nitric acid (100 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (3.8 g; 0.055 mol) in water (12.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated in one portion with a solution of diethyl acetonedicarboxylate (10.0 g; 0.05 mol) and sodium acetate (28.7 g; 0.35 mol) in methanol (80.0 ml) and water (80.0 ml) and the mixture was stirred at room temperature for 17 h.

Filtration gave a cream solid which was washed with water to afford the less stable isomer B of diethyl-2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-
m.p. 87 - 93°, $\nu_{\text{max}}$ 3570, 3380, 3200 - 2500 br (NH) and 1740 br and 1710 (CO) cm$^{-1}$, whose $^1$H and $^{13}$C n.m.r. spectra in (CD$_3$)$_2$SO and t.l.c. in methylene chloride over silica were identical to those of the more stable isomer obtained in (a) before.

The Conversion of the Unstable Form (Isomer B) Diethyl 2,3-Dioxopentanoate 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) into the Stable Form (Isomer A)

A solution of the unstable form of diethyl 2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (0.36 g; 0.001 mol) in anhydrous ethanol (10.0 ml) was heated under reflux for 0.5 h.

Evaporation of the mixture afforded a brown oil which was triturated with ethanol-light petroleum to afford the stable form of the triazolylhydrazone (209) (0.24 g; 67%), m.p. 106 - 134°, identified by comparison (i.r. spectrum) with a sample prepared before.

Evaporation of the ethanol-light petroleum mother liquor afforded a brown oil (0.13 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The Attempted Acetylation of the Stable Form (Isomer A) of Diethyl 2,3-Dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209)

A solution of the stable form of diethyl 2,3-
dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (0.71 g; 0.002 mol) in anhydrous dioxane (20.0 ml) was stirred and treated at room temperature with triethylamine (0.44 g; 0.0044 mol) then dropwise with a solution of acetyl chloride (0.34 g; 0.0044 mol) in anhydrous dioxane (1.0 ml) and the mixture stirred at room temperature for 1 h.

The mixture was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give an oil. This was treated with water (10.0 ml) and the mixture extracted with methylene chloride to give an orange oil which was triturated with ether-methylene chloride to yield the unreacted triazolyl hydrazone (209) (0.20 g; 28%), m.p. 135 - 143°, identified by comparison (i.r. spectrum) with a sample prepared before.

Evaporation of the ether-methylene chloride mother liquor gave a yellow oil (0.4 g) whose t.l.c. in ether over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Acetylation of the Unstable Form (Isomer B) of Diethyl 2,3-Dioxopentanoate 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209)

A solution of the unstable form of diethyl 2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (0.71 g; 0.002 mol) in anhydrous
dioxane (20.0 ml) was stirred and treated at room temperature with triethylamine (0.22 g; 0.0022 mol) then dropwise with a solution of acetyl chloride (0.17 g; 0.0022 mol) in anhydrous dioxane (1.0 ml) and the mixture stirred at room temperature for 1 h.

The mixture was filtered to remove triethylamine hydrochloride and the filtrate was evaporated to give an oil. This was treated with water (10.0 ml) and the mixture extracted with methylene chloride to afford a yellow oil (0.54 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (10:1) gave a yellow oil (0.44 g) which was triturated with ethanol-light petroleum to give diethyl 2,3-dioxopentanoate 2-(1-acetyl-4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (210) (0.12 g; 15%), which formed yellow crystals, m.p. 99 - 102° (with resolidification and remelting at 107 - 109°) (from ethanol-light petroleum), \( \nu_{\text{max}} \) 3160 br (NH) and 1795, 1745, 1720 and 1705 (CO) cm\(^{-1}\), \( \delta_H[(\text{CD}_3)_2\text{SO}] \) 12.65 (1H, s, NH)(exch), 4.51 - 3.82 (9H, m, \(2\times\text{CH}_2\text{CH}_3, \text{CH}_2, \text{CH}_3\)), 2.77 (3H, s, CH\(_3\)) and 1.38 - 1.02 (6H, m, \(2\times\text{CH}_2\text{CH}_3\))

Found: C, 46.1; H, 4.9; N, 18.0%; m/z (FAB ms), 398.1312 [(M+H)+]

C\(_{15}\)H\(_{19}\)N\(_5\)O\(_8\) requires: C, 45.3; H, 4.8; N, 17.6%; (M+H), 398.1312

Evaporation of the ethanol-light petroleum mother liquor gave an intractable orange oil whose t.l.c. in ether showed it to be a complex mixture which was not further investigated.
Cyclisation Reactions of Diethyl 2,3-Dioxopentanoate 2-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209)

(a) A solution of the unstable form (Isomer B) of diethyl 2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (3.6 g; 0.01 mol) and toluene-4-sulphonic acid (0.05 g) in anhydrous benzene (40.0 ml) was heated under reflux for 3 h.

Evaporation of the mixture gave an orange oil which was triturated with toluene-diethyl ether to afford the unstable form (isomer B) of methyl 6-ethoxycarbonyl-5-ethoxy-carbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (3.4 g; quant.), m.p. 95 - 101°, ν_max 3140 (NH) and 1750 and 1730 (CO) cm⁻¹ which was converted into the stable form (isomer A) of the triazolotriazine (211) on crystallisation from ethanol-light petroleum, m.p. 103 - 105°, ν_max 3140 (NH) and 1745 and 1730 (CO) cm⁻¹, δ_H[(CD₃)₂SO] 12.00 (s, NH of alkylidene tautomer)(exch.), 5.86 (s, CH of alkylidene tautomer), 4.48 (q, J₇Hz, CH₂), 4.45 (q, J₇Hz, CH₂), 4.40 (s, CH₂ of methylene tautomer), 4.23 (q, J₇Hz, CH₂), 4.14 (q, J₇Hz, CH₂), 3.96 (s, CH₃), 3.92 (s, CH₃), 1.38 (t, J₇Hz, CH₃), 1.35 (t, J₇Hz, CH₃), 1.26 (t, J₇Hz, CH₃), 1.21 (t, J₇Hz, CH₃), δ_C[(CD₃)₂SO] 169.0 (quat.), 168.2 (quat.), 161.0 (quat.), 160.1 (quat.), 159.8 (quat.), 159.6 (quat.), 154.4 (quat.), 143.6 (quat.), 140.7 (quat.), 136.1 (quat.), 135.4 (quat.), 132.3 (quat.), 127.4
(quat.), 118.2 (quat.), 92.2 (CH), 63.3 (CH₂), 61.2 (CH₂), 60.7 (CH₂), 52.1 (CH₃), 52.0 (CH₃), 42.8 (CH₂), 14.0 (CH₃), 13.8 (CH₃), 13.7 (CH₃).

**Found:** C, 45.8; H, 4.4; N, 20.7%; m/z (EI ms), 337 (M⁺).

**C₁₃H₁₅N₅O₆ requires:** C, 46.3; H, 4.4; N, 20.8%; M, 337.

(b) A solution of the stable form (isomer A) of diethyl 2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (0.71 g; 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1 h.

The mixture was evaporated to give a red oil which was triturated with diethyl ether-toluene to afford an orange solid which was combined with further material obtained by evaporating the diethyl ether-toluene mother liquor and triturating the resulting oil with methanol to give the stable form (isomer A) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.45 g; 65%), m.p. 95 - 101°C, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the methanol mother liquor gave an orange oil (0.17 g) which was not further investigated.

(c) A solution of the stable form (isomer A) of diethyl 2,3-dioxopentanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (209) (0.71 g, 0.002 mol) in anhydrous ethanol (10.0 ml) was heated under reflux for 3 h.
The mixture was evaporated to give an orange oil which was triturated with diethyl ether to afford the stable form (isomer A) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.25 g; 37%), m.p. 94 - 99°, identified by comparison with a sample prepared before.

Evaporation of the ethereal mother liquor and trituration of the residue with toluene afforded the unstable form (isomer B) of the unreacted triazolylhydrazone (209) (0.16 g; 31%), m.p. 122 - 126°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Evaporation of the toluene filtrate gave an orange gum (0.15 g) which was not further investigated.

The Thermal Isomerisation of the Unstable Form (Isomer B) of Methyl 6-Ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211)

A solution of the unstable form (isomer B) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.34 g; 0.001 mol) in anhydrous ethanol (10.0 ml) was heated under reflux for 0.5 h.

Evaporation of the mixture and trituration of the residue with ethanol-light petroleum afforded a yellow solid which was combined with further material obtained by evaporating the ethanol-light petroleum filtrate and
subsequent crystallisation of the residual oil to yield the stable form (isomer B) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.34 g; quant.), m.p. 111 - 118°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

The Attempted Thermal Isomerisation of the Stable Form (Isomer A) of Methyl 6-Ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211)

A solution of the stable form (isomer A) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (7.1 g; 0.02 mol) in anhydrous ethanol (25.0 ml) was heated under reflux for 0.5 h.

Evaporation of the mixture and trituration of the residual oil with diethyl ether afforded the unchanged isomer A of the triazolotriazine (211) (6.7 g; 94%), m.p. 105 - 135°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The Acid Catalysed Hydrolysis of the Stable Form (Isomer A) of Methyl 6-Ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211)

A solution of the stable form (isomer A) of methyl B6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.68 g; 0.002 mol) in ethanol (10.0 ml) was treated with 2M aqueous hydrochloric acid (5.0 ml) and the mixture heated under reflux for 3 h.

Evaporation of the mixture gave a red oil which was triturated with ethanol-light petroleum to afford a yellow solid which was combined with further material which precipitated from this mother liquor on standing to yield methyl 6-ethoxycarbonyl-5-methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (213) (0.10 g; 19%), which formed tan plates, m.p. 143 - 145° (from ethanol), $\nu_{\text{max}}$ 1750 and 1730 (CO) cm$^{-1}$, $\delta_H[(\text{CD}_3)_2\text{SO}]$ 4.53 (2H, q, 37Hz, CH$_2$), 3.97 (3H, s, CH$_3$), 2.89 (3H, s, CH$_3$) and 1.42 (3H, t, J7Hz, CH$_3$).

Found: C, 45.3; H, 4.2; N, 26.4%; m/z (EI ms), 265 (M$^+$).

C$_{10}$H$_{11}$N$_5$O$_4$ requires: C, 45.3; H, 4.1; N, 26.4%; M, 265.

Evaporation of the ethanol-light petroleum mother liquor gave a red oil (0.63 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

Ethyl 2,3-Dioxobutanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (214)

A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (1.8 g; 0.01 mol) in 2M aqueous nitric acid (20.0 ml) was stirred and treated
dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (0.76 g; 0.011 mol) in water (5.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with a solution of ethyl acetoacetate (1.6 g, 0.012 mol) and sodium acetate (5.7 g, 0.07 mol) in methanol (30.0 ml) and water (15.0 ml) and the mixture was stirred in the melting ice bath for 2 h.

Filtration of the mixture gave a pink solid which was combined with further material obtained by concentrating the aqueous methanolic liquor and extraction of the aqueous residue with methylene chloride to afford ethyl 2,3-dioxobutanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (214) (2.7 g; 96%), which formed colourless needles, m.p. 134 - 137° (from ethanol-light petroleum), \( \nu \text{max} \) 3330 \( \text{br} \) (NH) and 1735 and 1715 (CO) cm\(^{-1}\), \( \delta \text{H} \) [(CD\(_3\))]\(_2\)SO 12.48 (1H, s, NH), 7.89 (1H, s, NH), 4.26 (2H, q, J\( \text{7Hz} \), CH\(_2\)), 3.83 (3H, s, CH\(_3\)), 2.26 (3H, s, CH\(_3\)), 1.28 (3H, t, J\( \text{7Hz} \), CH\(_3\)).

**Found:** C, 42.6; H, 4.7; N, 25.0%; m/z (EI ms), 283 (M\(^+\)).

**C\(_{10}\)H\(_{13}\)N\(_5\)O\(_5\)** requires: C, 42.4; H, 4.6; N, 24.7%; M, 283.

**Methyl 6-Ethoxycarbonyl-5-methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (213)**

A solution of ethyl 2,3-dioxobutanoate 2-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (214) (0.28 g; 0.001 mol) and toluene-4-sulphonic acid (0.01 g) in anhydrous benzene (10.0 ml) was heated under reflux for 3 h.
The mixture was evaporated and treated with methylene chloride then filtered to remove some dark insoluble material. The filtrate was evaporated to afford methyl 6-ethoxycarbonyl-5-methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (213) (0.20 g; 74%), m.p. 130 - 135°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

5-Ethoxycarbonylmethyl-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylic Acid (216)

(a) A suspension of the unstable form (isomer B) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (211) (1.4 g, 0.004 mol) in aqueous sodium hydroxide (6.0 ml) and water (25.0 ml) was warmed gently to dissolve the suspended solid. Hot filtration yielded the unreacted triazolotriazine (211) (0.15 g; 11%), m.p. 96 - 101°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The cooled alkaline filtrate was acidified with 2M aqueous hydrochloric acid to give 5-ethoxycarbonylmethyl-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylic acid (216) (0.90 g; 82%), which formed yellow plates of a monohydrate m.p. 88 - 89 ° (with resolidification and remelting at 125 - 127°), $\nu_{\text{max}}$ 3560 (NH),, 3300 - 2400 br (OH), 1760 and 1735 (CO) and 1635 (C=C) cm$^{-1}$, $\delta_H [(\text{CD}_3)_2\text{SO}]$ 12.00 (s, NH of alkylidene
tautomer) (exch.), 5.88 (s, CH of alkylidene tautomer), 4.39 (s, CH₂ of methylene tautomer), 4.22 (q, J7Hz, CH₂CH₃), 4.14 (q, J7Hz, CH₂CH₃), 3.96 (s, CH₃), 3.91 (s, CH₃), 1.26 (t, J7Hz, CH₂CH₃) and 1.20 (t, J7Hz, CH₂CH₃), δₐ ([(CD₃)₂SO]
169.1 (quat.), 168.2 (quat.), 162.6 (quat.), 161.4 (quat.), 160.2 (quat.), 159.7 (quat.), 154.8 (quat.), 145.1 (quat.), 141.7 (quat.), 136.1 (quat.), 135.7 (quat.), 132.3 (quat.), 127.3 (quat.), 118.2 (quat.), 92.1 (CH), 61.1 (CH₂), 60.6 (CH₂), 52.1 (CH₃), 52.0 (CH₃), 43.0 (CH₂), 14.0 (CH₃) and 13.9 (CH₃).

Found: C, 40.4; H, 4.0; N, 21.6%; m/z (FAB ms), 310 [(M+H)+H₂O]

C₁₁H₁₁N₅O₆·H₂O requires: C, 40.4; H, 4.0; N, 21.4%; M, 327.

Extraction of the acidic filtrate with methylene chloride afforded no further material.

(b) A suspension of the stable form (isomer A) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine (211) (1.4 g, 0.004 mol) in 2M aqueous sodium hydroxide (6.0 ml) and water (30.0 ml) was warmed gently to dissolve the solid. The cooled alkaline solution was then acidified dropwise with 2M aqueous hydrochloric acid (6.5 ml) to afford 5-ethoxycarbonylmethyl-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylic acid (216) (0.92 g; 70%), m.p. 111 - 114°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.
Extraction of the acidic aqueous mother liquor with methylene chloride afforded no further material.

Methyl 5-Ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (218)

A suspension of 5-ethoxycarbonylmethyl-3-methoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylic acid (216) (0.65 g, 0.002 mol) and toluene-4-sulphonic acid (0.01 g) in anhydrous benzene (10.0 ml) was heated under reflux for 1 h. The mixture was evaporated to yield methyl 5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (218) (0.53 g; quant.), which formed tan needles, m.p. 187 - 189° (from dimethylformamide-toluene), \( \nu_{\text{max}} \) 3200 (NH), 1695 and 1665 (CO) and 1640 (C=N) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\))\(_2\)SO] 11.25 (s, NH of alkylidene tautomer)(exch.), 8.27 (d, J7Hz, CH of alkylidene tautomer)(collapses to a singlet on exch.), 5.59 (s, CH), 4.24 (s, CH\(_2\) of methylene tautomer), 4.21 (q, J7Hz, CH\(_2\)CH\(_3\)), 4.19 (q, J7Hz, CH\(_2\)CH\(_3\)), 3.94 (3H, s, CH\(_3\)), 3.90 (3H, s, CH\(_3\)), 1.26 (t, J7Hz, CH\(_2\)CH\(_3\)) and 1.24 (t, J7Hz, CH\(_2\)CH\(_3\)), \( \delta_C \) [(CD\(_3\))\(_2\)SO] 168.6 (quat.), 160.3 (quat.), 147.4 (CH), 137.2 (quat.), 132.1 (quat.), 118.3 (quat.), 92.9 (CH), 60.2 (CH\(_2\)), 51.7 (CH\(_3\)) and 13.9 (CH\(_3\)).

