Title: Investigations of the synthesis and reactivity of heterocycles containing a vicinal triazole nucleus

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INVESTIGATIONS OF THE SYNTHESIS AND
REACTIVITY OF HETEROCYCLES CONTAINING A
VICINAL TRIAZOLE NUCLEUS

by

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SUMMARY

A series of 1,2,3-triazolo[1,5-a]quinoxaline derivatives have been synthesised using diazo transfer reactions of toluene-$p$-sulphonyl azide with known quinoxalin-2(1H)-ones containing suitable active methylene side-chains in the 3-position. The structures of the triazoloquinoxalines have been established by stepwise degradation to known quinoxalinediones. The mechanism of the formation of the triazoloquinoxaline derivatives is discussed.

Examples of the hitherto unknown 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system have been prepared by condensing 4-phenyl-1H-1,2,3-triazole-5-diazonium chloride with active methylene compounds in the presence of sodium acetate. The structure of the triazolotriazines has been confirmed and an investigation of their triazole scission to 1,2,4-triazine derivatives in acidic media has been carried out. The potential of the 1,2,4-triazine derivatives obtained, as intermediates in azapteridine synthesis has been evaluated. The synthesis of 3-benzyl-1,2,4-triazine derivatives using known methods has also been investigated.

Possible synthetic routes to 1,2,3-triazolo-1,2,4-triazole derivatives have been studied. Methods for the preparation of suitable intermediates (5-hydroxytriazoles, 5-chlorotriazoles and 5-thiomethyltriazoles) have been investigated and a synthesis of 1-amino-5-anilino-4-phenyl-1,2,3-triazole has been devised.
Attempts to synthesise 1,2,3-triazolo[1,5-b]-1,2,4-triazole derivatives from the last compound proved unsuccessful. However, a series of 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives were successfully prepared by condensing 1-amino-5-anilino-4-phenyl-1,2,3-triazole with 1,2-dicarbonyl compounds. 4-phenyl-1H-1,2,3-triazole-5-diazonium chloride has been reduced using sulphur dioxide to the corresponding 5-hydrazinotriazole which reacts in situ with 1,2-dicarbonyl compounds to yield 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives. An attempted synthesis of a 1,2,3-triazolo[5,1-c]-1,2,4-triazole derivative from 5-hydrazino-4-phenyl-1H-1,2,3-triazole in situ was unsuccessful. Synthetic routes to 1-aminotriazoles have been investigated culminating in the preparation of 1,5-diamino-4-ethoxycarbonyl-1,2,3-triazole which has been used to prepare a series of 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives. Again, attempts to utilise 1,5-diamino-4-ethoxycarbonyl-1,2,3-triazole for the synthesis of 1,2,3-triazolo[1,5-b]-1,2,4 triazoles, were unsuccessful.
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CHAPTER 1

SOME ASPECTS OF THE CHEMISTRY OF 1,2,3-TRIAZOLES
1.1. Introduction

The energy gained by the simultaneous formation of molecular nitrogen provides the powerful driving force for the 1,2,3-triazole nucleus (1) to undergo homolytic or heterolytic ring scission to yield products by way of diradicals (4), carbenes (5), nitrenes (6), 1H-aziridines (7), or diazonium cations (3) (Scheme 1).

Furthermore, the possibility that such triazole scission is preceded by ring opening [(1) \rightarrow (2)] to the diazo tautomer (2) implies the existence of 1,2,3-triazole-diazoalkylideneamine tautomerism [(1) \rightleftharpoons (2)].

Few heterocycles containing a fused 1,2,3-triazole nucleus (1) are known and consequently the reactivity of such ring systems
has been relatively little investigated. The purpose of the present studies was to develop suitable methods for the synthesis of a number of such ring systems and to study their chemical reactivity.

1.2. The Synthesis of 1, 2, 3-Triazole Derivatives

The first 1, 2, 3-triazole derivatives were reported in 1860 but they were not recognised as such until 1876. In a study of the nitration of azoxybenzene (8), Zinin\(^1\) obtained two products, one of which was subsequently shown\(^2\) to be 2-phenylbenzotriazole-1-N-oxide (9). Simultaneously, Hofmann\(^3\) obtained a compound from the diazotisation of a nitrophenylenediamine (10) which differed in properties from the diazo compounds usually isolated and it was later formulated as a nitro-1H-1, 2, 3-benzotriazole (11).

During the next twenty years, many similar reactions of certain phenylenediamines were reported and by 1876 the concept of positional isomerism on the benzene ring had been sufficiently well established for Ladenburg\(^4\) to make the generalisation that abnormal diazotisations occurred with o-phenylenediamines. Ladenburg proposed two structures (12) and (13) for benzotriazole derivatives, favouring (13) because of the stability of the compounds. However, it became evident from subsequent work that the products were best represented by structure (12) and the structures of 1, 2, 3-triazoles and benzo-1, 2, 3-triazoles are now firmly established as (14) and (15).
Scheme 2
The first fused 1,2,3-triazoles containing a bridgehead nitrogen atom were not reported until 1945 when Halcrow obtained the triazoloquinolone (17) by the diazotisation of the quinolone (16). The triazolocinnolone (19) has been prepared by an analogous method \[(18) \rightarrow (19)\].

In later years, methods \[(20) \rightarrow (21)\] involving the oxidation of hydrazones (20) with a variety of oxidising agents (manganese dioxide, silver oxide, lead tetraacetate, potassium ferricyanide or \(N\)-bromosuccinimide) were developed. The triazolium salt \(7\) (23), obtained from the phenylhydrazone (22), was the first example of a fused triazole to be prepared by this type of cyclisation. Later, Boyer extended this method to the synthesis of 1,2,3-triazolo-[1,5-a]pyridines (25) and Reimlinger demonstrated that the triazole (27) could be formed directly from the ketone (26) using toluene-\(p\)-sulphonyl hydrazine in the presence of base (Scheme 2).