Found: C, 45.2; H, 4.1; N, 26.1%; m/z (EI ms), 265 (M\(^+\)).

C\(_{10}\)H\(_{11}\)N\(_5\)O\(_4\) requires: C, 45.3; H, 4.1; N, 26.4%; M, 265.
3-Ethoxycarbonylacetoxytriphenyliophosphonium Chloride (221)

A solution of triphenylphosphine (5.2 g, 0.02 mol) in anhydrous toluene (25.0 ml) was stirred and treated dropwise at 80° (oil bath) with ethyl-4-chloroacetoacetate (3.3 g, 0.02 mol) and then the mixture was heated under reflux for 19 h.

The mixture was cooled and the supernatant liquor was decanted off to leave an orange gum which was triturated with ethanol-light petroleum to afford 3-ethoxycarbonylacetoxytriphenyliophosphonium chloride (221) (6.9 g; 83%), m.p. 105 - 107°, which was used without further characterisation.

The ethanol-light petroleum mother liquor was evaporated to give an orange oil (1.8 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture which was not further investigated.

3-Ethoxycarbonylacetoxyidenetriphenyliophosphorane (222)

A suspension of 3-ethoxycarbonylacetoxytriphenyliophosphonium chloride (221) (6.9 g, 0.017 mol) in 10% w/v aqueous sodium carbonate solution was stirred at room temperature for 17 h.

The mixture was filtered to afford a tan solid which was crystallised from benzene to yield 3-ethoxycarbonylacetoxyidenetriphenyliophosphorane (222) (3.5 g; 55%), m.p. 107 - 109°, (lit 64, 104 - 105°).
Methyl 5-Ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (218)

A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (0.71 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0 - 5°C (ice-salt bath) with a solution of sodium nitrite (0.30 g, 0.0044 mol) in water (5.0 ml). The mixture was stirred at 0 - 5°C for 15 min then treated with stirring with a solution of 3-ethoxycarbonylacetonylidenetriphenylphosphorane (222) (1.6 g, 0.004 mol) and sodium acetate (2.3 g, 0.028 mol) in methanol (20.0 ml) and water (10.0 ml) and the mixture stirred in the melting ice-bath for 2 h.

Filtration of the mixture afforded a yellow solid which was purified by crystallisation to give methyl 5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (218) (0.37 g; 34%), m.p. 170 - 175°C, identified by comparison (i.r. spectrum) with a sample prepared before.

The mother liquor was concentrated to remove methanol and extracted with methylene chloride to give a brown gum (1.9 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of Methyl 5-Ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (218) with Aqueous Hydrochloric Acid

A suspension of methyl 5-ethoxycarbonylmethyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (218) (0.26 g; 0.001 mol) in ethanol (7.5 ml) and 2M aqueous hydrochloric acid (2.5 ml) was heated under reflux for 1 h. Hot filtration yielded a tan solid which was combined with further solid obtained by evaporation of the filtrate and treatment of the residue with water (5.0 ml) to afford the unreacted triazolotriazine (218) (0.15 g; 58%), m.p. 177° (decomp.) identified by comparison (i.r. spectrum) with a sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride afforded no further material.

The Attempted Forcing Alkaline Hydrolysis of Methyl 6-Ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211)

A solution of the stable form of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.67 g, 0.002 mol) in ethanol (10.0 ml) was treated with 2M aqueous sodium hydroxide (5.0 ml) and the mixture was heated under reflux for 1 h.

The mixture was evaporated and the residue was treated with water and extracted with methylene chloride but this did not afford any further material.

Acidification of the alkaline mother liquor with concentrated hydrochloric acid and extraction with methylene chloride afforded only a small amount of a brown solid (0.07
g) which was not further investigated.

Neutralisation of the acidic aqueous mother liquor with solid sodium acetate and extraction with methylene chloride afforded no further material.

**Methyl 6-Carbamoyl-5-ethoxycarbonylmethyl-1,2,3-triazolo-[1,5-b]-1,2,4-triazine-3-carboxylate (227)**

(a) The stable form (isomer A) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (3.4 g, 0.01 mol) was added in portions with stirring at -78°C (acetone-solid CO₂ bath) to liquid ammonia (100 ml) and the mixture was stirred at -78°C for 1 h.

The mixture was allowed to evaporate at room temperature overnight and the residue was treated with methanol and filtered to afford methyl 6-carbamoyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227) (2.5 g; 81%) which formed yellow crystals, m.p. 205 - 207°C (from dimethylformamide-water), ν_max 3460, 3340 and 3140 (NH), 1705 and 1680 (CO) and 1635 (C=C) cm⁻¹, δ_H [((CD₃)₂SO], 8.72 (s, NH of alkylidene tautomer), 8.42 (s, NH of alkylidene tautomer), 8.24 (s, NH of alkylidene tautomer), 5.84 (s, CH of alkylidene tautomer), 4.38 (s, CH₂ of methylene tautomer), 4.20 (q, J7Hz, CH₂CH₃), 4.11 (q, J7Hz, CH₂CH₃), 3.95 (s, CH₃), 3.91 (s, CH₃), 1.25 (t, J7Hz, CH₂CH₃) and 1.19 (t, J7Hz, CH₂CH₃).
Found: C, 43.0; H, 4.0; N, 27.4%; m/z (EI ms), 308 (M⁺).

C₁₁H₂₆N₆O₅ requires: C, 42.9; H, 3.9; N, 27.3%; M, 308.

Evaporation of the methanol filtrate gave a brown solid (0.43 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

(b) The unstable form (isomer B) of methyl 6-ethoxy-carbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (0.34 g, 0.001 mol) was added in portions with stirring at -78° to liquid ammonia (10.0 ml) and the mixture was stirred at -78° for 1 h.

The mixture was allowed to evaporate at room temperature overnight and the residue was triturated with methylene chloride to give an orange solid which was washed with methanol to yield methyl 6-carbamoyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227) (0.11 g; 61%), m.p. 205 - 207°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Evaporation of the methanolic mother liquor afforded no further identifiable material. Evaporation of the methylene chloride mother liquor gave an orange gum which was triturated with ethanol-light petroleum to give the unreacted triazolotriazine derivative (211) (0.14 g; 41%), m.p. 97 - 101°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.
The Attempted Deamination of Methyl 6-Carbamoyl-5-ethoxy-carbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227)

A solution of methyl 6-carbamoyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227) (0.62 g, 0.002 mol) in 90% w/v aqueous sulphuric acid (5.0 ml) was stirred and treated dropwise at 30° (water bath) with a solution of sodium nitrite (0.14 g, 0.002 mol) in water (4.0 ml). The mixture was then diluted with water (3.0 ml) and stirred at 30° for 1 h.

Dilution of the mixture with water (5.0 ml) yielded a yellow solid which was combined with further material obtained by extracting the aqueous mother liquor with methylene chloride and filtering the resulting three phase mixture to afford the unreacted amide (227) (0.12 g; 19%), m.p. 190 - 194°, identified by comparison (i.r. spectrum) with a sample prepared previously. Evaporation of the methylene chloride extract afforded no further material.

Neutralisation of the acidic aqueous mother liquor with solid potassium hydroxide and extraction with methylene chloride afforded no further identifiable material.

The Attempted Cyclisation of Methyl 6-Carbamoyl-5-ethoxy-carbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227)

A solution of methyl 6-carbamoyl-5-ethoxycarbonyl-
methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227) (0.62 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h.

The mixture was evaporated to give a yellow solid which was washed with methanol to afford the unreacted triazolotriazine (227) (0.47 g; 76%), m.p. 205 - 208°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Evaporation of the methanol filtrate gave only a small amount of an intractable brown solid (0.08 g) which was not further investigated.

Ethyl 6-Hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229b)

A stirred suspension of methyl 6-carbamoyl-5-ethoxy-carbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (227) (0.62 g, 0.002 mol) in anhydrous ethanol (10.0 ml) was treated with a solution of sodium (0.05 g, 0.002 g. atom) in anhydrous ethanol (5.0 ml) and the mixture was stirred at room temperature for 1 h then heated under reflux for 1 h.

The mixture, containing an insoluble solid was evaporated and the residue was dissolved in water and the solution acidified with 2M aqueous hydrochloric acid to precipitate a yellow solid which was collected, dried and dry flash-chromatographed over silica.

Elution with ethyl acetate-methylene chloride (1:1)
followed by ethyl acetate yielded the unreacted triazolotriazine derivative (227) (0.17 g; 27%), m.p. 191 - 194°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Further elution with ethyl acetate-methanol (3:1) then methanol afforded the tautomeric ethyl 6-hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229b) (0.17 g; 42%), which formed yellow crystals, m.p. 247 - 250° (decomp.) (from glacial acetic acid), $\nu_{max}$ 3300 - 2600 br (OH, NH), 1740, 1715 and 1675 (CO) and 1625 (C=N) cm$^{-1}$, $\delta_H [(CD_3)_2SO] 11.40$ (s, NH)(exch.), 11.30 (s, NH)(exch.), 5.99 (d, J2Hz, CH)(collapses to singlet on exch.), 5.53 (d, J2Hz, CH)(collapses to a singlet on exch.), 4.38 (q, J7Hz, CH$_2$CH$_3$), 4.32 (q, J7Hz, CH$_2$CH$_3$), 4.00 br (s, OH), 1.33 (t, J7Hz, CH$_2$CH$_3$) and 1.26 (t, J7Hz, CH$_2$CH$_3$).

Found: C,43.0; H,2.8; N,30.4%; m/z (EI ms), 276 (M$^+$).

C$_{10}$H$_8$N$_6$O$_4$ requires: C,43.4; H,2.9; N,30.4%, M, 276.

The acidic filtrate on extraction with methylene chloride afforded no further material.

Evaporation of the aqueous filtrate afforded a green solid (0.05 g) whose t.l.c. in ethyl acetate was a mixture which was not further investigated.
Methyl 6-Hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a)

(a) A solution of the stable form (isomer A) of the triazolotriazine derivative (211) (0.67 g, 0.002 mol) in anhydrous dioxane (10.0 ml) was treated with concentrated aqueous ammonia (S.G. 0.88) (2.6 g, 0.15 mol) and the mixture was stirred at room temperature for 17 h.

The mixture was filtered and the insoluble green ammonium salt (0.21 g) was slurried with 2M aqueous hydrochloric acid and the solid collected to afford methyl 6-hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a) (0.17 g; 32%), which formed orange needles, m.p. 244 - 247° (decomp.) (from glacial acetic acid - dimethylformamide), $v_{\text{max}}$ 3250 - 2500 br (OH, NH), 1730, 1700 and 1650 br (CO) and 1625 (C=N) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 11.70 (s, NH)(exch.), 6.27 (d, J2Hz, CH)(collapses to a singlet on exch.), 5.73 (d, J2Hz, CH)(collapses to a singlet on exch.), 3.93 (s, CH$_3$) and 3.90 (s, CH$_3$), $\delta_C$ [(CD$_3$)$_2$SO] 164.1 (quat.), 163.9 (quat.), 160.3 (quat.), 159.6 (quat.), 158.7 (quat.), 157.9 (quat.), 140.0 (quat.), 137.3 (quat.), 135.3 (quat.), 133.2 (quat.), 132.9 (quat.), 129.0 (quat.), 122.1 (quat.), 118.5 (quat.), 95.0 (CH), 93.2 (CH), 52.3 (CH$_3$) and 52.0 (CH$_3$).

Found: C,40.9; H,2.0; N,32.5%; m/z (EI ms), 262 (M$^+$), C$_9$H$_6$N$_6$O$_4$ requires: C,41.2; H,2.3; N,32.1%, M, 262.

The aqueous alkaline mother liquor was concentrated to
remove the dioxane and the residue was diluted with water (5.0 ml), acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give an orange gum which was triturated with methylene chloride to afford methyl 6-carbamoyl-5-ethoxycarbonylmethyl-1,2,3-triazolo-[1,5-b]-1,2,4-triazine-3-carboxylate (227) (0.04 g; 7%), m.p. 198 - 201°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the methylene chloride mother liquor afforded a brown oil (0.25 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(b) The stable form (isomer A) of the triazolotriazine derivative (211) (3.4 g; 0.01 mol) was added to concentrated aqueous ammonia (S.G. 0.88) (2.2 g, 1.3 mol) and the resulting gummy suspension was stirred at 50° (oil bath) for 0.5 h.

The mixture was filtered and the insoluble green ammonium salt was slurried with 2M aqueous hydrochloric acid and the solid collected to afford methyl 6-hydroxy-1,2,3-triazolo[1,5-b]-pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a) (2.2 g; 77%), m.p. 250° (decomp.), identical (m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the aqueous alkaline mother liquor gave a green solid which was slurried with 2M aqueous
hydrochloric acid to give an orange solid (0.35 g) whose
t.l.c. in ethyl acetate over silica showed it to be a
complex mixture which was not further investigated.

(c) The stable form (isomer A) of the triazolotriazine
(211) (0.67 g, 0.002 mol) was added to concentrated aqueous
ammonia (S.G. 0.88) (2.6 g, 0.15 mol) and the resulting
gummy suspension was diluted with water (10.0 ml) and warmed
gently. When the suspended material lost its gumminess and
became green in colour, the mixture was filtered and the
green solid obtained was combined with further solid which
precipitated from the aqueous filtrate on cooling to yield
the ammonium salt of methyl 6-hydroxy-1,2,3-triazolo[1,5-b]-
pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a)
(0.35 g; 63%), m.p. 265 - 270° (decomp.), \( \nu_{\text{max}} \) 3500 - 2500
br (OH, NH) and 1740 - 1620 (CO and C=N) cm\(^{-1}\), which was
treated with 2M aqueous hydrochloric acid to afford the free
triazolopyridotriazine derivative (229a), m.p. 240°
decomp.) identical (m.p. and i.r. spectrum) with a sample
prepared in (a) before.

The aqueous alkaline mother liquor was neutralised with
concentrated hydrochloric acid then 2M aqueous sodium
hydroxide to afford methyl 6-hydroxy-1,2,3-triazolo-
[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate
(229a) (0.04 g; 8%), m.p. 240° (decomp.), identical (m.p.
and i.r. spectrum) to a sample prepared before. Extraction
of the neutral aqueous mother liquor with methylene chloride afforded no further material.

Methyl 6-Hydroxy-7-methyl-1,2,3-triazolo[1,5-b]pyrido-[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (232)

(a) A solution of the stable form (isomer A) of the triazolotriazine triester (211) (0.67 g, 0.002 mol) in anhydrous 1,4-dioxane (10.0 ml) was treated with a 33% w/v solution of methylamine in ethanol (0.37 g, 0.004 mol) and the mixture was stirred at room temperature for 17 h.

The mixture was evaporated and the red oil obtained was triturated with ethanol-diethyl ether to afford the unreacted triazolotriazine derivative (211) (0.46 g; 68%), m.p. 99 - 103°, identical (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the diethyl ether-ethanol mother liquor gave a red oil (0.16 g) whose t.l.c. in diethyl ether over silica showed it to be a complex mixture which therefore was not further investigated.

(b) A suspension of the stable form (isomer A) of methyl 6-ethoxycarbonyl-5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (211) (2.7 g, 0.008 mol) in anhydrous ethanol (50.0 ml) was treated with a 33% w/v solution of the methylamine in ethanol (1.3 g, 0.04 mol) followed by a solution of sodium (0.74 g, 0.032 g. atom) in anhydrous ethanol (40.0 ml). The resulting mixture was
then stirred at room temperature with the exclusion of atmospheric moisture for three days.

The mixture was filtered to afford a yellow salt which was slurried with 2M aqueous hydrochloric acid and the solid collected to afford methyl 6-hydroxy-7-methyl-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (232) (0.14 g; 6%) which formed yellow needles, m.p. 241 - 244° (decomp.) (from dimethylformamide-glacial acetic acid), $\nu_{\text{max}}$ 3200 - 2500 br (OH), 1705 and 1660 br (CO) and 1640 (C=C) cm$^{-1}$.

Found: C, 43.6; H, 3.1; N, 29.4%; m/z (EI ms), 276.0615, (M$^+$).

C$_{10}$H$_8$N$_6$O$_4$ requires: C, 43.5; H, 2.9; N, 30.4%; M, 276.0607.

Extraction of the aqueous acidic mother liquor with methylene chloride yielded no further identifiable material.

The original ethanolic mother liquor was evaporated and the residue was treated with water (20.0 ml) and the resulting solution acidified with 2M aqueous hydrochloric acid to afford methyl 6-N-methylcarbamoyl-5-N-methylcarbamoylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (230) (0.66 g; 27%) which formed orange crystals, m.p. 236 - 238° (from dimethylformamide - water), $\nu_{\text{max}}$ 3440 br and 3360 (NH) and 1750 (CO) and 1640 (C=N) cm$^{-1}$.

Found: C, 43.1; H, 4.2; N, 32.0%; m/z (EI ms), 307 (M$^+$).

C$_{11}$H$_{13}$N$_7$O$_4$ requires: C, 43.0; H, 4.2; N, 31.9%; M, 307.
Methylation of Methyl 6-Hydroxy-1,2,3-triazolo[1,5-b]pyrido-[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a)

A suspension of sodium hydride (0.19 g, 0.008 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated at room temperature with a suspension of the triazolopyridotriazine derivative (229a) (1.0 g, 0.004 mol). The mixture was stirred at room temperature for 15 min then treated with methyl iodide (1.1 g, 0.008 mol) and stirred at this temperature for 18 h (with exclusion of atmospheric moisture).

The mixture was diluted with water (10.0 ml) and the precipitated green solid was collected and slurried with 2M aqueous hydrochloric acid to yield the unreacted triazolotriazine (229a) (0.31 g; 29%), m.p. 230 °C (decomp.), identified by comparison (i.r. spectrum) with a sample prepared before.

Evaporation of the aqueous dimethylformamide mother liquor and treatment of the residue with water (10.0 ml) followed by extraction with methylene chloride afforded no further material.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give a brown oil. This was triturated with ethanol-diethyl ether to give methyl 6-methoxy-4-methyl-1,2,3-triazolo-[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(4H)-one-3-carboxylate (234) (0.28 g; 34%), which formed yellow prisms, m.p. 236 - 238° (from glacial acetic acid), ν max 1730 and 1705 (CO),
1675 (C=N) and 1645 (C=C) cm$^{-1}$, $\delta_H^{[(CD_3)_2SO]}$ 6.44 (1H, s, CH), 4.28 (3H, s, OCH$_3$), 3.95 (3H, s, OCH$_3$) and 3.24 (3H, s, NCH$_3$).

Found: C, 45.2; H, 3.4; N, 29.0%; M, 290.

C$_{11}$H$_{10}$N$_6$O$_4$ requires: C, 45.5; H, 3.4; N, 29.0%; M, 290.

The ethanol-diethyl ether mother liquor on standing deposited a solid which was collected to give methyl 6-hydroxy-7-methyl-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (232) (0.10 g; 13%), m.p. 240° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the ethanol-diethyl ether mother liquor afforded only a small amount of oil which was not further investigated.

The Attempted Hydrolysis of Methyl 6-Hydroxy-1,2,3-triazolo-[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a) with Aqueous Alkali

A suspension of the triazolopyridotriazine derivative (229a) (0.52 g, 0.002 mol) in 2M aqueous sodium hydroxide (8.0 ml) and water (10.0 ml) was heated under reflux for 1 h.

Hot filtration of the mixture gave an orange solid (0.08 g) which was slurried with 2M aqueous hydrochloric acid to yield a yellow intractable solid (0.04 g) from which no identifiable material could be obtained.
Acidification of the cooled aqueous alkaline mother liquor with 2M aqueous hydrochloric acid gave an orange solid which was combined with further material obtained by extraction of the acidic aqueous mother liquor with ethyl acetate to afford an intractable orange solid (0.15 g) which resisted attempts at characterisation.

The Attempted Acid-Catalysed Hydrolysis of Methyl 6-Hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one-3-carboxylate (229a)

(a) A suspension of the triazolopyridotriazinone derivative (229a) (0.52 g, 0.002 mol) in glacial acetic acid (10.0 ml) was treated with 2M aqueous hydrochloric acid (2.5 ml) and the mixture was heated under reflux for 15 min. The orange solid which separated from the hot mixture was combined with material deposited from the mother liquor on cooling to afford an intractable orange solid which resisted all attempts to purify it for characterisation. Evaporation of the acetic acid mother liquor afforded the unreacted triazolopyridotriazinone derivative (229a) (0.13 g; 25%), m.p. 200° (decomp.), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(b) A suspension of the triazolopyridotriazinone derivative (229a) (0.52 g, 0.002 mol) in glacial acetic acid (10.0 ml) and 2M aqueous hydrochloric acid (5.0 ml) was
heated under reflux for 3 h.

Hot filtration of the mixture gave the unreacted triazolopyridotriazinone derivative (229a) (0.11 g; 21%), m.p. 200° (decomp.), identified by comparison (i.r. spectrum) with a sample prepared before.

Evaporation of the aqueous acetic acid mother liquor gave a brown residue which was washed with methanol-methylene chloride leaving an insoluble, intractable orange solid (0.27 g) from which no identifiable material could be obtained.

Evaporation of the methanol-methylene chloride mother liquor afforded 3-chloromethyl-6-hydroxypyrido[4,3-e]-1,2,3-triazin-8(7H)-one (237) as a monohydrate (0.05 g; 15%), m.p. 255 - 259° (decomp.), $\nu_{\text{max}}$ 3250 - 2500 br (NH, OH), 1735 and 1700 (CO) and 1650 (C=N) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 13.90 (1H, brs, NH or OH)(exch.), 11.25 (1H, s, OH or NH)(exch.), 5.41 (1H, d, J2Hz, CH)(collapses to a singlet on exch.) and 4.46 (2H, s, CH$_2$).

**Found:** C, 36.6; H, 2.4; N, 23.2%; m/z (EI ms), 214 and 212 (M$^+$-H$_2$O).

**C$_7$H$_5$ClN$_4$O$_2$.H$_2$O requires:** C, 36.4; H, 3.0; N, 24.3%; M, 232 and 230.

**Found:** m/z (FAB ms), 215.0150 and 213.0179 [(M+H)$^+$].

**C$_7$H$_5$ClN$_4$O$_2$ requires:** (M+H), 215.0150 and 213.0179.

(c) A suspension of the triazolopyridotriazinone derivative (229a) (0.52 g, 0.002 mol) in glacial acetic acid (10.0 ml) and 2M aqueous hydrochloric acid 92.5 ml) was heated under
reflux for 22 h.

The mixture was evaporated to give a brown gum. This was triturated with water to afford a dark intractable solid (0.30 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was therefore not further investigated.

Diethyl 2,3-Dioxopentanoate 2-(4-Carboxy-1H-1,2,3-triazol-5-yl)hydrazone (239) and Diethyl 2,3-Dioxopentanoate 2-(1H-1,2,3-triazol-5-yl)hydrazone (238)

A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (3.8 g, 0.03 mol) in 2M aqueous nitric acid (60.0 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (2.3 g, 0.033 mol) in water (6.0 ml).

The mixture was stirred at 0 - 5° for 15 min then treated with a solution of diethyl acetonedicarboxylate (6.1 g, 0.03 mol) and sodium acetate (17.2 g, 0.21 mol) in methanol (50.0 ml) and water (50.0 ml) and the mixture was stirred in the melting ice bath for 2 h.

After standing at room temperature overnight, the mixture was filtered and the yellow solid was slurried with 2M aqueous hydrochloric acid to give diethyl 2,3-dioxopentanoate 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (239) (8.4 g; 82%), m.p. 100 - 103°, ν_max 3450 br, 3200 br and 3100 - 2000 br OH, NH), 1735, 1710 and 1670 (CO) and 1650 br (C=N) cm⁻¹, δ_H [(CD₃)₂SO] 13.40 (1H, brs,
NH)(exch.), 8.20 (1H, brs, NH)(exch.), 4.25 (2H, q, J7Hz, CH₂), 3.94 (2H, s, CH₂), 3.90 (2H, q, J7Hz, CH₂), 1.26 (3H, t, J7Hz, CH₃) and 1.00 (3H, t, J7Hz, CH₃), δ_C[(CD₃)₂SO] 168.8 (quat.), 162.4 (quat.), 161.7 (quat.), 135.4 (quat.), 131.4 (quat.), 120.2 (quat.), 79.5 (quat.), 61.5 (CH₂), 60.7 (CH₂), 41.8 (CH₂), 14.3 (CH₃) and 14.0 (CH₃), which was converted by crystallisation from toluene in quantitative yield into diethyl 2,3-dioxopentanoate 2-(1H-1,2,3-triazol-5-yl)hydrazone (238) which formed tan needles, m.p. 96 - 99°, υ_max 3200 br (NH) and 1735 and 1675 (CO) cm⁻¹, δ_H[(CD₃)₂SO] 12.20 (1H, s, NH)(exch.), 7.91 (1H, s, NH)(exch.), 7.31 (1H, s, CH), 4.21 (2H, q, J7Hz, CH₂), 3.97 (2H, s, CH₂), 3.87 (2H, q, J7Hz, CH₂), 1.26 (3H, t, J7Hz, CH₃) and 1.00 (3H, t, J7Hz, CH₃).

**Found:** C, 44.6; H, 5.1; N, 23.8%; m/z (FAB ms), 298 [(M+H)⁺].

**C₁₁H₁₅N₅O₅ requires:** C, 44.4; H, 5.0; N, 23.6%; M, 297.

Extraction of the aqueous alkaline mother liquor with methylene chloride before and after acidification with 2M aqueous hydrochloric acid afforded no further material.

**Ethyl 5-Ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylate (240)**

A solution of diethyl 2,3-dioxopentanoate 2-(4-carboxy-1H-1,2,3-triazol-5-yl)hydrazone (239) (10.2 g, 0.03 mol) and toluene-4-sulphonic acid (0.50 g) in anhydrous benzene (50.0 ml) was heated under reflux for 2 h.
The mixture was evaporated to afford ethyl 5-ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylate (240) as a red oil which was purified by dry flash-chromatography in toluene-methylene chloride (1:1), yield 8.4 g (quant.), $\nu_{\text{max}}$ 1735 br (CO) cm$^{-1}$, $\delta_H[(CD_3)_2SO]$ 8.69 (1H, s, CH), 4.45 (2H, q, J7Hz, CH$_2$), 4.31 (2H, s, CH$_2$), 4.13 (2H, q, J7Hz, CH$_2$), 1.38 (3H, t, CH$_3$) and 1.19 (3H, t, J7Hz, CH$_3$).

Found: C, 47.4; H, 4.7; N, 24.5%; m/z (EI ms), 279 (M$^+$.)

$C_{11}H_{13}N_5O_4$ requires: C, 47.3; H, 4.7; N, 25.1%; M, 279.

The Attempted Reaction of Ethyl 5-Ethoxycarbonylmethyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-6-carboxylate (240) with Liquid Ammonia

The triazolotriazine (240) (0.56 g, 0.002 mol) was added in portions with stirring to liquid ammonia (40.0 ml) at -78° (acetone-solid CO$_2$ bath) and the mixture was stirred at -78° for 1 h.

The mixture was allowed to evaporate and the solid residue was treated with methanol (10.0 ml) and the solution was filtered to remove some insoluble solid and the filtrate evaporated to give a brown gum (0.36 g) which was subjected to dry flash-chromatography over silica.

Elution with toluene-methylene chloride (5:1) followed by methylene chloride-ethyl acetate (9:1) afforded the unreacted triazolotriazine (240) as a yellow oil (0.28 g; 50%), identical (i.r. spectrum) to a sample prepared
previously.

Further elution with ethyl acetate-methanol (5:1) through to methanol afforded no further identifiable material.

6-Hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one (242A)

The triazolotriazine derivative (240) (2.8 g, 0.01 mol) was added in portions with stirring to concentrated aqueous ammonia (S.Gr. 0.88) (22 g, 1.3 mol) and the mixture was stirred at 60° for 0.5 h.

The mixture was filtered to give an orange solid which was slurried with 2M aqueous hydrochloric acid to afford 6-hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one (242A) (1.0 g; 49%), m.p. 241° (decomp.), $\nu_{\text{max}}$ 3230 - 2500 br (NH, OH), 1710 (CO), 1670 (C=N) and 1635 (C=C) cm$^{-1}$, $\delta_H[(CD_3)_2SO]$ 11.4 (1H, brs, NH)(exch.), 8.07 (1H, s, CH), 6.13 (1H, d, J2Hz, CH)(collapses to singlet on exch.) and 4.00 (brs, OH).

**Found:** C, 40.6; H, 2.1; N, 39.9%; m/z (FAB ms), 205.0474 [(M+H)$^+$].

$C_7H_4N_6O_2$ requires: C, 41.2; H, 2.0; N, 41.2%; (M+H), 205.0474.

Evaporation of the aqueous alkaline mother liquor gave an intractable brown gum from which no identifiable material could be obtained.
3-Acetoxyethyl-6-hydroxypyrido[4,3-e]-1,2,4-triazin-8(7H)-one (243)

A suspension of 6-hydroxy-1,2,3-triazolo[1,5-b]pyrido-[4,3-e]-1,2,4-triazin-8(7H)-one (242A) (0.41 g, 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 6 h.

The mixture was hot filtered to give an orange solid which was combined with further material obtained by evaporating the acetic acid filtrate and triturating the residue with methylene chloride to give 3-acetoxyethyl-6-hydroxypyrido[4,3-e]-1,2,4-triazin-8(7H)-one (243) (0.40 g; 85%), which formed orange crystals, m.p. 243 - 246° (decomp.)(from glacial acetic acid-toluene), $\nu_{\text{max}}$ 3300 - 2500 br (OH, NH), 1755, 1730 and 1700 (CO) and 1670 (C=N) cm$^{-1}$, $\delta_{\text{H}}[(CD_3)_2SO]$ 13.60 (1H, brs, NH or OH), 11.20 (1H, brs, OH or NH), 5.35 (1H, d, J2Hz, CH)(collapses to singlet on exch.), 4.87 (2H, s, CH$_2$) and 2.12 (3H, s, CH$_3$).

Found: C,46.1; H,3.6; N,23.4%; m/z (FAB ms), 237 [(M+H)$^+$].

C$_9$H$_8$N$_4$O$_4$ requires: C,45.8; H,3.4; N,23.7%; M, 236.

Evaporation of the methylene chloride mother liquor gave only a small amount of an orange solid (0.01 g) which was not further investigated.

3-Chloromethyl-6-hydroxypyrido[4,3-e]-1,2,4-triazin-8(7H)-one (244)

A suspension of 6-hydroxy-1,2,3-triazolo[1,5-b]pyrido-[4,3-e]-1,2,4-triazin-8(7H)-one (242A) (0.55 g, 0.003 mol)
in glacial acetic acid (4.0 ml) and acetyl chloride (6.0 ml) was heated under reflux for 6 h.

The mixture was filtered hot to give a tan solid which was combined with further material obtained by evaporating the acetic acid mother liquor and triturating the residue with methylene chloride and dry flash-chromatographed in ethyl acetate over silica to afford 3-chloromethyl-6-hydroxy[4,3-e]-1,2,4-triazin-8(7H)-one (244) (0.60 g; quant.), m.p. 255 - 259° (decomp.), identical (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Reaction of 6-Hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one (242A) with Aqueous Sulphuric Acid

A suspension of 6-hydroxy-1,2,3-triazolo[1,5-b]pyrido[4,3-e]-1,2,4-triazin-8(7H)-one (242A) (0.41 g, 0.002 mol) in 20% w/v sulphuric acid (2.5 ml) was stirred at 100° (oil bath) for 5 h.