The formation of fused triazoles by diazo exchange from toluene-\(p\)-sulphonyl azide \[(28) \rightarrow (29)\; R, \text{ electron withdrawing}] has been reviewed by Regitz. Recently, a number of new fused 1,2,3-triazole ring systems have been synthesised starting from a 1,2,3-triazole derivative and building up to the second ring \(e.g.\) \((30) \rightarrow (31)\), as opposed to the previous approaches described above. These synthetic methods will be discussed later in greater detail.
1.3. **Homolytic Scission of 1,2,3-Triazole Derivatives**

One facet of the diazo character of 1,2,3-triazoles is demonstrated by their ability to undergo homolytic ring scission to give products derived from intermediate carbenes and nitrenes. Thiele and Schleussner\(^\text{12}\) found that the triazolotriazole (32), when heated in ethanol, loses nitrogen to give 4-acetylamino-2-phenyl-1,2,3-triazole (33). However, the Graebe-Ullman\(^\text{13}\) reaction was the first report of the thermolytic extrusion of nitrogen from a 1,2,3-triazole. Thus, 1-phenylbenzotriazole (34), when heated in a glass tube until nitrogen evolution has ceased, gives a quantitative yield of carbazole (35). Similar reactions involving chlorinated\(^\text{14}\) and fluorinated\(^\text{15}\) benzotriazoles have been reported. The mechanism of the Graebe-Ullman reaction is believed to involve the intermediate formation of the carbene (36) and its subsequent insertion into an adjacent aromatic C-H bond. Modifications of the Graebe-Ullman reaction have been used to prepare quinindoline (38)\(^\text{16}\) and phenanthridine (40)\(^\text{17}\).

The flash vacuum thermolysis of triazolo[1,5-a]pyridines has recently been studied by Crow and co-workers.\(^\text{18,19}\).

The thermolysis of triazolo[1,5-a]pyridine (41)\(^\text{18}\) gave a high yield of azobenzene (45) over wide temperature (450° - 850°) and pressure (0.02 - 0.05 mm) ranges and contrasts with the thermolysis of phenyl azide (47), 5-phenyltetrazole (48), pyrid-4-yldiazomethane (49) and pyrid-3-yldiazomethane (50) which gave,
under identical conditions, the ring-contracted product, 1-cyano-cyclopentadiene (46) (Scheme 4).

It is suggested that loss of nitrogen from the triazolo-pyridine (41) leads to 2-pyridylcarbene (42) which isomerises to phenylnitrene (44) via ring expansion to (43) with subsequent ring contraction (Scheme 3). Dimerisation of the nitrene (44) affords azobenzene (45). However, phenylnitrene derived from other sources (Scheme 4) undergoes ring contraction to 1-cyano-cyclopentadiene (46). The mechanism of the ring contraction has been investigated by Crow \textsuperscript{20,21} but the exact sequence has not been fully elucidated. However, 1-cyano-cyclopentadiene (46) is believed to arise from the singlet state of phenylnitrene (44) (Scheme 4) whereas azobenzene (45) (Scheme 3) must be the result of intersystem crossing (Scheme 5) to the groundstate of phenyl-nitrene (44).

Cleavage of the 1,5-bond (Scheme 5) is assumed to occur with spin conservation to give the singlet biradical (51) and loss of nitrogen from (52) may be expected to yield triplet (53) because the rotational interconversion [(51) ↔ (52)] provides the means of populating the triplet state of the biradical (51). Once formed by the electronic reorganisation of (53), conversion of 2-pyridyl-carbene (42) into phenylnitrene (44), with conservation of spin, can be represented by the usual expansion-contraction scheme.
Confirmation of the proposed mechanism (Scheme 3) is found in the thermolysis\textsuperscript{19} of 6-methyl-3-phenyl-1,2,3-triazolo[1,5-a]pyridine (54) and 3-methyl-1,2,3-triazolo[1,5-a]pyridine (56). In the case of (56), the intermediate carbene of type (42) is trapped by insertion into the adjacent C-H bond to give 2-vinylpyridine (57). The intermediate nitrene of type (44), derived from (54), inserts into a C-H bond of the adjacent phenyl group to give the carbazole (55).

![Scheme 3 diagram]

\[ \text{H-Aziridines (58) are cyclic, planar, } 4\pi \text{ electron systems, isoelectronic with the cyclopropenyl anion, and are destabilised by electron delocalisation. The homolysis of 1,2,3-triazoles might be expected to lead to this ring system (58) either by insertion of} \]

![Aziridines 58 and 59]

\[ \text{(58)} \]
Scheme 6

R_1 \quad R_2
\begin{align*}
  a & \quad \text{CH}_3 \quad \text{CH}_3 \\
  b & \quad \text{Ph} \quad \text{Ph} \\
  c & \quad \text{CH}_3 \quad \text{Ph} \\
  d & \quad \text{Ph} \quad \text{CH}_3
\end{align*}

Scheme 7

(60c) → (62c) → (60d)
Scheme 8

\[
\text{Br} \quad \overset{\text{hv}}{\longrightarrow} \quad \text{PhC≡CN} \quad \leftrightarrow \quad \text{PhCCN} \quad (64)
\]

\[
\text{CH}_3\text{OH} \quad \downarrow
\]

\[
\text{PhCH}_2\text{CN} + \text{PhCHCN} \quad (65)
\]

\[
\text{OCH}_3
\]

\[
\text{PhCH}_2\text{CN} + \text{PhCHCN} \quad (66)
\]

Scheme 9

\[
\text{hv} \quad \overset{\text{hv}}{\longrightarrow} \quad \overset{\text{hv}}{\longrightarrow} \quad \overset{\text{hv}}{\longrightarrow}
\]

\[
R_1 \quad R_2 \quad R_3
\]

(67) \quad a \quad \text{Ph} \quad \text{H} \quad \text{H}

b \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}

c \quad \text{H} \quad \text{Ph} \quad \text{Ph}

d \quad \text{Ph} \quad \text{H} \quad \text{Ph}

(68) \quad \overset{\text{syn}}{\uparrow}

(69) \quad \overset{\text{anti}}{\uparrow}

Scheme 9
carbene or nitrane intermediates into adjacent bonds or by cyclisation of a diradical species.

Rees and co-workers\textsuperscript{22, 23} have proved the intermediacy of 1H-aziridines (58) in the production of 2H-aziridines (59) by the flash vacuum thermolysis of 1-phthalimido-1, 2, 3-triazoles (60). The triazoles (60a) and (60b) gave 2, 3-dimethyl-2-phthalimido-2H-aziridine (61a) and 2, 3-diphenyl-2-phthalimido-2H-aziridine (61b) respectively (Scheme 6). The proof of the intermediacy of the symmetrical 1H-aziridine (62c) is based on the identical isomer ratios observed in the thermolysis of the triazoles (60c) and (60d) to mixtures of the 2H-aziridines (61c) and (61d) (Scheme 7).