The stirred mixture was cooled (ice bath) and neutralised with 10M aqueous sodium hydroxide to give a dark intractable solid (0.42 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

Ethyl 4-Chloro-3-oxobutanoate 3-(4-Methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246)
A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (3.6 g, 0.02 mol) in 2M aqueous nitric acid (40.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (1.5 g, 0.022 mol) in water (8.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with stirring with a solution of ethyl 4-chloroacetoacetate (3.3 g, 0.02 mol) and sodium acetate (11.5 g, 0.14 mol) in methanol (40.0 ml) and water (30.0 ml) and the mixture stirred at room temperature for 17 h.

The precipitated solid was collected to afford ethyl 4-chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) (5.0 g, 79%), which formed cream needles, m.p. 142 - 145° (from glacial acetic acid-toluene), νmax 3340 and 3270 (NH) and 1720 br (CO) cm⁻¹, δH [(CD₃)₂SO] 12.86 (1H, s, NH), 8.81 (1H, s, NH), 4.84 (1H, d, J11Hz, CH), 4.67 (1H, d, J11Hz, CH), 4.30 (2H, q, J7Hz, CH₂), 3.86 (3H, s, CH₃), 1.30 (3H, t, J7Hz, CH₃).

Found: C,37.6; H,3.7; N,21.7%; m/z (EI ms), 319 and 317 (M⁺).

C₁₀H₁₂ClN₅O₅ requires: C,37.8; H,3.8; N,22.0%; M, 319 and 317.

The aqueous mother liquor was concentrated to remove the methanol and extracted with ethyl acetate to give a brown oil from which no other identifiable material could be obtained.

Ethyl 4-Chloro-2,3-dioxobutanoate 2-(1-Acetyl-4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (247)
A suspension of ethyl 4-chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) (0.63 g, 0.002 mol) in acetic anhydride (1.0 ml) was heated gently at 100° (water bath) for 5 min.

The mixture was cooled and the solution then treated dropwise with diethyl ether to give a colourless solid which was collected and combined with further material which precipitated from the filtrate on standing overnight to afford ethyl 4-chloro-3-oxobutanoate 3-(1-acetyl-4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (247) (0.38 g; 53%), which formed yellow prisms, m.p. 143 - 145° (from ethanol), \( \nu_{\text{max}} \) 3580 (NH) and 1770 br and 1680 (CO) cm\(^{-1} \), \( \delta_{H} \) [(CD\(_3\))]\(_2\)SO 12.80 (1H, s, NH)(exch.), 4.95 (1H, d, J6Hz, CH), 4.74 (1H, d, J6Hz, CH), 4.30 (2H, q, J7Hz, CH\(_2\)), 3.85 (3H, s, CH\(_3\)), 2.77 (3H, s, CH\(_3\)) and 1.30 (3H, t, J7Hz, CH\(_3\)).

Found C, 39.7; H, 4.0; N, 19.8%; \( m/z \) (FAB ms), 362 and 360 [(M+H)+].

\( \text{C}_{12}\text{H}_{14}\text{ClN}_{5}\text{O}_{6} \) requires: C, 40.0; H, 3.9; N, 19.5%; M, 362 and 360.

Evaporation of the ethereal mother liquor gave an orange oil (0.22 g), whose t.l.c. in ethyl acetate over silica was a complex mixture which therefore was not further investigated.

**Methyl 5-(3-Ethoxycarbonyl-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (250)**

A suspension of the triazolyllhydrazone (246) (0.60 g, 0.002 mol) in 2M aqueous sodium hydroxide (2.5 ml) was
stirred at room temperature for 10 min.

The mixture was acidified by the dropwise addition of 2M aqueous hydrochloric acid (2.5 ml) and stirred for a further 5 min then filtered and the yellow solid combined with further material obtained by extracting the acidic mother liquor with ethyl acetate to afford methyl 5-(3-ethoxycarbonyl-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (250) (0.47 g; 90%), which formed tan needles, m.p. 177 - 181° (from ethanol-light petroleum), $\nu_{\max}$ 3400 (NH), 3330 - 2500 br (OH) and 1725 and 1705 (CO) cm$^{-1}$, $\delta_{\text{H}}$ [(CD$_3$)$_2$SO] 14.65 (1H, brs, OH or NH(exch.), 7.89 (1H, s, NH or OH)(exch.), 6.42 (1H, s, CH), 2.80 (2H, q, J7Hz, CH$_2$), 2.34 (3H, s, CH$_3$), -0.20 (3H, t, J7Hz, CH$_3$).

Found: C, 42.8; H, 3.9; N, 25.0%; m/z (EI ms), 281.

C$_{10}$H$_{11}$N$_5$O$_5$ requires: C, 42.7; H, 3.9; N, 24.9%; M, 281.

Methyl 1-Acetyl-5-(4-acetoxy-3-ethoxycarbonyl-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (251)

A suspension of methyl 5-(3-ethoxycarbonyl-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (250) (0.56 g, 0.002 mol) in acetic anhydride (1.5 ml) was heated gently at 100° (water bath) for 8 min.

The mixture was cooled, diluted with diethyl ether and the precipitated solid collected to afford methyl 1-acetyl-5-(4-acetoxy-3-ethoxycarbonyl-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (251) (0.50 g; 68%), which formed tan prisms, m.p. 148 - 150° (from ethanol-light petroleum), $\nu_{\max}$
The Hydrolysis of Methyl 5-(3-Ethoxycarbonyl-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (250) with Aqueous Sodium Hydroxide

A solution of methyl 5-(3-ethoxycarbonyl-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylate (250) (1.1 g), 0.004 mol) in 2M aqueous sodium hydroxide (5.0 ml) and water (2.5 ml) was heated under reflux for 0.5 h.

The mixture was cooled and filtered to give a yellow salt, which was slurried with 2M aqueous hydrochloric acid and combined with further material which precipitated from the acidic aqueous mother liquor on standing to give 5-(3-carboxy-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole-4-carboxylic acid (253) (0.40 g; 42%), which formed tan crystals, m.p. 230 - 234 ° (from water), $v_{\text{max}}$ 3520, 3460 and 3400 - 2500 br (NH, OH), 1725 and 1690 (CO) and 1630 (C=N)

Evaporation of the diethyl ether mother liquor gave an intractable brown gum (0.16 g), whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which therefore was not further investigated.
cm\(^{-1}\), \(\delta_H\) [(CD\(_3\))\(_2\)SO] 7.87 (1H, d, J2Hz, CH) and 7.50 (brs, OH).

\textit{Found}: C, 33.8; H, 2.9; N, 26.8%; m/z (EI ms), 195.0392 (M\(^+\)-CO\(_2\)).

\(\text{C}_7\text{H}_5\text{N}_5\text{O}_5\cdot\text{H}_2\text{O}\) \textit{requires}: C, 32.7; H, 2.7; N, 27.2%; (M-CO\(_2\)), 195.0392.

Acidification of the original aqueous alkaline mother liquor with 2M aqueous hydrochloric acid afforded a solid which was combined with further material obtained by extracting the aqueous acidic mother liquor to give

5-(3-ethoxycarbonyl-4-hydroxy-1H-pyrazol-1-yl)-1H-1,2,3-triazole (252) (0.59 g; 55%), which formed tan needles, m.p. 204 - 206° (from ethanol-light petroleum), \(\nu_{max}\) 3200 - 2500 br (NH, OH) and 1700 br (CO) cm\(^{-1}\), \(\delta_H\) [(CD\(_3\))\(_2\)SO] 7.91 (1H, s, CH), 4.28 (2H, q, J7Hz, CH\(_2\)), 3.50 (brs, OH, NH) and 1.29 (3H, t, J7Hz, CH\(_3\)).

\textit{Found}: C, 39.6; H, 3.3; N, 26.0%; m/z (EI ms), 267 (M\(^+\)).

\(\text{C}_9\text{H}_9\text{N}_5\text{O}_5\) \textit{requires}: C, 40.4; H, 3.4; N, 26.2%; M, 267.

\textbf{Methyl 5-Chloromethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249)}

(a) A solution of ethyl 4-chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) (5.0 g, 0.016 mol) in anhydrous dioxane (40.0 ml) was heated under reflux for 19 h.

The mixture was filtered to remove some insoluble material and the filtrate was evaporated giving a solid
which was washed with diethyl ether to afford methyl 5-
chloromethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-
triazine-3-carboxylate (249) (4.2 g; 92%), which formed
cream needles, m.p. 118 - 119° (from ethanol-light
petroleum), \( \nu_{\text{max}} \) 1725 br (CO) cm\(^{-1}\), \( \delta_H [\text{(CD}_3\text{)}_2\text{SO}] \) 5.26 (2H, s, CH\(_2\)), 4.54 (2H, q, J\(_{7\text{Hz}}\), CH\(_2\)), 3.98 (3H, s, CH\(_3\)), 1.43
(3H, t, J\(_{7\text{Hz}}\), CH\(_3\)), \( \delta_C [\text{(CD}_3\text{)}_2\text{SO}] \) 160.8 (quat.), 159.7
(quat.), 155.3 (quat.), 140.4 (quat.), 136.3 (quat.), 127.8
(quat.), 63.7 (CH\(_2\)), 52.5 (CH\(_2\)), 44.6 (CH\(_3\)) and 14.0 (CH\(_3\)).
Found: C, 40.0; H, 3.3; N, 23.2%; m/z (EI ms), 301 and 299 (M\(^+\)).

\( \text{C}_{10}\text{H}_{10}\text{ClN}_5\text{O}_4 \) requires: C, 40.1; H, 3.3; N, 23.4%; M, 299.5.

Evaporation of the ethereal filtrate gave an orange oil
which was triturated with diethyl ether-toluene-methylene
chloride to yield the unreacted triazolylhydrazone (246)
(0.17 g; 3%), m.p. 116 - 122°, identified by comparison
(m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the diethyl ether-toluene-methylene
chloride gave an orange oil (0.73 g) whose t.l.c. in ethyl
acetate over silica showed it to be a multicomponent mixture
which therefore was not further investigated.

(b) A solution of ethyl 4-chloro-3-oxobutanoate 3-
(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246)
(1.3 g, 0.004 mol) in glacial acetic acid (10.0 ml) was
heated under reflux for 1 h.

The mixture was evaporated to give a red oil which was
flash-chromatographed over silica. Elution with toluene-
methylene chloride (5:2) afforded methyl 5-chloromethyl-6-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249) (0.29 g; 26%), m.p. 115 - 117°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Further elution with toluene-methylene chloride (5:2) gave an intractable orange gum (0.55 g) whose t.l.c. in methylene chloride-ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

Elution with toluene-methylene chloride through to methylene chloride-ethyl acetate (9:1) gave a series of gums and solids (total 0.08 g) none of which yielded any identifiable material.

Elution with methylene chloride-ethyl acetate (3:2) afforded the unreacted triazolohydrazone (246) (0.14 g; 11%), m.p. 136 - 138°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Final elution with ethyl acetate-methanol gave only an intractable brown solid (0.05 g) which was not further investigated.

(c) A solution of ethyl 4-chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) (0.63 g, 0.002 mol) and toluene-4-sulphonic acid (0.01 g) in anhydrous 1,4-dioxane (10.0 ml) was heated under reflux for 1 h.
The mixture was evaporated and the solid residue was treated with water (10.0 ml) and filtered to give a brown solid which was washed with methylene chloride to afford the unreacted triazolylhydrazone (246) (0.35 g; 56%), m.p. 134 - 137°, identical (m.p. and i.r. spectrum) with a sample prepared previously.

The methylene chloride filtrate was evaporated to give a brown oil which was triturated with toluene-methanol to afford a brown solid (0.23 g) whose t.l.c. in diethyl ether over silica showed it to be a multicomponent mixture which was not further investigated.

Extraction of the aqueous mother liquor with methylene chloride afforded no further material.

Attempted Syntheses of Methyl 5-Cyanomethyl-6-ethoxy-carbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (254)

(a) A solution of methyl 5-chloromethyl-6-ethoxy-carbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249) (0.60 g, 0.002 mol) in 1,4-dioxane (10.0 ml) was treated with a solution of potassium cyanide (0.26 g, 0.004 mol) in water (2.0 ml) and the mixture was stirred at room temperature for 17 h.

The mixture was evaporated to give a purple gum which was treated with water (15.0 ml) and the mixture extracted with methylene chloride to afford only a negligible amount of solid material.
Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid yielded an intractable brown solid (0.15 g) from which no identifiable material could be obtained.

(b) A solution of methyl 5-chloromethyl-6-ethoxy-carbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249) (0.60 g, 0.002 mol) in glacial acetic acid (5.0 ml) was stirred and treated dropwise at 10° (ice-water bath) with a solution of potassium cyanide (0.26 g, 0.004 mol) in water (1.0 ml) and the mixture was stirred at room temperature for 15 h.

The mixture was filtered to afford the unreacted triazolotriazine (249) (0.13 g; 22%), m.p. 144 - 117°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The aqueous acetic acid mother liquor was diluted with water (10.0 ml) and as no material was precipitated was evaporated and the resulting oil treated with water (5.0 ml) then extracted with ethyl acetate to give an orange oil which was triturated with methylene chloride to afford ethyl 4-chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) (0.10 g; 16%), m.p. 152 - 154°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Evaporation of the methylene chloride mother liquor
gave a brown gum (0.31 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which was not further investigated.

(c) A solution of methyl 5-chloromethyl-6-ethoxy-carbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (249) (0.60 g, 0.002 mol) in anhydrous acetonitrile (5.0 ml) was treated with a solution of tetraethylammonium cyanide (0.31 g, 0.002 mol) in anhydrous acetonitrile (3.0 ml) and the mixture was stirred at room temperature for 2.5 h, then heated at 50° (oil bath) for a further 2 h.

Evaporation of the mixture gave a dark oil which was treated with water (8.0 ml) and the mixture filtered to yield a black solid (0.54 g) which was subjected to flash-chromatography over silica.

Elution with ethyl acetate-methylene chloride (4:1) through to ethyl acetate then methanol gave only a series of intractable solids (total 0.21 g) from which no identifiable material could be obtained.

The Attempted Reaction of Ethyl 4-Chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) with Sodium Cyanide in Dimethylformamide

A solution of ethyl 4-chloro-3-oxobutanoate 3-(4-methoxycarbonyl-1H-1,2,3-triazol-5-yl)hydrazone (246) (0.63 g, 0.002 mol) in anhydrous dimethylformamide (2.5 ml)
was treated with a suspension of sodium cyanide (0.20 g, 0.004 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 17 h.

The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to afford an intractable purple oil (0.54 g) from which no identifiable material could be obtained.
Chapter 4

Investigations of the Synthesis and Reactivity of 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine Derivatives en Route to Imidazo[4,5-e]-1,2,4-triazine (6-Azapurine) and Pyrrolo[2,3-e]-1,2,4-triazine (6-Aza-7-deazapurine) Derivatives
Scheme 69
Investigations of the Synthesis and Reactivity of
5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-
triazine Derivatives en Route to Imidazo[4,5-e]-1,2,4-
triazine (6-Azapurine) and Pyrrolo[2,3-e]-1,2,4-triazine
(6-Aza-7-deazapurine) Derivatives

4.1 Introduction

The biological importance of heterocyclic compounds
(Scheme 69) containing the imidazo[4,5-d]pyrimidine (purine)
ring system (256) is well known and has prompted
investigations of the synthesis and biological activity of
azapurine and deazapurine derivatives most notably those
based on fused pyrimidine frameworks (Scheme 69). Thus
derivatives of the 1,2,3-triazolo[4,5-d]pyrimidine (8-
azapurine) ring system (257) exhibit antiviral and
anticancer activity and their synthesis has therefore been
extensively investigated. Derivatives of the
pyrrolo[3,2-d]pyrimidine (9-deazapurine) ring system (258)
and the pyrrolo[2,3-d]pyrimidine (7-deazapurine) ring system
(259) also show anticancer and antiviral activity and
synthetic routes to such heterocycles are well known. In contrast nothing is known about the biological activity
of aza- and deazapurine derivatives containing fused 1,2,4-
triazine frameworks (Scheme 69) largely because of the lack
of appropriate general methods for the synthesis of such
heterocycles. Thus only seven publications on the
synthesis of derivatives of the imidazo[4,5-e]-1,2,4-
Scheme 70

[ R¹ = H or Me ]
[ X = OH, OCO.Me, Cl, Br ]
triazine (6-azapurine) ring system (260) have appeared in the literature to date. Correspondingly derivatives of the pyrrolo[2,3-e]-1,2,4-triazine (6-aza-7-deazapurine) ring system (261) are presently known.

Because of the inaccessibility of potentially biologically active derivatives of the imidazo[4,5-e]-1,2,4-triazine and pyrrolo[2,3-e]1,2,4-triazine ring systems (260) and (261) it was of interest in the context of the present studies to investigate general synthetic methods for such heterocycles based on triazole scission reactions of appropriately fused 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives. The general synthetic strategy investigated (Scheme 70) involved 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazines with appropriate ester or carboxyl functionality at the 3-position (262; R=Me or H) as key starting materials. It was envisaged that the benzenesulphonyl group in these heterocycles would readily undergo nucleophilic displacement by amino compounds or appropriate stabilised carbanions to afford intermediates of the types (263) and (264). Depending on the nature of the R¹ substituent in the former or the R² substituent in the latter, these intermediates were expected to undergo spontaneous or contrived annulation providing flexible, general routes to usefully functionalised triazoloimidazo-triazine and triazolopyrrolotriazine frameworks (265) and (266) and (267). These heterocycles were in turn set up for further manipulation and ultimate acid-catalysed triazole
scission$^{41-43}$ to variously substituted imidazo[4,5-\(\text{e}\)]-1,2,4-triazines (268) and pyrrolo[2,3-\(\text{e}\)]-1,2,4-triazines (269) and (270). The attempted implementation of this general synthetic strategy for imidazo[4,5-\(\text{e}\)]-1,2,4-triazines (268) and pyrrolo[2,3-\(\text{e}\)]-1,2,4-triazines (269) and (270) is described in the following sections.
(133) \[ \text{QR} \]

\[ \text{HN} \]

\[ \text{HN} \]

\[ \text{I} \]

\[ \text{II} \]

\[ \text{SO}_2\text{Ph} \]

\[ \text{NH} \]

\[ \text{PhSO}_2 \]

\[ \text{C} \equiv \text{N} \]

\[ (271) \]

\[ (273) \]

\[ (274) \]

\[ \text{(i) NaNO}_2, 2\text{M HNO}_3, \text{H}_2\text{O}, 0^\circ. \]

\[ \text{(ii) NaOAc, MeOH, H}_2\text{O, room temp.} \]

Scheme 71
4.2 Investigations of the Synthesis and Reactivity of 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine Derivatives en Route to Imidazo[4,5-e]-1,2,4-triazine Derivatives

The initial objective in the development of the general synthetic strategy already outlined in Scheme 70 was the synthesis of the previously undescribed methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) required as a key starting-material. In practice coupling of the 1,2,3-triazole diazonium cation(Scheme 71 (135), generated in situ under standard conditions from either the amino-1,2,3-triazole ester (133) or its hydrochloride (134) with the readily available73 compound benzenesulphonylacetonitrile (271) afforded excellent yields (85 - 87%) of a single product. This compound analysed correctly and showed i.r. and $^1$H n.m.r. absorption supporting its formulation as the required 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivative (274). The compound's lack of i.r. cyano absorption in particular excludes the alternative isomeric triazolylhydrazone structure (273). On the other hand, the possibility that the compound has the angularly fused 1,2,3-triazolo[5,1-γ]-1,2,4-triazine structure (272) cannot be rigorously excluded. However as already discussed (see chapter 2, pages 29-30 and chapter 3, page 149) 1,2,3-triazolo[5,1-γ]-1,2,4-
CO₂Me

H₂N

PhSO₂

(274)

(i) - (iii)

CO₂Me

H₂N

X

(276)

(iv)

N

RN

NH₃ (liq.), -78°.

MeNH₂, EtOH, room temp.

PhCH₂NH₂, 1,4-dioxane, room temp.

AcOH, reflux.

Scheme 72
triazine structures [e.g. (272)] for the products of the coupling reactions of 1,2,3-triazolediazonium cations with stabilised carbanions are excluded in favour of the isomeric 1,2,3-triazolo[1,5-b]-1,2,4-triazine structures [e.g. (274)] on the basis of the x-ray analysis of one such compound in the present thesis (see chapter 3, page 173). On the other hand, both the triazolylhydrazone (273) and the 1,2,3-triazolo[5,1-g]-1,2,4-triazine derivative (272) must be intermediates in the formation of the product (274) from the triazolediazonium cation (135) and benzenesulphonyl-acetonitrile (271).

With the aminobenzenesulphonyltriazolotriazine (274) available, effort was next directed (Scheme 72) to its conversion into 5,6-diaminotriazolotriazine derivatives (275) required for the acylative annulation to the corresponding 5H-1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine derivatives [e.g. (276)]. It was found that the benzenesulphonyl substituent in the triazolotriazine derivative (274) underwent general nucleophilic displacement with various amino compounds (Scheme 72) giving the previously undescribed 5,6-diaminotriazolotriazine derivatives (275; a-c) in uniformly high yield. Thus, reaction with liquid ammonia afforded the parent 5,6-diaminotriazolotriazine (275a) in 87% yield. Correspondingly the N-methyl and N-benzyl derivatives (275b) and (275c) resulted in 84% and 70% yield respectively when the aminobenzenesulphonyltriazolotriazine (274) was reacted
Scheme 73:

(i) NH₂NH₂·H₂O, 1,4-dioxane, room temp.
(ii) NaN₃, 1,4-dioxane, H₂O, room temp.
(iii) NaNO₂, HNO₃, H₂O, 0-5°C.
(iv) Ph₃P, Me₂NCH=O.
at room temperature with methylamine in ethanol or benzyamine in 1,4-dioxane. The 5,6-diaminotriazolotriazine derivatives (275; a-c) all analysed correctly and had mass, i.r. and $^1H$ n.m.r. spectra fully consistent with their assigned structures.

Disappointingly, the attempted annulation of the 5,6-diaminotriazolotriazine (275a) to the 1,2,3-triazolo[1,5-b]-imidazo[4,5-e]-1,2,4-triazine derivative (276) by heating with glacial acetic acid was unsuccessful under conditions which succeeded for the conversion of 1,2-diaminoarenes to benzimidazoles. In the case of the 5,6-diaminotriazolotriazine derivative (275a) the starting material was recovered unchanged in high yield (80%). This result indicates that one or other or both of the amino substituents in the 5,6-diaminotriazolotriazines (275; a-c) are insufficiently nucleophilic to undergo acylative annulation to give an imidazole ring.

In view of this it was decided to investigate an alternative approach (Scheme 73) based on the triphenylphosphiniminotriazolotriazine derivative (279). It was anticipated that this type of intermediate by analogy with simpler N-aryl triphenylphosphinimines would undergo an aza-Wittig type condensation with carboxylic acid chlorides to afford the corresponding imino chlorides (280). Spontaneous cyclisation of the latter ought then to yield the respective triazoloimidazotriazine compound (281).
Initially the azidotriazolotriazine (278) required as the immediate precursor of the phosphinimine (279) was synthesised in good yield (72%) by diazotisation of the hydrazinotriazolotriazine derivative (277). The latter compound was in turn available in high yield (81%) by the nucleophilic displacement of the benzenesulphonyl substituent in the triazolotriazine derivative (274) with hydrazine hydrate. The hydrazino and azidotriazolotriazine products (277) and (278) gave analytical and spectroscopic data in full accord with their assigned structures. It was subsequently found that the azidotriazolotriazine derivative (278) was formed in high yield (85%) directly from the benzenesulphonyltriazolotriazine derivative (274) by reaction with sodium azide in aqueous 1,4-dioxane at room temperature. The azidotriazolotriazine derivative (278) reacted as expected with triphenylphosphine in dimethylformamide at room temperature then at 60° to afford the required triphenylphosphiniminotriazolotriazine (279) in excellent yield (95%). This compound analysed correctly and gave mass, i.r. and 1H n.m.r. spectra entirely consistent with its structure. Unfortunately however, because of its relative insolubility and susceptibility to hydrolysis to the diaminotriazolotriazine (275a), the phosphiniminotriazolotriazine derivative (279) was considered unsuitable as a starting material for the synthesis of the required 5H-1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine derivatives (281).
(i) NaH, Me₂NCH=O then H₂NCO₂Et, room temp.

(ii) NaNHCN, 1,4-dioxane, H₂O, room temp.

(iii) 2M HCl, H₂O, room temp.

Scheme 74
In a further attempt to exploit the displaceability of the benzenesulphonyl substituent in the benzenesulphonyl-triazolotriazine (274) for the synthesis of 1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine derivatives, reaction with the amide anions derived from ethyl carbamate and cyanamide were investigated (Scheme 74). Thus it was hoped that reaction of the benzenesulphonyltriazolotriazine derivative (274) with the sodium salt of ethyl carbamate would afford the urethane derivative (282) capable of spontaneous or induced cyclisation with elimination of ethanol to afford the triazoloimidazotriazinone derivative (284). In practice however, the attempted reaction (Scheme 74) of the benzenesulphonyltriazolotriazine derivative (274) with the sodium salt of ethyl carbamate (generated in situ by reaction with sodium hydride) in dimethylformamide at room temperature gave only a complex mixture which yielded no characterisable material. In contrast the benzenesulphonyltriazolotriazine (274) reacted readily with sodium cyanamide in aqueous 1,4-dioxane at room temperature to afford a quantitative yield of a salt tentatively formulated as the (N-cyano)aminotriazolotriazine derivative (283) on the basis of the presence of cyano absorption in its i.r. spectrum. However the attempted purification of this product by crystallisation from aqueous dimethyl sulphoxide resulted in its quantitative conversion into a second salt which lacked i.r. cyano absorption and analysed
(i) NaNO₂, 2M HNO₃, H₂O, 0°.
(ii) NaOAc, MeOH, H₂O, room temp.
(iii) 2M HCl, H₂O, room temp.
(iv) 1,4-dioxane, reflux.

Scheme 75
correctly for a trihydrate of the triazoloimidazotriazine structure (285). This structure was further substantiated by the compound's mass and $^1$H n.m.r. spectra and by its conversion by acidification into the parent aminotriazolo-imidazotriazine derivative (286). This compound analysed correctly and showed a mass spectrum and i.r. and $^1$H n.m.r. absorption which fully substantiated its assigned structure.

Because of the difficulties encountered in attempting to hydrolyse ester substituents attached to the triazole ring of other fused 1,2,3-triazoles (see chapter 2, page 56 and chapter 3, pages 163-165) it was decided not to attempt to hydrolyse the aminotriazoloimidazotriazine ester (286) in the general strategy for the synthesis of imidazo[4,5-e]-1,2,4-triazine derivatives [i.e. see Scheme 70; (265; R=Me, $R^1$=H, $R^2$=NH$_2$) --> --> (268; $R^1$=H, $R^2$=NH$_2$)]. Instead it was decided to synthesise the required triazoloimidazotriazine carboxylic acid [i.e. Scheme 70; (265; R=$R^1$=H, $R^2$=NH$_2$)] via the diazotative synthesis (Scheme 75) and aminative cyclisation with sodium cyanamide of the aminobenzenesulphonyltriazolotriazine carboxylic acid (290). In practice, the carboxytriazolediazonium betaine (120), either preformed or generated in situ by diazotisation of the aminotriazole carboxylic acid (119), coupled readily with benzenesulphonylacetonitrile (271) in weakly basic solution to afford acceptable yields of the isolable aminobenzenesulphonyltriazolotriazine carboxylic acid sodium salt (289) from which the required aminobenzenesulphonyl-
(i) H₂O, reflux.

(ii) 1,4-dioxane, H₂O, reflux.

(iii) AcOH, reflux.

(iv) AcCl, AcOH, reflux.

Scheme 76
triazolotriazine carboxylic acid (290) was liberated by treatment with aqueous hydrochloric acid. As in similar triazolediazonium cation coupling reactions described before, the product of the reaction of the triazolediazonium betaine (120) with benzenesulphonylacetetonitrile (271) is assumed to have the 1,2,3-triazolo[1,5-b]-1,2,4-triazine structure (290) derived by initial formation of the triazolylhydrazone intermediate (288) followed by cyclisation of the latter and spontaneous rearrangement of the resulting 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivative (287). All attempts to purify the triazolotriazine carboxylic acid (290) by crystallisation for further characterisation led to decarboxylation to the parent aminobenzenesulphonyltriazolotriazine (291). This product was also formed in poor yield when the carboxylic acid (290) was heated under reflux in 1,4-dioxane and had analytical and spectroscopic properties fully consistent with its assigned structure.

In an effort to obtain an improved synthesis for the aminobenzenesulphonyltriazolotriazine (291), the carboxylic acid sodium salt (289) was heated under reflux in aqueous solution. It was hoped that under these conditions decarboxylation to the parent aminobenzenesulphonyltriazolotriazine derivative (291) would be more efficient. In fact, the product obtained (Scheme 76) in moderate yield (50%) gave a combustion analysis indicating the molecular
formula \( \text{C}_{10}\text{H}_{10}\text{N}_{4}\text{O}_{3}\text{S} \). This was confirmed by the presence of a parent ion at m/z 266 in its mass spectrum. The compound showed i.r. absorption attributable to a primary amino group and an alcoholic hydroxyl group the presence of which as a hydroxymethyl substituent was indicated by the compound's \( ^1\text{H} \) n.m.r. spectrum. This contained an exchangeable one-proton triplet and a two-proton doublet which collapsed to a singlet on exchange, assignable to the hydroxyl and methylene protons respectively of a hydroxymethyl substituent. On the basis of this spectroscopic evidence and the compound's analytical and mass spectral data it is assigned the 3-hydroxymethyl-1, 2, 4-triazine structure (292). This product was also isolated in somewhat lower yield (32%) when the triazolotriazine carboxylic acid sodium salt (289) was heated under reflux in aqueous 1,4-dioxane, and its formation from the latter can be viewed as yet another example of the hydrolytic triazole scission well known\(^{41-43}\) for other bridgehead-fused 1,2,3-triazole derivatives. Acid-catalysed triazole scission (Scheme 76) of the carboxylic acid sodium salt (289) or of the free carboxylic acid (290) also occurred on heating under reflux in glacial acetic acid. However the product formed in essentially quantitative yield in both cases analysed correctly and had mass, i.r. and \( ^1\text{H} \) n.m.r. spectral properties allowing its formulation as the tautomeric acetoxymethyltriazine derivative \([ (293) \rightleftharpoons (294) ] \). This product is obviously derived from the carboxylic acid (290) or its sodium salt
(i) NaNHNCN, 1,4-dioxane, H₂O, room temp.

(ii) 2M HCl, H₂O, room temp.

(iii) MeOH, Me₂NCH=O, heat.

Scheme 77
(289) by acid-catalysed triazole scission with concomitant hydrolytic replacement of the benzenesulphonyl substituent. The existence of the potentially tautomeric acetoxyethyltriazine derivative [(293) ⇌ (294)] predominantly in the triazinone tautomeric form (294) is indicated by absorption at 3250 - 2500 and 1670 cm⁻¹ in its i.r. spectrum assignable to the amino and carbonyl components respectively of a lactam structure. The carboxylic acid (290) and its sodium salt (289) also underwent more orthodox triazole scission on heating with acetyl chloride in glacial acetic acid. Under these conditions the same product was formed in moderate yield and had analytical and spectroscopic properties allowing its formulation as the chloromethyltriazine derivative (295) expected by analogy with similar triazole scission reactions of other bridgehead-fused 1,2,3-triazole derivatives.