The photolysis of simple 1, 2, 3-triazoles has been studied briefly by Boyer\textsuperscript{24} and in more detail by Burgess\textsuperscript{25}. In the photolysis of 5-bromo-4-phenyl-1H-1, 2, 3-triazole (63)\textsuperscript{24} the major product was phenylacetonitrile (65) which is thought to be formed by the photoelimination of nitrogen and hydrogen bromide to give the intermediate carbene (64), followed by hydrogen abstraction from the solvent (Scheme 8). Insertion of the carbene (64) into the O-H bond of methanol then accounts for the formation of the minor product, 2-methoxyphenylacetonitrile (66).

The photolysis of the substituted triazoles (67) is more complex and it was hoped that the diradical (68) or the carbene (69) might undergo ring closure to the 1H-aziridine system (58).
(Scheme 9). However, in the photolysis of (67a)\textsuperscript{24} the major product was again phenylacetonitrile (65) which must arise by subsequent rearrangement of the initially produced phenylketenimine (70).

\[
\text{hv} \\
\begin{array}{ccc}
(67a) & \rightarrow & \text{PhCH} - C = \text{NH} \\
\text{MeOH} & & (65)
\end{array}
\]

(70)

The photolysis of (67b)\textsuperscript{25} led to stable phenylketenimines (72b-d) and substituted indoles (71b-d) by insertion of the intermediate carbene (69) into a C-H bond of the adjacent phenyl group. The distribution of (71) and (72) (Scheme 10) may reflect the partition of (68) between the \textit{syn} and \textit{anti} isomers of (69), \textit{syn}-sterechemistry being more favourable in cases leading to higher yields of (71).

The photolysis of benzotriazoles has been extensively studied by several groups\textsuperscript{26-28} who have all shown that, as in thermolysis, 1-phenylbenzotriazole (73) gives a high yield of carbazole (35). However, evidence is lacking as to whether the reactive intermediate in this reaction is a carbene (74), a diradical (75) or a charged species (76) although one group\textsuperscript{26} has shown that the intermediate cannot be a 1H-aziridine (77). The photolysis\textsuperscript{26} of 5-chloro-1-(4'-chlorophenyl) benzotriazole (78) affords a high yield of the carbazole (79), but, because of the
Scheme 12

Scheme 13
electronegativity of the chlorine atom at C-5, it would be expected that a 1H-aziridine intermediate (80) would ring open to give the carbazole (81) (Scheme 11).

The photolysis of benzotriazole\(^\text{27}\) (82) in methanol yields photoproducts (83) and (84) which are perfectly consistent with the formation of an intermediate carbene (74). Thus, the amine products are explicable by hydrogen abstraction by the carbene (74) from the solvent to give aniline (83) and insertion into the O-H bond of methanol to give the anisidine (84). However, in principle, the products could also be explained in terms of a delocalised species (75) or (76).

Meier and Menzel\(^\text{28}\) have shown that 1-benzoyl-benzo-1,2,3-triazole (85) yielded on photolysis 2-phenylbenzoxazole (87), and not a 1H-aziridine (86), by a radical process (Scheme 12). It has been shown\(^\text{26}\) that flash thermolysis of (85) also gave the benzoxazole (87).

The only reported\(^\text{27}\) photolysis of a fused 1,2,3-triazole system is that of 1,2,3-triazolo[1,5-a]pyridine (41) which does not undergo a ring transformation, but yields products (88), (89) and (90) derived exclusively by insertion indicating the intermediacy of 2-pyridylcarbene (42) (Scheme 13).

1.4. Heterolytic Scission of 1,2,3-Triazole Derivatives

Fused 1,2,3-triazole systems (1) undergo heterolytic ring
cleavage to give products (91), derived (at least in theory) from diazonium intermediates (3).

\[
\begin{align*}
\text{(1)} & \quad \text{(2)} & \quad \text{(3)} & \quad \text{(91)} \\
N=\text{N} & \quad N=\text{N}^+ & \quad \text{H}^+ & \quad \text{A}^- \\
\end{align*}
\]

The first report of 1,2,3-triazole scission of a fused system (1) in an acidic medium is that of Boyer\textsuperscript{24,25} who found that, unlike tetrazolo[1,5-a]pyridine (93), 1,2,3-triazolo[1,5-a]pyridine (41) and 3-phenyl-1,2,3-triazolo[1,5-a]pyridine (95) were cleaved by a variety of carboxylic acids and phenol at 80-100° to give pyridine derivatives (94) and (96) respectively (Scheme 14).

This work has been greatly extended\textsuperscript{11,31-34} to include the scission in acidic media of 1,2,3-triazolo[1,5-a]quinazolines (97),\textsuperscript{31,32} 1,2,3-triazolo[5,1-c]benzotriazines (98),\textsuperscript{33} and 1,2,3-triazolo [1,5-a]pyrimidines (99).\textsuperscript{11,34} The scope of the reaction, with respect to the type of reagents used, and the effect of substituents on the scission have been studied and these aspects will be discussed, in detail, later.

Kermack\textsuperscript{35} reported in 1950 that the Graebe-Ullman reaction can be catalysed by polyphosphoric acid suggesting that such reactions are examples of acid catalysed heterolytic ring scission. Thus, 4-(benzotriazol-1-yl)quinoline (100),\textsuperscript{35} which fails to react under typical Graebe-Ullman conditions, was readily
Scheme 15
converted to 2,3-benz-\(\gamma\)-carboline (101) in the presence of polyphosphoric acid. A previous report\(^6\) had indicated that zinc chloride, a Lewis acid, catalysed the formation of 3-carboline (103) from 2-(benzotriazol-1-yl)pyridine (102). A mechanism (Scheme 15), involving the protonation of the triazole ring, readily explains the acid catalysis of those reactions.

The diazo character of triazoles has been demonstrated by Regitz\(^{36}\) in the reaction of 3-substituted triazolo[1,5-a]pyridines (104) with perchloric acid. The protonated triazole ring opened to give the diazopyridinium perchlorates (105) which were isolated as reasonably stable solids. The perclorates (105) are reconverted into the starting triazoles (104) by heating under reflux in ethanol.

A further example\(^{37}\) of the acid catalysed scission of a 1,2,3-triazole system, followed by trapping of the intermediate salt, is illustrated by the reaction of 8-oxoindolo[1,2-d]-1,2,3-triazole (106) with anhydrous ethereal hydrogen chloride. Protonation of the triazole ring occurs followed by ring opening to give the stable hydrochloride (107), which on treatment with dilute alkali was reconverted to the
triazole (106) and was decomposed to 2-diazoidan-1,3-dione (108) by heating under reflux in water.

1.5. 1,2,3-Triazole-Diazoalkylideneamine Equilibria in 1,2,3-Triazole Derivatives

The reactions discussed above indicate a tendency for the 1,2,3-triazole nucleus (1) to exhibit diazo character (2) and it is tempting to explain this chemical behaviour in terms of the existence of 1,2,3-triazole-diazoalkylideneamine equilibria

\[ [(1) \rightleftharpoons (2)] \]

The operation of equilibria \([(1) \rightleftharpoons (2)]\) in simple 1,2,3-triazole derivatives was first demonstrated by Dimroth in the course of his work with 5-hydroxytriazoles (109). On the basis of his studies, Dimroth believed that the equilibrium was unimolecular with respect to the enol tautomer. However, a re-interpretation
of his data led to the conclusion that the tautomeric change is bimolecular and ionic in nature, a proton attacking the substituted nitrogen atom to initiate the indicated change \([(109) \xrightleftharpoons{(110)}]\) (Scheme 16).

It has been asserted that the ring closure step \([(112) \rightarrow (113)]\) which allows triazoles to be formed from α-diazoketones \((111)\) and compounds containing an amino group (e.g. hydroxylamines, primary amines and hydrazines) occurs irreversibly. However, recently the existence of 1, 2, 3-triazole-diazoalkylideneamine equilibria in certain 1, 2, 3-triazoles of this type has been demonstrated (Scheme 17) and extensive work has been carried out on the systems \([(i) - (iv)]\) (Scheme 18). Again the equilibria seem to be bimolecular and ionic in nature and extensive \(^1\)H n.m.r. studies of the system (iii) have been used to determine solvent effects on the position of the equilibria. Moreover, it is significant that in each case \([(i) - (iv)]\) the triazole tautomer is destabilised by an electron withdrawing group (phenyl or sulphonyl).

Direct analogy for 1, 2, 3-triazole-diazoalkylideneamine tautomerism is provided by tetrazole-azidomethine equilibria which have been studied in greater detail. In the equilibrium \([(122) \xrightleftharpoons{(123)}]\) cyclisation occurs to the nitrogen bearing the most electron donating substituent, electron withdrawing substituents stabilising the azido form. Thus, it has been shown that,
Scheme 19
although 1-β-naphthyl-5-methyltetrazole (124) exists predominantly in the tetrazole form, the trifluoromethyl analogue (125) is most stable as the azide tautomer (125).

1, 2, 3-triazole-diazoalkylideneamine equilibria of the type described before, are also embodied in the rearrangement of aminotriazoles [(126) ⇌ (127)], first observed by Dimroth. This rearrangement was shown to be base catalysed or thermally induced but Dimroth's studies were carried out under non-equilibrium conditions, either using a basic solvent, which favours the acidic isomer (127), or by allowing the higher melting isomer, usually (127), to crystallise from the melt. Lieber confirmed these results and extended the study, under true equilibrium conditions, to a variety of alkyl and aryl 1, 2, 3-triazoles in homogeneous melts at 185°. The results obtained for the electron releasing benzyl
\[
\begin{align*}
&\text{(130)} \quad N = N - \text{SH} \quad \leftrightarrow \quad N = N - \text{NHR} \\
&\text{(131)} \\
&\text{RCOCH}_2CNHR' + \text{TsN}_3 \xrightarrow{\text{acetic acid}} \text{RT.} \\
&\text{(132)} \quad R \quad R' \\
&\text{Ph} \quad \text{Ph} \\
&\text{CH}_3 \quad \text{PhCH}_3(p) \\
&\text{OEt} \quad \text{PhOCH}_3(p) \\
&\quad \text{PhOCH}_3(o) \\
&\quad \text{PhNO}_2(p) \\
&\text{(133)} \\
&\text{(134)} \\
&\text{(135)} \\
&\text{Scheme 20} \\
&\text{(136)} \\
&\text{(137)} \\
&\text{Scheme 21}
\end{align*}
\]
group and the electron withdrawing 4-nitrophenyl group are compared in Scheme 19. Electron withdrawing groups, therefore, cause rearrangement to the isomer (127) and this result is paralleled in the corresponding tetrazole series [(128) ⇌ (129)], also studied by Lieber.

Processes [(130) ⇌ (131)], closely related to the Dimroth rearrangement [(126) ⇌ (127)], have also been observed with mercaptotriazoles (130). It has been shown that both isomers (130) and (131) are present in solution, their respective concentrations being dependent on solvent polarity. Studies of such equilibria [(130) ⇌ (131)] have shown that the base stable isomer is the thiol (130), which, when warmed in acid, undergoes rearrangement to the aminothiadiazole (131). An example of this rearrangement is shown in Scheme 20. The thiadiazoles (133), initially produced in the reaction of the thioamides (132) with toluene-\(p\)-sulphonyl azide, were converted into the triazolethiols (135) on warming with piperidine and the thiadiazoles (133) were regenerated by warming the thiols (135) in glacial acetic acid.

Montgomery and co-workers have investigated Dimroth type rearrangements of triazolo[4,5-b]pyridines (137) and triazolo[4,5-d]pyrimidines (138). The isomeric triazolopyridines (136) and (137), unambiguously synthesised, were heated in a sealed tube at 150° for 120 h. The triazolo[5,4-c]pyridine
(136) was converted (85%) to the triazolo[5,4-b]pyridine (137), the latter being recovered (85%) from the identical reaction, showing that the triazolo[5,4-b]pyridine system is the thermodynamically more stable (Scheme 21). Similarly, the triazolo[5,4-d]pyrimidines (138) and (140) have been shown to be present in equilibrium [(138) ⇌ (140)] (Scheme 22) when each isomer is heated in dimethylacetamide (b.p. 163^°), the latter being thermodynamically more stable. However, when treated with base, the isomer (140) rearranged to the more acidic isomer (138), an attempt to trap the diazo intermediate (139), by heating (140) in pyridine containing β-naphthol, proving to be unsuccessful.