Since the carboxylic acid sodium salt (289) was the most readily available of the three aminobenzenesulphonyl-triazolotriazines (289), (290) and (291), effort was devoted to its annulation with sodium cyanamide (Scheme 77) to give the aminotriazoloimidazotriazine carboxylic acid (296) which it was hoped would undergo simultaneous decarboxylation and acid-catalysed triazole scission to afford the corresponding aminimidazo[4,5-e]-1,2,4-triazine derivatives [see Scheme 70; (268; R¹=H, R²=NH₂, X=OH, OAc, Cl)]. In practice the carboxylic acid sodium salt (289) reacted readily with
sodium cyanamide in aqueous dioxane at room temperature to afford a moderate yield (58\%) of a product which analysed correctly for a monohydrate of the disodium salt structure (297). The spectroscopic properties of the product were also in accord with this structure. In particular the compound showed i.r. cyano absorption thus excluding the disodium salt of the expected aminotriazoloimidazotriazine carboxylic acid (296) as an alternative structure. Surprisingly, treatment of the disodium salt (297) with dilute aqueous hydrochloric acid afforded a compound tentatively identified as the monosodium salt (298). This structure assignment is based on the compound's i.r. cyano absorption and its decarboxylation on attempted purification by crystallisation from methanol-dimethylformamide to give the (N-cyano)aminotriazolotriazine sodium salt (299). The latter compound analysed correctly as a dihydrate and showed spectroscopic properties supporting its assigned structure. The failure of any one of the (N-cyano)amino sodium salts (298) or (299) to undergo spontaneous cyclisation to the corresponding aminotriazoloimidazotriazine is both surprising and disappointing. Unfortunately lack of time prevented the further investigation of the unexpected stability of the salts (297) - (299) towards formation of the respective aminotriazoloimidazotriazine derivatives, the successful synthesis of which will require further detailed studies.
(i) MeCOCH₂COPh, NaH, DMF, room temp.
(ii) EtO₂CCH₂CO₂Et, NaH, DMF, room temp.
(iii) AcOH, heat,
(iv) MeO₂CCH₂CN, NaH, DMF, room temp.
(v) 2M HCl, H₂O, room temp.

Scheme 78
4.3 Investigations of the Reactivity of 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine Derivatives en Route to Pyrrolo[2,3-e]-1,2,4-triazine Derivatives

As already outlined in general (see Scheme 70) it was anticipated that appropriate aminobenzenesulphonyltriazolotriazine derivatives (262) would react with stabilised carbanions with nucleophilic displacement of the benzenesulphonyl moiety to afford products (264) set up for cyclisation to 1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine derivatives (266) and (267). It was further anticipated that the latter heterocycles would be convertible, either directly or after further manipulation by acid-catalysed triazole scission into the corresponding pyrrolo[2,3-e]-1,2,4-triazine derivatives (269) and (270). This novel and potentially general route to such previously undescribed 6-aza-7-deazapurine derivatives was initially investigated (Scheme 78) using the now readily available aminobenzenesulphonyltriazolotriazine ester (274) as starting material.

In an initial model study (Scheme 78) it was found that reaction of the triazolotriazine derivative (274) with one equivalent of the sodium salt of benzoylaceton in dimethylformamide at room temperature gave a moderate yield (38%) of the expected triazolopyrrolotriazine derivative (303). This compound analysed correctly for a monohydrate
and gave mass, i.r. and $^1$H n.m.r. spectra fully in accord with its assigned structure. In particular its formation as the 7-benzoyl-6-methyl isomer (303) rather than the alternative 7-acetyl-6-phenyl structure is based on the presence in the i.r. spectrum of low frequency carbonyl absorption at 1670 cm$^{-1}$ assignable to a benzoyl group rather than an acetyl group.

The aminobenzenesulphonyltriazolotriazine derivative (274) also reacted with one equivalent of the sodium salt of diethyl malonate in dimethylformamide at room temperature to afford a moderate yield of an isolable sodium salt which analysed correctly for a monohydrate of the triazolopyrrolotriazine structure (305). This structure was verified by the compound's mass, i.r. and $^1$H n.m.r. spectra and by its conversion on acidification into the free triazolopyrrolotriazine derivative (307). This compound gave accurate mass data and showed i.r. and $^1$H n.m.r. absorption entirely consistent with its assigned structure. The formation of the triazolopyrrolotriazine products (303) and (307) in the reactions of the aminobenzenesulphonyltriazolotriazine ester (274) with sodio benzoylacetone and sodio diethyl malonate presumably involves the intermediacy of the carbanion salts (300) and (302). Since the conjugate acids derived from these are predictably stronger acids than benzoylacetone or diethyl malonate, formation of the carbanion salts (300) and (302) will be at the expense of protonation of sodio benzoylacetone or sodio diethyl malonate i.e. these reagents
(i) MeO\(_2\)CH\(_2\)CN, NaH, 1,4-dioxane, room temp.

(ii) 2M HCl, H\(_2\)O, room temp.

(iii) Me\(_2\)NCH=O, toluene, heat.

(iv) AcOH, reflux.

Scheme 79
will be inactivated due to protonation by the conjugate acids of the initial reaction products (300) and (302). As a consequence the use of stoichiometric amounts of the aminobenzenesulphonyltriazolotriazine ester (274) and sodio benzoylacetone or sodio diethyl malonate will lead to low yields of the final products (303) and (307) as observed. In accord with this reasoning, reaction of the aminobenzenesulphonyltriazolotriazine ester (274) with two equivalents of sodio diethyl malonate in dimethylformamide at room temperature raised the yield of the triazolopyrrolotriazine sodium salt (305) to 94%. A similarly enhanced yield of product was also obtained in the reaction of aminobenzenesulphonyltriazolotriazine ester (274) with two equivalents of sodio methyl cyanoacetate in dimethylformamide at room temperature. However, the product isolated in high yield (87%) under these conditions showed i.r. cyano absorption and is therefore assigned the carbanion salt structure (301) on this basis and its cyclisation on acidification to the aminotriazolopyrrolotriazine derivative (306). The structure of this compound follows from its combustion analysis and its mass, i.r. and $^1$H n.m.r. spectra.

Having demonstrated the readiness with which stabilised carbanion salts react with the aminobenzenesulphonyltriazolotriazine ester (274) to afford the corresponding triazolopyrrolotriazine derivatives [i.e. (303), (306) and (307)] attention was next turned (Scheme 79) to the
aminobenzenesulphonyltriazolotriazine carboxylic acid sodium salt (289) as a starting material in this type of transformation. The expectation was that the resulting triazolopyrrolotriazine carboxylic acid products would be amenable to acid-catalysed triazole scission to the corresponding pyrrolo[2,3-e]-1,2,4-triazine derivatives. It was found that the triazolotriazine carboxylic acid sodium salt (289) reacted as a suspension with sodio methyl cyanoacetate in 1,4-dioxane at room temperature to afford the triazolopyrrolotriazine carboxylic acid disodium salt (308) in excellent yield (90%). This compound analysed as a pentahydrate and though having a featureless i.r. spectrum showed $^1$H n.m.r. absorption consistent with its structure. Acidification of the disodium salt afforded the parent carboxylic acid (310) which showed i.r. absorption in accord with its structure but underwent decarboxylation on attempted crystallisation to give the parent aminotriazolopyrrolotriazine exter (309). This compound gave accurate mass data and showed i.r. and $^1$H n.m.r. data which substantiate its structure. As expected, heating the aminotriazolopyrrolotriazine carboxylic acid (310) in glacial acetic acid resulted in its smooth decarboxylation and acid-catalysed triazole scission to afford the acetoxymethylpyrrolo[2,3-e]-1,2,4-triazine derivative (311) in excellent yield (98%). The structure of this product was fully substantiated by accurate mass data and by its i.r. and $^1$H n.m.r. absorption. The efficient formation of the
compound (311) demonstrates the utility of the acid-
catalysed triazole scission of triazolopyrrolothiazine
derivatives such as (310) for the synthesis of pyrrolo[2,3-
e]-1,2,4-triazine derivatives such as (311). However,
future, more extensive studies will be needed in order to
demonstrate the general applicability of this new synthetic
approach to pyrrolo[2,3-e]-1,2,4-triazine derivatives.
4.4 Experimental

**Benzenesulphonylacetonitrile (271)**

Benzenesulphonylacetonitrile was prepared (yield 85%) by the reaction of benzenesulphonic acid sodium salt with chloroacetonitrile as described by Troger and Hille and had m.p. 110 - 113° (lit. 114°).

**Methyl 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274)**

(a) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate (133) (0.57 g, 0.004 mol) in 2M aqueous nitric acid (8.0 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (0.30 g, 0.0044 mol) in water (5.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with stirring with a suspension of benzenesulphonylacetonitrile (271) (0.72 g, 0.004 mol) and sodium acetate (2.3 g, 0.028 mol) in methanol (12.0 ml) and water (6.0 ml) and the mixture stirred in the melting ice bath for 2 h.

The mixture was filtered and the yellow solid was washed with water and ethyl acetate and combined with further material obtained by concentrating the original mother liquor to remove the methanol to afford methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (1.2 g; 87%), which formed yellow needles, m.p. 231 - 233° (decomp.) (from
dimethylformamide-water), $\nu_{\text{max}}$ 3450 and 3200 - 2500 br (NH), 1700 (CO) and 1635 (C=N) cm$^{-1}$, $\delta_H [(\text{CD}_3)_2\text{SO}]$ 8.23 - 8.11 (2H, m, ArH), 7.92 - 7.74 (3H, m, ArH) and 3.83 (3H, s, CH$_3$).

**Found:** C, 43.3; H, 2.9; N, 25.4%; m/z (FAB ms) 257 [(M+H)$^+$-C$_6$H$_6$].

C$_{12}$H$_{10}$N$_6$O$_4$S requires: C, 43.1; H, 3.0; N, 25.2%; M, 334.

Extraction of the aqueous mother liquor with ethyl acetate before and after acidification with 2M aqueous hydrochloric acid yielded no further material.

(b) A suspension of methyl 5-amino-1H-1,2,3-triazole-4-carboxylate hydrochloride (134) (14.2 g, 0.08 mol) in 2M aqueous nitric acid (160 ml) was stirred treated at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (6.1 g, 0.088 mol) in water (20.0 ml). The mixture was stirred at 0 - 5° for 15 min then treated with stirring with a suspension of benzenesulphonylacetonitrile (271) (14.5 g, 0.08 mol) and sodium acetate (45.9 g, 0.56 mol) in methanol (240 ml) and water (120 ml) and the mixture stirred in the melting ice bath for 2 h.

Filtration gave a yellow solid which was washed with water and ethyl acetate and combined with further material which precipitated from the aqueous methanolic mother liquor on standing to yield methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (22.7 g; 85%) m.p. 226 - 228°, identical (m.p. and i.r.
spectrum) to a sample prepared in (a) before.

Evaporation of the original aqueous methanolic mother liquor, treatment of the residue with water and extraction with methylene chloride yielded no further identifiable material.

**Methyl 5,6-Diamino-1,2,3-triazolo[1,5-b]1,2,4-triazine-3-carboxylate (275a)**

Methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (3.3 g, 0.01 mol) was added in portions with stirring to liquid ammonia (250 ml) at -78° (acetone-solid CO₂ bath).

The mixture was allowed to evaporate at room temperature overnight and the solid residue was treated with water (70.0 ml) to yield an orange solid which was washed with warm methanol to give methyl 5,6-diamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275a) (1.9 g; 87%), as tan crystals, m.p. 275 - 278° (decomp.) (from dimethylformamide-water) ν max 3450, 3400, 3340 br and 3220 - 3170 br (NH), 1705 (CO) and 1640 br (C=N) cm⁻¹, δ_H [(CD₃)₂SO] 8.04 (2H, brs, NH₂), 7.26 (2H, brs, NH₂) and 3.79 (3H, s, CH₃).

**Found:** C, 34.1; H, 3.0; N, 44.7%; m/z (FAB ms), 210.0739 [(M+H)⁺].

**C₆H₇N₇O₂ requires:** C, 34.4; H, 3.3; N, 46.9%; (M+H)⁺, 210.0739.

Further workup of the aqueous mother liquor afforded no other identifiable material.
Methyl 5-Amino-6-methylamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275b)

A suspension of methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (0.67 g, 0.002 mol) in anhydrous dioxane (25.0 ml) was stirred and treated in one portion with a 33% w/v solution of methylamine in ethanol (0.12 g, 0.004 mol) and the mixture was stirred at room temperature for 1 h.

The mixture was evaporated and the residue was treated with water (10.0 ml) and the insoluble solid collected to afford methyl 5-amino-6-methylamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275b) (0.38 g; 84%), which formed colourless needles of the monohydrate, m.p. 271 - 273° (decomp.) (from toluene-dimethylformamide) \( \nu_{\text{max}} \) 3370, 3310, 3250 and 3200 (NH), 1735 (CO) and 1665 (C=N) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\))\(_2\)SO] 8.05 (2H, brs, NH\(_2\)), 7.52 (1H, s, NH), 3.79 (3H, s, CH\(_3\)) and 2.92 (3H, s, CH\(_3\)).

Found: C, 34.8; H, 4.4; N, 40.5%; m/z (EI ms), 223 (M\(^+\)-H\(_2\)O).

\( \text{C}_7\text{H}_9\text{N}_7\text{O}_2\cdot\text{H}_2\text{O} \) requires: C, 34.8; H, 4.6; N, 40.7%; M, 241.

Extraction of the aqueous mother liquor with methylene chloride gave no further identifiable material.
Methyl 5-Amino-6-benzylamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275c)

A suspension of methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (0.67 g, 0.002 mol) in anhydrous dioxane (25.0 ml) was stirred and heated in one portion with benzylamine (0.43 g, 0.004 mol) and the mixture stirred at room temperature for 22 h.

The mixture was evaporated and the residual oil was treated with water (10.0 ml) and methanol (10.0 ml) and the insoluble yellow solid collected and combined with further material obtained by acidifying the aqueous mother liquor with 2M aqueous hydrochloric acid to afford methyl 5-amino-6-benzylamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275c) (0.43 g; 70%), which formed tan prisms of a monohydrate, m.p. 246 - 248° (from glacial acetic acid), $\nu_{\text{max}}$ 3440, 3380 and 3280 (NH), 1690 br (CO) and 1660 (C=N) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 8.20 (2H, brs, NH$_2$) (exch.), 7.88 (1H, t, J5Hz, NH) (exch.), 7.45 - 7.30 (5H, m, ArH), 4.59 (2H, d, J5Hz, CH$_2$) (collapses to singlet on exch.) and 3.79 (3H, s, CH$_3$).

Found: C, 49.3; H, 4.7; N, 30.9%; m/z (EI ms) 299 (M$^+$-H$_2$O).

C$_{13}$H$_{13}$N$_7$O$_2$ requires: C, 49.2; H, 4.8; N, 30.9%; M, 317.

Extraction of the aqueous mother liquor with methylene chloride gave no further identifiable material.
The Attempted Annulation of Methyl 5,6-Diamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275a) with Glacial Acetic Acid

A suspension of methyl 5,6-diamino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (275a) (0.42 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 0.5 h.

The mixture was cooled and filtered to afford the unreacted triazolotriazine derivative (0.38 g; 90%), m.p. 274 - 277° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Evaporation of the original glacial acetic acid mother liquor yielded no further identifiable material.

Methyl 5-Amino-6-hydrazino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (277)

A suspension of methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (1.3 g, 0.004 mol) in anhydrous 1,4-dioxane (20.0 ml) was stirred and treated with a single portion of 100% hydrazine monohydrate (0.80 g, 0.016 mol) and the mixture was stirred at room temperature for 75 min.

The mixture was evaporated and the orange residue was treated with water (20.0 ml) and the insoluble solid collected to afford methyl 5-amino-6-hydrazino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (277) (0.78 g;
which formed orange crystals of the monohydrate, m.p. 187 - 189° (from methanol-water), $\nu_{\max}$ 3570, 3450, 3300, 3200 and 3160 (NH), 1715 (CO) and 1655 (C=N) cm$^{-1}$, 
$\delta_H$ [(CD$_3$)$_2$SO] 8.70 (1H, brs, NH), 8.00 (2H, brs, NH), 4.70 (2H, brs, NH) and 3.79 (3H, s, CH$_3$).

**Found:** C, 29.7; H, 4.0; N, 46.4%; m/z (EI ms), 224 (M$^+$$\cdot$H$_2$O).

**C$_6$H$_8$N$_8$O$_2$·H$_2$O requires:** C, 29.8; H, 4.1; N, 46.3%; M, 242.

Further workup of the aqueous mother liquor yielded no other identifiable material.

**Methyl 5-Amino-6-azido-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (278)**

(a) A suspension of methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (0.67 g, 0.002 mol) in 1,4-dioxane (40.0 ml) was stirred and treated in one portion with a solution of sodium azide (0.52 g, 0.008 mol) in water (2.0 ml) and the mixture was stirred at room temperature for 1 h.