Studies 58-61 on the fused tetrazoloheterocyclic systems, tetrazolo[1,5-a]pyridines (141), tetrazolo[1,5-č]pyrimidines (142), tetrazolo[1,5-a]pyrazines (143), and tetrazolo[1,5-č]-1,2,4-triazoles (144) 61 show that these heterocycles exist as equilibrium mixtures of the tetrazole and azide forms, with the former predominating (Scheme 23). In the corresponding 1,2,3-triazole systems 8,9,11,34 which have been prepared to date, no diazo tautomer seems to be present.

Dimroth type rearrangements [(145) ⇌ (146)] of tetrazolo-[1,5-a]pyrimidines (145) and (146) have been demonstrated by Montgomery 62 (Scheme 24). The tetrazolopyrimidinone (147) exists as structure (147) in the solid state but in solution the isomeric tetrazolopyrimidinone (148) is also present. This type of
Scheme 25
ring chain tautomerism with attendant Dimroth rearrangement has also been observed by Montgomery in the more complex azidopurine derivatives (149), (150) and (151).

The triazolo[1,5-a]pyrimidine ring system (99) has also been investigated in an attempt to observe the Dimroth rearrangement [(152) \( \Leftrightarrow \) (153)], a type which had not been previously reported. The condensation of 5-amino-4-phenyl-1H-1,2,3-triazole (154) with ethyl acetoacetate in the presence of piperidine yielded a solid product, which if dried at room temperature proved to be an isomer mixture [(155) (80%); (156) (20%)]. However, if dried at 140° for 1h, the mixture changed in composition, with the thermodynamically more stable isomer (156) (80%) predominating. Moreover, when the crude product is crystallised, the isomer (156) is obtained in pure form. Also, if the isomer (156) is heated with piperidine, it is reconverted to the more acidic isomer (155) (Scheme 25).

As an extension of the latter work, an investigation of synthetic routes to, and studies of, the reactivity of the 1,2,3-triazolo[1,5-a]quinoxaline (156), 1,2,3-triazolo[5,1-c]-1,2,4-triazine (157), 1,2,3-triazolo[1,5-b]-1,2,4-triazine (158), 1,2,3-triazolo-
[5,1-c]-1,2,4-triazole (159), and the 1,2,3-triazolo[1,5-b]-1,2,4-triazole (160) ring systems was undertaken. A further interesting aspect of these hitherto unknown ring systems is their potential pharmaceutical activity. The results of these investigations constitute the subject matter of the present thesis.
CHAPTER 2

STUDIES ON THE SYNTHESIS AND REACTIVITY OF 1,2,3-TRIAZOLO[1,5-a]QUINOXALINE DERIVATIVES

DISCUSSION
2.1. Introduction

Only three examples of the 1,2,3-triazolo[1,5-a]quinoxaline ring system (156) have been reported in the literature\(^\text{64-66}\) and information on the physical and chemical properties of 1,2,3-triazolo[1,5-a]quinoxaline derivatives is almost entirely lacking.

The first reported\(^\text{64}\) synthesis of the ring system (156) involved the oxidation of the phenylhydrazone (161) to the triazolium salt (162), using \(\text{N}\)-bromosuccinimide in acetic acid. A by-product of the deoxygenation of the \(\text{o}\)-nitrophenyltriazole (163) by tributyl phosphite has been formulated\(^\text{65}\) as the 1,2,3-triazoloquinoxaline (164), although firm evidence for the assigned structure is lacking. The triazolo[1,5-a]quinoxalinone (175b) has been prepared\(^\text{66}\) by the diazotisation of the amine (166), but again the physical and chemical properties of the compound were not reported. However, none of these methods is ideally suited to the general synthesis of 1,2,3-triazolo[1,5-a]quinoxalines.

It is known\(^\text{8}\) that dehydrogenation of the hydrazone of pyridine-2-carboxaldehyde (167) yields, not 2-pyridyldiazenemethane (168), but the cyclic isomer 1,2,3-triazolo[1,5-a]pyridine (41). In closely related processes, Regitz\(^\text{67,68}\) has used diazo group transfer from sulphonyl azides to active methylene groups to convert alkyl and aryl (2-pyridyl) methyl and (2-quinolyl) methyl ketones (169) and (171) into 1,2,3-triazolo[1,5-a]pyridines (170).
Ts = toluene-p-sulphonyl
and 1,2,3-triazolo[1,5-a]quinolines (172). Since the quinoxalinones (173) and their N-methyl derivatives (174) are readily available, it was of interest to study their reactions with toluene-p-sulphonyl azide, as a means for the general construction of 1,2,3-triazolo-[1,5-a]quinoxaline derivatives.

2.2. **Synthesis of 1,2,3-Triazolo[1,5-a]quinoxaline Derivatives**

Due to the possible complication of the presence of two acidic centres in the quinoxalinones (173), it was decided to concentrate initial studies of the diazo transfer reaction on the N-methyl derivatives (174). Methylation of the quinoxalinones (173), according to the literature, using methyl iodide and potassium carbonate in acetone, was relatively inefficient, presumably due to the insolubility of the quinoxalinones (173). However, methylation of the quinoxalinones (173) occurred in high yield, using methyl iodide and sodium hydride in dimethylformamide as solvent. The quinoxalinone (173d) did not prove to be amenable to this treatment and it was prepared by the literature method.72

Due to the high insolubility of even the N-methylquinoxalinones (174), it proved impossible to effect diazo group transfer reactions in alcoholic solvents. On the other hand, reaction occurred when the N-methylquinoxalinones (174) were allowed to react with toluene-p-sulphonyl azide in dimethylformamide in the presence of piperidine. Under these conditions, the quinoxalinone (174d)
afforded the triazoloquinoxalinone (176d) smoothly and in excellent yield. However, reaction was complicated by the formation of a by-product, whose melting point, spectral properties and analysis are consistent with the structure (177). The sulphonamide (177) is presumably formed by the nucleophilic substitution of toluene-\(p\)-sulphonyl azide by piperidine. The difficulty of separating the compound (177) from product resulted in low conversions of the quinoxalinones (174a and b) into the triazoloquinoxalinones (176a and b). However, formation of the by-product (177) could be avoided by using triethylamine as the base. Thus, the ester (174b) reacted smoothly with toluene-\(p\)-sulphonyl azide in the presence of triethylamine to give the triazoloquinoxalinone (176b), but the acetyl compound (174a) failed to react under these conditions.

The benzoylquinoxalinone (174c) also failed to react with toluene-\(p\)-sulphonyl azide in dimethylformamide in the presence of piperidine, even after prolonged treatment. In contrast, reaction of the ketone (174c) occurred readily in the presence of sodium hydride to give the triazoloquinoxalinone (176c). The nitrile (176d) was similarly formed in high yield from the quinoxalinone (174d). However, reaction of the quinoxalinones (174a and b) with toluene-\(p\)-sulphonyl azide in the presence of sodium hydride took a different course from the reactions
(174a) \[ \quad \rightarrow \quad (183) \]

Scheme 26

(178b)

(184) \[ \quad \xrightarrow{\text{EtO}^-} \quad (181b) \]
employing piperidine or triethylamine as base. In the case of
the ketone (174a), the product was acidic and is formulated as the
toluene-p-sulphonylaminoquinoxalinone (178b). The structure
(178b) is further supported by the hydrolysis of the acidic product
to the known amine 73 (178c). The precise mode of formation of
the compound (178b) is not clear, but appears to involve the
replacement of the acetonyl side-chain in (174a) by the toluene-p-
sulphonylamino group. Direct nucleophilic displacement by
toluene-p-sulphonylamino anion [(174a) → (183) → (178b)] (Scheme 26),
may find some analogy in the conversion of the quinoxalinone (184)
into the quinoxalinedione (181a) by heating under reflux in ethanolic
sodium ethoxide 74 (Scheme 26). However, none of the anticipated
triazoloquinoxalinone (176a) could be isolated and, consequently,
the availability of toluene-p-sulphonamide, (a normal by-product
in diazo group transfer reactions) demanded by this mechanism,
is not straightforward. Moreover, the preferential ejection of
acetonyl anion in competition with toluene-p-sulphonylamino anion
[(183) → (178b)] is unlikely. The details of the course of the
transformation [(174a) → (178b)] must await the outcome of further
experimental work.

In the reaction of the ester (174b) with toluene-p-sulphonyl
azide in the presence of sodium hydride, the product was again
acidic and analysed correctly for the triazoloquinoxalinone structure
(176f). This structure was firmly established by the spectral properties of the compound (notably, the $^1$H n.m.r. spectrum, which clearly shows the presence of a toluene-p-sulphonyl group) and by its hydrolysis to the carboxylic acid (176g) of proven structure (see later). The mode of formation of the compound (176f) is discussed later.

Using the information obtained from the diazo group transfer reactions of the $\mathbf{N}$-methyl compounds (174), attention was turned to the study of the acidic quinoxalinones (173). Reaction of the compounds (173b and d) with toluene-p-sulphonyl azide occurred smoothly in the presence of triethylamine to afford the triazoloquinoxalinones (175b and d) in high yield. In the presence of sodium-hydride, the ester (173b) and the ketone (173c) yielded the products (175f and c) respectively, the toluene-p-sulphonyl-amino derivative (178a) accompanying the latter as a by-product. Formation of the compound (178a) is similar to that of (178b) and may involve nucleophilic displacement of the phenacyl group in (173c) by toluene-p-sulphonylamino anion (see before). However, the ketone (173c) was unchanged on attempted reaction with toluene-p-sulphonamide in the presence of sodium hydride.

The methyl ketone (173a) failed to react with toluene-p-sulphonyl azide in the presence of piperidine or triethylamine and using sodium hydride in dimethylformamide the products were
multicomponent gums. However, a low yield of the triazolo-
quinoxalinone (175a) was obtained using methanolic sodium methoxide as catalyst.

2.3. Structure and Reactivity of Triazoloquinoxalinone Derivatives

The triazoloquinoxalinone derivatives (175) and (176) are highly insoluble, colourless, crystalline solids which fluoresce in ultra violet light and are generally light sensitive. In the pure state they lack bands at 2500-2000 cm\(^{-1}\) in their i.r. spectra, demonstrating the absence of the diazo tautomer in the solid state. A chloroform solution of the compound (176a) is likewise transparent in the triple bond region.

The triazoloquinoxaline ring system in (175) and (176) proved to be stable in general to strong base (20\% w/v ethanolic potassium hydroxide under reflux), strong acid (polyphosphoric acid at 80\(^{\circ}\)) and powerful oxidising agents (sodium hypochlorite and hydrogen peroxide). Consequently, it was possible to utilise these reagents to establish the assigned structures (175) and (176).

The presence of a fused 1,2,3-triazole nucleus in (175) and (176) is supported by their mass spectra which exhibit abundant fragment ions at \((M^+ - N_2)\) as well as a strong parent ion.

The structures of the triazoloquinoxalinones (175b-f) and (176a-f) were firmly established by a combination of hydrolysis
N=N

\[ N^O \]  
\[ I \]  
\[ R \]  
\( (175h) \)  
or  
\( (176h) \)  

\[ N \]  
\[ CH_20Ac \]  
\[ (ISO) \]  

Scheme 27
and oxidation, and subsequent triazole scission to quinoxalinones of known structure. Thus, the esters (175b) and (176b), the nitriles (175d) and (176d) and the amides (175e) and (176e) [derived from the nitriles (175d) and (176d) by acidic hydrolysis] were smoothly hydrolysed under alkaline conditions to the acids (175g) and (176g). The structures of (175g) and (176g) were firmly established by decarboxylation and triazole scission and in the case of (175g) by independent synthesis.

Heated under reflux in glacial acetic acid, the acids (175g) and (176g) underwent decarboxylation and triazole scission to afford readily separated mixtures of the products (175h) and (176h) and the acetoxy methylquinoxalinones (180a) and (180b) (Scheme 27). The structures of the acetoxy compounds (180a and b) were established by oxidation to the quinoxalinediones (181a and b). Formation of the quinoxalinediones, rather than the acids (182a and b) (Scheme 27), reflects the apparent ease of removal of a carbon substituent at C-3 in a quinoxalinone, as already discussed [cf. page 22 and Scheme 26].