The mixture was filtered to give methyl 5-amino-6-azido-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (278) (0.40 g; 85%), which formed yellow prisms, m.p. 230 - 233° (decomp.) (from dimethylformamide - water), $\nu_{\max}$ 3320 br and 3180 br (NH), 2150 (N=N), 1715 br (CO) and 1650 br (C=N) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 9.42 (1H, s, NH), 9.14 (1H, s, NH) and 3.80 (3H, s, CH$_3$).

**Found:** C, 30.6; H, 2.0; N, 53.9%; m/z (EI ms), 235 (M$^+$).

**C$_6$H$_5$N$_9$O$_2$ requires:** C, 30.6; H, 2.1; N, 53.6%; M, 235.
Evaporation of the original aqueous dioxane mother liquor, treatment of the residue with water and extraction with methylene chloride yielded no other identifiable material.

(b) A suspension of methyl 5-amino-6-hydrazino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (277) (0.45 g, 0.002 mol) in concentrated nitric acid (S.Gr. 1.42) (0.4 ml) and water (1.5 ml) was stirred and treated dropwise at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (0.12 g, 0.004 mol) in water (9.0 ml) and the mixture was stirred at 0 - 5° for 15 min.

Filtration afforded a brown solid which was washed with water followed by anhydrous ethanol to yield methyl 5-amino-6-azido-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (278) (0.34 g; 72%), m.p. 207° (decomp.), identified by comparison (m.p., i.r. spectrum and t.l.c. in ethyl acetate over silica) with a sample prepared in (a) before.

Extraction of the original filtrate with methylene chloride afforded no further material.

Methyl 5-Amino-6-triphenylphosphinimino-1,2,3-triazolo-[1,5-b]-1,2,4-triazine-3-carboxylate (279)

A solution of the azidotriazolotriazine (278) (0.47 g, 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was
stirred and treated in one portion with a solution of triphenylphosphine (0.52 g, 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 0.5 h and then at 60° (oil bath) for a further 1 h.

Evaporation of the mixture afforded methyl 5-amino-6-triphenylphosphinimino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (279) (0.90 g; 96%), which formed colourless crystals, m.p. 284 - 285° (from glacial acetic acid), $\nu_{\text{max}}$ 3470 and 3180 br (NH), 1720 (CO) and 1640 (C=N) cm$^{-1}$, $\delta_H[(\text{CD}_3)_2\text{SO}]$ 8.50 (1H, brs, NH) (exch.), 8.01 - 7.55 (16H, m, ArH and NH) and 3.77 (3H, s, CH$_3$).

Found: C, 61.2; H, 4.3; N, 20.9%; m/z (FAB ms), 470 [(M+H)$^+$].

C$_{24}$H$_{20}$N$_7$O$_2$P requires: C, 61.4; H, 4.3; N, 20.9%; M, 469.

**Attempted Base-catalysed Reaction of Methyl 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) with Ethyl Carbamate**

A suspension of sodium hydride (0.048 g, 0.002 mol) in anhydrous dimethylformamide (5.0 ml) was stirred at room temperature and treated in one portion with a solution of ethyl carbamate (0.20 g, 0.0022 mol) in anhydrous dimethylformamide (2.0 ml). The mixture was stirred at room temperature with the exclusion of atmospheric moisture for 10 min, then treated in one portion with a suspension of the triazolotriazine derivative (274) (0.67 g, 0.002 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture
stirred at room temperature for 19 h.

Evaporation of the mixture gave a red oil which was treated with water (5.0 ml) and extracted with methylene chloride, to afford no material.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid yielded a brown solid (0.19 g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which therefore was not further investigated.

Constant extraction of the aqueous mother liquor with methylene chloride afforded no identifiable material.

**Methyl 6-Amino-5H-1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine-3-carboxylate (286)**

A suspension of the triazolotriazine derivative (274) (2.0 g, 0.006 mol) in dioxane (30.0 ml) was treated with a solution of sodium cyanamide (1.5 g, 0.024 mol) in water (5.0 ml) and the mixture was stirred at room temperature for 2.5 h.

The mixture was filtered and the solid was washed with water (25.0 ml) to afford a product tentatively identified as the sodium salt of methyl 5-amino-6-(N-cyano)amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (283) (1.7 g; quant.), m.p. > 300°, $\nu_{\text{max}}$ 3600, 3470 and 3150 br (NH), 2170 (C=O), 1735 (CO) and 1650 (C=N) cm⁻¹, which was converted by crystallisation from dimethyl sulphoxide - water into yellow
needles of the trihydrate of the sodium salt of methyl 6-amino-5H-1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine-3-carboxylate (285), m.p. 269 - 272° (decomp.), $\nu_{\text{max}}$ 3510, 3390, 3240 and 3150 br, 1690 (CO) and 1670 (C=N) cm$^{-1}$, $\delta_H [(CD_3)_2SO]$ 7.52 (2H, brs, NH) and 3.83 (3H, s, CH$_3$).

Found: C, 27.2; H, 3.6; N, 36.7%; m/z (FAB ms), 257 (M$^+$-3H$_2$O).

C$_7$H$_6$N$_8$O$_2$Na.3H$_2$O requires: C, 27.1; H, 3.5; N, 36.1%; M, 311.

The sodium salt of methyl 6-amino-5H-1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine-3-carboxylate (285) (0.30 g, 0.001 mol) was dissolved in warm water (5.0 ml) and the resulting solution was acidified with 2M aqueous hydrochloric acid and the solid collected to yield methyl 6-amino-5H-1,2,3-triazolo[1,5-b]imidazo[4,5-e]-1,2,4-triazine-3-carboxylate (286) (0.22 g; 94%), which formed colourless crystals, m.p. 266 - 268° (decomp.) (from dimethylformamide - water), $\nu_{\text{max}}$ 3300 - 2500 br (NH) and 1700 br (CO) cm$^{-1}$, $\delta_H [(CD_3)_2SO]$ 8.67 (3H, brs, NH) and 3.87 (3H, s, CH$_3$).

Found: C, 35.8; H, 2.7; N, 47.6%; m/z (FAB ms), 235 [(M+H$^+$)].

C$_7$H$_6$N$_8$O$_2$ requires: C, 35.9; H, 2.6; N, 47.9%; M, 234.

5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (290) and its Sodium Salt (289)

(a) A suspension of 5-amino-1H-1,2,3-triazole-4-carboxylic acid (119) (5.1 g, 0.04 mol) in 2M aqueous nitric acid (80.0 ml) was stirred at 0 - 5° (ice-salt bath) and
treated dropwise with a solution of sodium nitrite (3.0 g, 0.044 mol) in water (5.0 ml). The mixture was stirred at 0 \(-5^\circ\) for 15 min then treated in one portion with a suspension of benzenesulphonylacetonitrile (271) (7.2 g, 0.04 mol) and sodium acetate (23.0 g, 0.28 mol) in methanol (120 ml) and water (60.0 ml) and the mixture stirred in the melting ice bath for 3 h.

The mixture was concentrated to remove the methanol and the yellow solid which precipitated was collected to give the sodium salt of 5-amino-6-benzenesulphonyl-1,2,3-triazolo-[1,5-b]-1,2,4-triazine-3-carboxylic acid (289) (9.3 g; 38%), \(\nu_{\text{max}}\) 3300 br (NH) and 1625 (CO) cm\(^{-1}\). This salt was slurried with 2M aqueous hydrochloric acid to afford 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (290) (8.5 g; 66%), m.p. 125 - 128° (gas evolution), \(\nu_{\text{max}}\) 3420 and 3300 (NH), 3160 - 2500 br (OH), 1685 (CO) and 1640 (C=N) cm\(^{-1}\) which underwent decarboxylation on attempted purification by crystallisation.

The original aqueous methanolic mother liquor was extracted with ethyl acetate to give a yellow solid which was washed with toluene to afford unreacted benzenesulphonylacetonitrile (271) (1.6 g; 22%), m.p. 110 - 113°, identical (m.p. and i.r. spectrum) with an authentic sample prepared before.
(b) A solution of 4-carboxy-1H-1,2,3-triazole-5-diazonium betaine (120) (1.4 g, 0.01 mol) in methanol (15.0 ml) and water (15.0 ml) was added dropwise at 0 - 5°C (ice-salt bath) to a stirred suspension of benzenesulphonyl-acetonitrile (271) (1.8 g, 0.01 mol) and sodium acetate (1.6 g, 0.02 mol) in methanol (20.0 ml) and water (10.0 ml) and the mixture was stirred in the melting ice bath for 2h.

The mixture was filtered and the yellow gummy solid obtained was slurried with 2M aqueous hydrochloric acid to yield 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (290) (1.1 g; 35%), m.p. 135 - 137°C, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared in (a) before.

A solid which precipitated from the original aqueous methanolic filtrate on standing was collected to afford the sodium salt of 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (289) (0.47 g; 14%), identified by comparison (i.r. spectrum) with an authentic sample prepared in (a) before.

The original aqueous methanolic mother liquor was concentrated to remove the methanol and extracted with ethyl acetate to give unreacted benzenesulphonylacetonitrile (0.03 g; 2%), m.p. 110 - 113°C, identical (m.p. and i.r. spectrum) with an authentic sample prepared before.
5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (291)

(a) A solution of 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (290) (0.64 g, 0.002 mol) in anhydrous dioxane (5.0 ml) was heated under reflux for 10 min.

Evaporation of the mixture gave an orange solid residue which was washed with methylene chloride to afford 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (291) (0.09 g; 16%), which formed orange crystals, m.p. 135 - 137° (from toluene), $\nu_{\text{max}}$ 3460 and 3360 (NH) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 8.23 - 7.65 (8H, m, ArH, CH and NH).

Found: C,43.8; H,2.7; N,29.4%; m/z (EI ms) 276.0431 (M$^+$).
C$_{10}$H$_8$N$_6$O$_2$S requires: C,43.5; H,2.9; N,30.4%; M, 276.0429.

Evaporation of the methylene chloride mother liquor afforded a black, intractable gum (0.40 g) which was not further investigated.

5-Amino-6-benzenesulphonyl-3-hydroxymethyl-1,2,4-triazine (292)

(a) A solution of the sodium salt of 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (289) (1.4 g, 0.004 mol) in dimethylformamide (10.0 ml) and water (5.0 ml) was heated under reflux for 2 h.

Evaporation of the mixture gave a brown oil which was
treated with water (10.0 ml) to afford an orange solid which was washed with methanol to give a solid which was combined with further material obtained by evaporation of the combined methanolic and aqueous mother liquors and retrituration of the resulting residue with methylene chloride - methanol to afford 5-amino-6-benzenesulphonyl-3-hydroxymethyl-1,2,4-triazine (292) (0.34 g; 32%), which formed colourless needles, m.p. 85 - 88° (from water), $\nu_{\text{max}}$ 3440, 3330 br and 3140 br (NH and OH) and 1620 (C=N) cm$^{-1}$, $\delta_{\text{H}}$ [(CD$_3$)$_2$SO] 8.73 (1H, brs, NH), 8.17 - 8.01 (2H, m, ArH), 7.83 - 7.56 (4H, m, ArH, NH), 5.36 (1H, t, J5Hz, OH) (exch.) and 4.50 (2H, d, J5Hz, CH$_2$) (collapses to singlet on exch.).

Found: C, 45.4; H, 4.0; N, 21.2%; M$^+$, 266.

C$_{10}$H$_{10}$N$_4$O$_3$S requires: C, 45.1; H, 3.8; N, 21.1%; M, 266.

Evaporation of the methylene chloride - methanol mother liquor gave a red gum (0.45 g), whose t.l.c. in ethyl acetate over silica showed it to be a complex multicomponent mixture which was not further investigated.

(b) A solution of the sodium salt of 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (289) (1.4 g, 0.004 mol) in water (30.0 ml) was heated under reflux for 1 h.

The mixture was cooled to give a tan solid which was combined with further solid material obtained by extraction of the aqueous mother liquor with methylene chloride and
then with ethyl acetate before and after acidification with 2M hydrochloric acid to afford 5-amino-6-benzenesulphonyl-
3-hydroxymethyl-1,2,4-triazine (292) (0.54 g; 50%), m.p. 85 - 88°, identified by comparison (m.p. and i.r. spectrum)
with an authentic sample prepared in (a) before.

3-Acetoxyethyl-5-amino-6-hydroxy-1,2,4-triazine (293)

(a) A solution of 5-amino-6-benzenesulphonyl-1,2,3-
triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (290) (0.64
g, 0.002 mol) in glacial acetic acid (5.0 ml) was heated
under reflux for 3 h.

The mixture was hot filtered to give a solid which was
combined with further material obtained by evaporation of
the acetic acid filtrate and trituration of the residue with
water to afford 3-acetoxyethyl-5-amino-6-hydroxy-1,2,4-
triazine (293) (0.40 g; quant.), which formed tan plates,
m.p. 277 - 279° (from dimethylformamide - water), ᴜ max 3380
and 3250 - 2500 (NH, OH), 1740 and 1670 (CO) and 1635 (C=N)
cm⁻¹, δH [(CD₃)₂SO] 12.52 (1H, s, NH or OH) (exch.), 8.10
(1H, brs, NH) (exch.), 7.76 (1H, brs, NH) (exch.), 4.72 (2H,
s, CH₂) and 2.05 (3H, s, CH₃).

Found: C,39.5; H,4.2; N,30.7%; m/z (EI ms), 184, (M⁺).
C₆H₈N₄O₃ requires: C,39.1; H,4.3; N,30.4%; M, 184.

(b) A solution of the sodium salt of 5-amino-6-
benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-
carboxylic acid (289) (0.68 g, 0.002 mol) in glacial acetic
acid (15.0 ml) was heated under reflux for 2 h.

Evaporation of the mixture gave a yellow, solid residue which was treated with water (8.0 ml) and the insoluble solid collected to afford 3-acetoxymethyl-5-amino-6-hydroxy-1,2,4-triazine (293) (0.34 g; 92%), m.p. 268 - 271°C, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

5-Amino-6-benzenesulphonyl-3-chloromethyl-1,2,4-triazine (295)

(a) A suspension of the sodium salt of 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (289) (1.4 g, 0.004 mol) in glacial acetic acid (6.0 ml) was heated under reflux for 3 h.

The mixture was hot filtered to afford a cream solid which was slurried with 10% w/v aqueous sodium hydrogen carbonate to yield 5-amino-6-benzenesulphonyl-3-chloromethyl-1,2,4-triazine (295) (0.72 g; 63%), which formed yellow needles, m.p. 127 - 129°C (from toluene), ν max 3410, 3300 and 3150 br (NH) and 1640 (C=N) cm⁻¹, δH[(CD₃)₂SO] 8.97 (2H, brs, NH), 8.15 - 8.00 (2H, m, ArH), 7.84 - 7.65 (3H, m, ArH) and (2H, s, CH₂).

Found: C, 42.4; H, 3.1; N, 19.6%; m/z (EI ms), 286 and 284 (M⁺).

C₁₀H₉ClN₄O₂S requires: C, 42.2; H, 3.2; N, 19.7%; M, 286 and 284.

Evaporation of the acetic acid - acetyl chloride mother liquor gave a red oil (0.57 g) which was slurried with 10%
w/v aqueous sodium bicarbonate to afford only a small amount of brown solid (0.09 g) whose i.r. spectrum was featureless. The solid was not further investigated.

Acidification of the sodium hydrogen carbonate mother liquors with 2M aqueous hydrochloric acid and extraction with ethyl acetate yielded no further material.

(b) A suspension of 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (290) (0.64 g, 0.002 mol) in glacial acetic acid (5.0 ml) and acetyl chloride (15.0 ml) was heated under reflux for 3 h.

The mixture was hot filtered to give a cream solid which was slurried with 10% w/v aqueous sodium hydrogen carbonate to afford 5-amino-6-benzenesulphonyl-3-chloromethyl-1,2,4-triazine (295) (0.30 g; 53%), m.p. 125-128°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The acetic acid - acetyl chloride mother liquor was evaporated to give an intractable red oil (0.23 g) whose t.l.c. in ether over silica showed it to be a complex mixture which, therefore, was not further investigated.

The Reaction of the Sodium Salt of 5-Amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic Acid (289) with Sodium Cyanamide

A suspension of the triazolotriazine carboxylic acid
sodium salt (289) (1.7 g, 0.005 mol) in dioxane (25.0 ml) was treated in one portion with a solution of sodium cyanamide (1.3 g, 0.02 mol) in water (5.0 ml) and the mixture was stirred at room temperature for 3 h.