In contrast to the ready triazole scission of the acids (175g) and (176g), the benzoyltriazoloquinoxalinone (176c) and the ester (176b) are stable to heating under reflux in glacial acetic acid. The stabilising effect of electron withdrawing groups on the tendency of fused 1,2,3-triazoles to undergo acid-catalysed
scission has been noted in fused systems\(^\text{3O-34}\). Since it was shown that the parent compounds (175h) and (176h) readily undergo scission in hot glacial acetic acid, the corresponding scission of the acids (175g) and (176g) probably occurs after initial decarboxylation.

The acid (175g) was synthesised (Scheme 28) by catalytic hydrogenation of the nitrophenyltriazole diester (163)\(^\text{65}\) to the N-hydroxy compound (179), followed by dithionite reduction to the NH-compound (175j), and subsequent hydrolysis to (175g). The lactam (175j) was also formed as a by-product in the catalytic hydrogenation of the diester (163), presumably as a result of complete reduction of the nitro group to the amine (184) and subsequent lactam formation, or by further reduction of (179) (Scheme 28).

An attempt to degrade the acetyltriazoloquinoxalinone (176a) under basic conditions to give the unsubstituted triazoloquinoxalinone (176h) yielded only starting material. However, Baeyer-Villiger oxidation of the ketone (176c) using peracetic acid, gave the acid (176g) and a solid which proved to be a mixture of the starting material and the phenyl ester (176i). Similar treatment of the NH-compound (175c) afforded only starting material, but the methyl ketone (176a) gave the acid (176g) in low yield, together with an unknown compound (X). The Baeyer-Villiger oxidation of the ketones (176a and c) to the acid (176g) serves to establish the
Scheme 29
assigned structure of these compounds. The apparent complete lack of migration (cf. Scheme 29) of the heterocyclic nucleus in competition with alkyl or aryl groups is in accord with the migration of the most electron rich fragment, well established\textsuperscript{75} for such rearrangements.

The unknown colourless compound (X) detonated on heating, and was reconverted into the starting ketone (176a) on attempted crystallisation and on treatment with concentrated sulphuric acid. Its i.r. spectrum showed hydroxyl absorption and contained a single carbonyl absorption [in contrast to the two carbonyl bands present in the i.r. spectrum of the original ketone (176a)]. The otherwise plausible hydroperoxide structure (185) is not in accord with the failure of (X) to liberate iodine from acidified potassium iodide solution.

The structure assigned to the phenyl ketone (175c) follows from its reaction with methyl iodide in the presence of sodium hydride. In this reaction, methylation was accompanied by loss of the benzoyl group to afford the N-methyl compound (176h).

Methylation of the triazoloquinazalinones (175f and h) occurred under similar conditions to afford the corresponding N-methyl derivatives (176f and h).

2.4. Mechanism of the Formation of the Triazoloquinazalinone Derivatives
Scheme 30

\[ (173) \text{ or } (174) \]

\[ (175) \text{ or } (176) \]

\[ \text{TsNH}_2 + R''_3N \rightarrow \text{TsNH} \overset{\ominus}{\rightarrow} NHR'' \]

\[ [R = H, \text{CH}_3; R^1 = \text{COCH}_3, \text{CO}_2\text{Et}, \text{CN}] \]
Scheme 31

(173) or (174) or (175)

$[R=H \text{ or } CH_3; \quad R^1=COPh, \text{ CN}]$
Scheme 32

(173b) or (174b)

(187)

(188)

(175f) or (176f)
In his review of the diazo transfer reaction using toluene-$p$-sulphonyl azide, Regitz observes that sulphonyl azides may be considered as diazoamides, and that the $N_2$ group is exchanged in a one step reaction for two hydrogen atoms of the active methylene compound with formation of toluene-$p$-sulphonamide and the diazo compound. The mechanism of diazo transfer from toluene-$p$-sulphonyl azide to the quinoxalinones (173) and (174) can be represented as in Scheme 30. The triazoloquinoxalinones formed in the transfer reaction are contaminated with small quantities of the diazo isomers (186) as can be seen from the presence of weak diazo bands in the i.r. spectra of the crude products. On purification of the crude triazoloquinoxalinones, these absorptions disappear, demonstrating the instability of the diazo tautomers (186), with respect to the triazole forms (175) and (176).

A similar type of mechanism accounts for the diazo group transfer reactions of the quinoxalinones (173) and (174) in the presence of sodium hydride (Scheme 31). However, the formation of the sulphonamide derivatives (175f) and (176f) from the reaction of the esters (173b) and (174b) with toluene-$p$-sulphonyl azide in the presence of sodium hydride can be explained by a course (Scheme 32) involving intramolecular condensation between the ester group and toluene-$p$-sulphonylamino anion [cf. (187)]. The
Scheme 33
resulting triazolone intermediate (188) would be expected to be unstable relative to the diazo tautomer (189), cyclisation of which would yield the final product (175f) or (176f). The possibility that the amides (175f) and (176f) are formed by subsequent reaction of the triazoloquinoxalinone esters (175b) and (176b) with the sodium salt of toluene-\(\pi\)-sulphonamide, produced as a by-product, is discounted by the fact that the ester (175b) failed to react with toluene-\(\pi\)-sulphonamide in the presence of sodium hydride.

It is interesting to note that in the diazo transfer reaction of the nitrile (174d) in the presence of sodium hydride, involvement of the cyano group with the toluene-\(\pi\)-sulphonylamino group in the intermediate (190), to give ultimately (191) or (192) (Scheme 33) is not observed, despite the observation of an analogous process in the base-catalysed reaction of cyanoacetamide with toluene-\(\pi\)-sulphonyl azide [cf. Section 7, page 129].
CHAPTER 3

STUDIES ON THE SYNTHESIS AND REACTIVITY OF 1,2,3-TRIAZOLO[1,5-a]QUINOXALINE DERIVATIVES

EXPERIMENTAL
Notes

Infra red (i.r.) spectra were measured for nujol suspensions (or, if stated, thin films) using a Pye-Unicam SP 200 Spectrophotometer; bands were either strong or very strong, unless otherwise specified (w) as weak or (br) as broad.

Ultra violet (u.v.) spectra were measured for solutions in absolute ethanol using a Pye-Unicam SP 800 Spectrophotometer; absorptions were well defined unless specified (sh) as shoulders or (inf) as inflections.

Nuclear magnetic resonance (n.m.r.) spectra were measured at 100 MHz using a Varian HA 100 instrument and at 60 MHz using a Varian EM 360 instrument.