Filtration gave a tan solid which was treated with water (40.0 ml), recollected, and combined with further material which had precipitated from the aqueous filtrate on standing to afford the disodium salt of 5-amino-6-(N-cyano)amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (297) (0.82 g; 58%), which formed yellow needles of a monohydrate, m.p. > 315° (from water), $\nu_{\text{max}}$ 3515, 3370 and 3200 - 2500 br (NH), 2180 (C=O), 1670 (CO) and 1640 (C=N) cm$^{-1}$, $\delta_{\text{H}} [(\text{CD}_{3})_{2}\text{SO}]$ 9.0 (1H, brs, NH) and 6.90 (1H, brs, NH).

Found: C,25.4; H,1.4; N,39.7%; m/z (FAB ms), 265 [(M+H)$^+$-H$_2$O].

requires: C,25.5; H,1.4; N,39.7%; M, 282.

The triazolotriazine disodium salt (297) (0.65 g, 0.002 mol) was slurried with 2M aqueous hydrochloric acid and the colourless solid was collected to give the monosodium salt of 5-amino-6-(N-cyano)amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylic acid (298) (0.48 g; quant.), m.p. > 300°, $\nu_{\text{max}}$ 3500 br, 3400, 3310 and 3250 - 2500 br (NH), 2190 (C=O) and 1690 (C=N) cm$^{-1}$, which on attempted crystallisation from dimethylformamide - methanol was converted into the monosodium salt of 5-amino-6-(N-cyano)amino-1,2,3-triazolo[1,5-b]-1,2,4-triazine (299) isolated as a dihydrate, m.p. > 315° (from toluene -
methanol), $\nu_{\text{max}}$ 3500 br, 3300 br and 3150 br (NH) and 2160 (C=\text{N}) cm$^{-1}$, $\delta_H$ [(CD$_3$)$_2$SO] 8.10 (1H, brs, NH) (exch.), 7.28 (1H, s, CH) and 6.92 (1H, brs, NH) (exch.).

**Found:** C, 25.7; H, 2.8; N, 47.6%; m/z (FAB ms), 199.0457

$$[(\text{M+H})^{+}-2\text{H}_2\text{O}].$$

C$_5$H$_4$N$_8$Na.2H$_2$O **requires:** C, 25.6; H, 3.0; N, 47.9%;

$$[(\text{M+H})^{+}-2\text{H}_2\text{O}], 199.0457.$$  

Concentration of the original aqueous dioxane mother liquor and acidification with 2M aqueous hydrochloric acid followed by extraction with methylene chloride yielded no further identifiable material.

**Methyl 7-Benzoyl-6-methyl-5H-1,2,3-triazolo[1,5-b]pyrrolo-[2,3-e]-1,2,4-triazine-3-carboxylate (303)**

A suspension of sodium hydride (0.24 g, 0.01 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated at room temperature with a single portion of benzoylacetone (1.8 g, 0.011 mol). The mixture was stirred at room temperature with the exclusion of atmospheric moisture for 10 min, then treated in one portion with a suspension of the triazolotriazine (274) (3.3 g, 0.01 mol) in anhydrous dimethylformamide (30.0 ml) and the mixture stirred at room temperature for 2 h.

The mixture was evaporated and the red oil obtained was treated with water (25.0 ml) to afford an orange solid. This was washed with ether and combined with further
material which had precipitated from the aqueous mother liquor on standing and then stirred with 2 M aqueous hydrochloric acid. The resulting solid was combined with further material obtained by acidifying the original aqueous filtrate with 2M aqueous hydrochloric acid to afford methyl-7-benzoyl-6-methyl-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylate (303) (1.3 g; 38%) which formed yellow crystals of the monohydrate, m.p. 226 - 230° (from dimethylformamide - water), νmax 3440 (NH), 1720 and 1670 (CO) and 1655 (C=N) cm⁻¹, δH [(CD₃)₂SO] 13.85 (1H, brs, NH), 7.95 - 7.51 (5H, m, ArH), 3.94 (3H, s, CH₃), 2.88 (3H, s, CH₃).

Found: C, 54.1; H, 4.1; N, 23.5%; m/z (FAB ms), 337 [(M+H)⁺-H₂O].

C₁₆H₁₂N₆O₃.H₂O requires: C, 54.2; H, 4.0; N, 23.7%; M, 354.

Evaporation of the ethereal mother liquor gave unreacted benzoylacetone (0.83 g), m.p. 46 - 50°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the combined aqueous acidic mother liquors with methylene chloride yielded no further identifiable material.

**Methyl 7-Ethoxycarbonyl-6-hydroxy-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylate (307) and its Sodium Salt (305)**

(a) A suspension of sodium hydride (0.40 g, 0.016 mol)
in anhydrous dimethylformamide (5.0 ml) was stirred at room
temperature and treated in one portion with diethyl malonate
(2.6 g, 0.016 mol) and the mixture was stirred at room
temperature with the exclusion of atmospheric moisture for
10 min. The mixture was then treated in one portion with a
suspension of the triazolotriazine derivative (274) (2.7 g,
0.008 mol) in anhydrous dimethylformamide (20.0 ml) and the
mixture stirred at room temperature with the exclusion of
atmospheric moisture for 19 h.

The mixture was evaporated and the resulting yellow residue was treated with water (50.0 ml) and filtered to
afford a yellow solid which was combined with further
material obtained by acidification of the aqueous alkaline filtrate with 2M aqueous hydrochloric acid to yield the sodium salt of methyl 7-ethoxycarbonyl-6-hydroxy-5H-1,2,3-
triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylate
(305) (2.6 g; 94%), which formed yellow crystals of a
monohydrate, m.p. 230 - 234° (from glacial acetic acid -
dimethylformamide), \( v_{\text{max}} \) 3540 br, 3410 br, 3150 - 2500 br
(NH, OH), 1715 br (CO) and 1640 (C=N) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\)]\(_2\)SO]
11.15 (1H, s, NH or OH) (exch.), 4.15 (2H, q, J7Hz, CH\(_2\)),
3.80 (3H, s, CH\(_3\)) and 1.23 (3H, t, J7Hz, CH\(_3\)).

Found: C, 37.9; H, 3.2; N, 24.2%; m/z (FAB ms), 329 [(M+H)\(^+\)-H\(_2\)O]
C\(_{11}\)H\(_9\)N\(_6\)O\(_5\)NaH\(_2\)O requires: C, 38.1; H, 3.2; N, 24.2%; M, 346.

This compound was converted by crystallisation from
glacial acetic acid into methyl 7-ethoxycarbonyl-6-hydroxy-
5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-
carboxylate (307), orange crystals, m.p. 220 - 224° (decomp.), \( \nu_{\text{max}} \) 3200 - 2500 br (NH, OH), 1710 br (CO) and 1630 (C=N) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\))\(_2\)SO] 11.03 (1H, brs, NH), 4.10 (2H, q, J7Hz, CH\(_2\)), 3.83 (3H, s, CH\(_3\)) and 1.24 (3H, t, J7Hz, CH\(_3\)).

Found: m/z (FAB ms), 307.0791 [(M+H)]\(^+\).

**C\(_{11}\)H\(_{10}\)N\(_6\)O\(_5\) requires**: (M+H), 307.0791.

(b) A suspension of sodium hydride (0.096 g, 0.004 mol) in anhydrous dimethylformamide (5.0 ml) was stirred at room temperature and treated in one portion with diethyl malonate (0.70 g, 0.0044 mol) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 10 min. The mixture was then treated in one portion with stirring at room temperature with a suspension of the triazolotriazine derivative (274) (1.3 g, 0.004 mol) in anhydrous dimethylformamide (15.0 ml) and the mixture stirred at room temperature with exclusion of atmospheric moisture for 19 h.

Evaporation of the mixture gave an orange oil which was treated with water (20.0 ml) to give an orange solid. This was collected and combined with further solid which precipitated from the aqueous mother liquor on standing to give the sodium salt of methyl 7-ethoxycarbonyl-6-hydroxy-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylate (305) (0.52 g; 38%), m.p. 206° (decomp.),
identified by comparison (i.r. spectrum) with an authentic sample prepared in (a) before.

Further workup of the aqueous mother liquor yielded no other identifiable material.

**Dimethyl 6-Amino-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3,7-dicarboxylate (306)**

A suspension of sodium hydride (0.24 g, 0.01 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated in one portion at room temperature with methyl cyanoacetate (1.1 g, 0.011 mol) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 10 min. The mixture was then treated in one portion at room temperature with stirring with a suspension of methyl 5-amino-6-benzenesulphonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (274) (3.3 g, 0.01 mol) in anhydrous dimethylformamide (30.0 ml) in one portion and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for a further 0.5 h. Evaporation of the mixture gave a red oil which was treated with water (25.0 ml) and the yellow solid collected to afford a product tentatively identified as the sodium salt of methyl 5-amino-6-(cyano methoxycarbonylmethyl)-1,2,3-triazolo[1,5-b]-1,2,4-triazine-3-carboxylate (301) (2.7 g; 87%), m.p. 265° (decomp.) ν max 3580, 3490, 3370 and 3300 br (NH), 2200 (C=O) and 1620 br (C=N) cm⁻¹, which on treatment with 2M aqueous hydrochloric acid was converted
into dimethyl-6-amino-5H-1,2,3-triazolo[1,5-b]pyrrolo-
[2,3-e]-1,2,4-triazine-3,7-dicarboxylate (306) (2.1 g; 72%),
which formed yellow prisms, m.p. 290° (decomp.) (from
dimethyl sulfoxide - water), $\nu_{\max}$ 3400, 3300 br, 3250 and
3100 - 2500 br (NH), 1710 and 1670 br (CO) and 1640 (C=N)
cm$^{-1}$, $\delta_H [(CD_3)_2SO]$ 3.87 (3H, s, CH$_3$) and 3.82 (3H, s, CH$_3$).
Found: C, 41.5; H, 3.1; N, 33.5%; m/z (FAB ms), 292 [(M+H)$^+$].
C$_{10}$H$_9$N$_7$O$_4$ requires: C, 41.2; H, 3.1; N, 33.7%; M, 291.

Further workup of the aqueous mother liquor yielded no
other identifiable material.

6-Amino-7-methoxycarbonyl-5H-1,2,3-triazolo[1,5-b]pyrrolo-
[2,3-e]-1,2,4-triazine-3-carboxylic Acid (310) and 6-Amino-
7-methoxycarbonyl-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-
1,2,4-triazine (309)

A suspension of sodium hydride (0.38 g, 0.016 mol) in
anhydrous 1,4-dioxane (10.0 ml) was stirred and treated in
one portion at room temperature with methyl cyanoacetate
(1.6 g, 0.016 mol) and the mixture was stirred at room
temperature with the exclusion of atmospheric moisture for 10
min. The mixture was then treated with stirring with a
suspension of the triazolotriazine sodium salt (289) (2.7 g,
0.008 mol) in anhydrous 1,4-dioxane (20.0 ml) and the
mixture stirred at room temperature with the exclusion of
atmospheric moisture for 19 h.

The mixture was filtered and the insoluble solid was
collected to give the disodium salt of 6-amino-7-methoxycarbonyl-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylic acid (308) (3.0 g; 90%), which formed tan crystals of a pentahydrate, m.p. 244 - 246° (decomp.) (from water), $\nu_{\text{max}}$ featureless, $\delta_H [(CD_3)_2SO]$ 8.25 (1H, brs, NH) (exch.), 7.50 (1H, brs, NH) (exch.) and 3.73 (3H, s, CH₃).

**Found:** C, 26.3; H, 3.5; N, 23.6%; m/z (FAB ms), 323 [$(M+2H)^+\cdot5H_2O$].

$C_9H_5N_7O_4Na_2\cdot5H_2O$ requires: C, 26.3; H, 3.6; N, 23.8%; M, 411.

This solid was converted by acidification with 2M aqueous hydrochloric acid into 6-amino-7-methoxycarbonyl-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylic acid (310) (1.9 g; 86%), m.p. 245 - 250° (decomp.), $\nu_{\text{max}}$ 3310 and 3190 (NH), 3100 - 2500 br (OH, NH) and 1675 (CO) cm⁻¹ which underwent decarboxylation on attempted purification by crystallisation to afford 6-amino-7-methoxycarbonyl-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine (309), which formed cream crystals, m.p. 261 - 263° (decomp.) (from toluene - dimethylformamide), $\nu_{\text{max}}$ 3400, 3300 and 3100 - 2500 br (NH), 1690 br (CO) and 1660 (C=N) cm⁻¹, $\delta_H [(CD_3)_2SO]$ 8.36 (3H, brs, NH), 7.99 (1H, s, CH) and 3.79 (3H, s, CH₃).

**Found:** m/z (FAB ms), 234.0739 [$(M+H)^+$].

$C_8H_7N_7O_2$ requires: $(M+H)$, 234.0739.

Further workup of the original aqueous dioxane mother liquor yielded no other identifiable material.
Methyl 3-Acetoxymethyl-6-amino-5H-pyrrolo[2,3-e]-1,2,4-triazine-7-carboxylate (311)

A suspension of 6-amino-7-methoxycarbonyl-5H-1,2,3-triazolo[1,5-b]pyrrolo[2,3-e]-1,2,4-triazine-3-carboxylic acid (310) (0.55 g, 0.002 mol) in glacial acetic acid (40.0 ml) was heated under reflux for 17 h.

The mixture was evaporated to afford methyl 3-acetoxymethyl-6-amino-5H-pyrrolo[2,3-e]-1,2,4-triazine-7-carboxylate (311) as a tan solid (0.52 g; 98%), m.p. 238 - 239 ° (decomp.) (from glacial acetic acid), \( \nu_{\text{max}} \) 3400 and 3200 - 2500 br (NH), 1755 and 1690 br (CO) and 1650 br (C=N) cm\(^{-1}\), \( \delta_H \) [(CD\(_3\))]\( \text{SO} \) 8.00 (2H, brs, NH), 5.20 (2H, s, CH\(_2\)), 4.83 (1H, s, NH), 3.78 (3H, s, CH\(_3\)) and 2.11 (3H, s, CH\(_3\)).

Found: m/z (FAB ms), 266.0889 [(M+H)].

C\(_{10}\)H\(_{11}\)N\(_5\)O\(_4\) requires: (M+H), 266.0889.
General Experimental Methods

Infra-red spectra were recorded using a Perkin-Elmer 781 Spectrophotometer and bands were strong and sharp unless specified w as weak or br as broad. Solids were measured as nujol mulls and liquids as liquid films.

$^1$H n.m.r. spectra were measured in the stated solvent at 80 MHz or 200 MHz using Bruker WP-80SY and WP-200SY instruments. Signals were sharp unless specified b as broad; s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. $^{13}$C spectra were recorded at 200 MHz using a Bruker WP-200SY spectrometer and were fully decoupled. Signals were sharp and quat. = quaternary carbon atom.

Quaternary carbon atoms and methylene groups were identified by DEPT $3\pi/4$ pulse sequence spectra.

Electron impact mass spectra were recorded at 70 eV on an A.E.I MS-902 instrument. Fast atom bombardment spectra were measured on a Kratos MS-50TC instrument for matrices in glycerol - dimethylformamide.

Microanalyses were determined on a Carlo-Erba Strumentazione 1106 elemental analyser. Melting points were carried out on a Gallenkampf apparatus and are uncorrected. Melting points of analytical samples were determined using a Kofler hot-stage microscope and are uncorrected.

All reagents were laboratory grade unless specified. Sodium hydride was a 50% suspension in mineral oil and was washed with anhydrous ether before use. Solvents were of
technical grade unless otherwise stated and unless specified
light petroleum had b.p. 60 - 80°. Organic extracts were
dried over anhydrous magnesium sulphate or sodium sulphate
prior to filtration and evaporation under reduced pressure.
All yields are based on unrecovered starting material.

Chromatography was carried out over silica (Merck
7734), flash-chromatography was carried out over silica
(Merck 9385) and dry column flash-chromatography was carried
out over silica (Merck 7736). Thin layer chromatography
(t.l.c.) was carried out on Polygram SIL G/UV254 precoated
plastic sheets.

X-ray diffraction data were collected using a Stoe-
Stadi-4 four circle diffractometer on single crystals grown
from the stated crystallisation solvent.
Bibliography


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