Mass spectra (m.s.) were measured at 100 Kv using an A.E.I. MS 902 instrument.

Microanalyses were carried out by the National Physical Laboratory and by Mr. Brian Clark and Mr. John Grünbaum, Department of Chemistry, University of Edinburgh. Melting points (uncorrected) of all analytical samples were determined on a Kofler-block.

Solvents were of technical grade, unless otherwise specified, and light petroleum had b.p. 60-80°C.

Recovery in chloroform or ether refers to extraction, drying over anhydrous magnesium sulphate and evaporation under
reduced pressure.

Thin layer chromatography (t.l.c.) was carried out over silica (Merck Kieselgel G. F. 254) in chloroform, unless otherwise stated. Column chromatography was effected over silica (100-200 mesh) or alumina (5% deactivated). Dry column chromatography was carried out over alumina (activity grade 3).
3.1. Synthesis of 1,2,3-Triazolo[1,5-a]quinoxalinone Derivatives

(a) Synthesis of the Quinoxalinones (173a-d)

(i) Ethyl acetopyruvate, prepared by the method described in Organic Synthesis, had b.p. 104-106°/20 mm (lit., 117-119°/29 mm).

(ii) 3-Acetylquinoxalin-2(1H)-one (173a)

Ortho-phenylenediamine (21.6g, 0.2 mol) in glacial acetic acid (100 ml) was treated with ethyl acetopyruvate (31.6g, 0.2 mol). The solution became warm and on cooling the orange product was collected and crystallised (22.6g), m.p. 264° (from aqueous acetic acid) (lit., 267°).

(iii) Ethyl quinoxalin-2(1H)-one-3yl acetate (173b)

The ester (173b), prepared by the method of L’Italien and Banks, had m.p. 206° (from glacial acetic acid) (lit., 214°).

(iv) 3-Phenacylquinoxalin-2(1H)-one (173c)

The quinoxalinone (173c), prepared by the method of Mason and Tennant, had m.p. 261° (from aqueous dimethylformamide) (lit., 275°).

(v) 3-(a-Cyanomethyl)-quinoxalin-2(1H)-one (173d)

The quinoxalinone (173d), prepared by the method of Tennant, had m.p. 300° (from aqueous dimethylformamide) (lit., 302°).
(b) Methylation of the Quinoxalinones (173a-c)

Solutions of the quinoxalinones (173a-c) (0.03 mol) in the minimum quantity of dry dimethylformamide (60-120 ml) were added to a vigorously stirred suspension of sodium hydride (0.8 g, O.033 mol) in dry dimethylformamide (12.0 ml). Stirring was continued at room temperature for a further 15 min. Methyl iodide (4.7 g, O.033 mol) was added and the reaction mixtures were stirred at room temperature for 17 h. The precipitated products were collected and combined with further crops obtained by diluting the filtrates with water, and were used without further purification.

(i) 3-Acetonyl-1-methylquinoxalin-2(1H)-one (174a)
(78%) had m.p. 192° (lit.69 200°).

(ii) Ethyl 1-methylquinoxalin-2(1H)-one-3-yl acetate (174b) (50%) had m.p. 120° (lit.70 128°).

(iii) 1-Methyl-3-phenacylquinoxalin-2(1H)-one (174c)
(89%) had m.p. 174° (lit.71 186°).

(iv) 3-(a-Cyanomethyl)-1-methylquinoxalin-2(1H)-one (174d)
Attempted methylation of the quinoxalinone (173d) by the above method yielded a black tar. The N-methylquinoxalinone (174d) was prepared by the method of Tennant,72 and had m.p. 207° (from aqueous dimethylformamide) (lit.72 208°).

(c) Reactions of the Quinoxalinones (173a-d) and (174a-d) with Toluene-p-sulphonyl Azide in the Presence of Base
Toluene-p-sulphonyl azide was prepared by the method in Organic Synthesis.\(^\text{77}\)

(i) In the Presence of Piperidine

Solutions of the quinoxalinones (174a, b and d) (0.005 mol) in the minimum quantity of dry dimethylformamide (20-30 ml) were treated with piperidine (0.5 g, 0.0055 mol). A solution of toluene-p-sulphonyl azide (2.0 g, 0.01 mol) in dry dimethylformamide (2.0 ml) was added and the mixtures were stirred at room temperature for 3 h. The precipitated solids were filtered off and combined with further crops obtained by diluting the filtrates with water (10 ml). Further dilution with water (10 ml) yielded the colourless toluene-p-sulphonamide (177) (1.5 - 2.5 g) m.p. 103\(^\circ\) (lit.\(^\text{78}\), 103\(^\circ\)).

Yields, melting points, m.s. and analytical data are collected in Table 1 and u.v. and \(^1\)H n.m.r. data in Tables 2 and 3 respectively.

The ketone (174a) gave, as light yellow needles, 3-acetyl-5-methyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (176a), \(v_{\text{max}}\) 1695 and 1660 (CO) cm\(^{-1}\). Dilution of the mother liquors from this product with water (100 ml) led to the starting material (174a) (identified by its i.r. spectrum) (40%).

The nitrile (174d) yielded, as colourless needles, 3-cyano-5-methyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (176d), \(v_{\text{max}}\)
2280 w (CN) and 1660 (CO) cm$^{-1}$.

In the case of the quinoxalinone (174b) no solid separated directly from the reaction mixture. Dilution with water (20 ml) caused precipitations of the product (176b) contaminated with the sulphonamide (177). This mixture was washed with ether and the insoluble triazoloquinoxalinone (176b) was collected and purified by crystallisation.

Attempted reactions of the quinoxalinones (173a) and (174c) with toluene-p-sulphonyl azide in the presence of piperidine gave the starting materials (identified by their i.r. spectra) (90-95%).

(ii) In the Presence of Triethylamine

Solutions of the quinoxalinones (173b and d) and (174b) (0.01 mol) in the minimum quantity of dry dimethylformamide (40-50 ml) were treated with triethylamine (2.75g, 0.022 mol) followed by a solution of toluene-p-sulphonyl azide (4.00g, 0.022 mol) in dry dimethylformamide (2.0 ml). The mixtures were stirred at room temperature for 3h and were then diluted with water (100 ml) and extracted with chloroform. The extracts, washed with dilute aqueous hydrochloric acid, yielded light coloured gums which afforded the solid products on trituration with a little ether. The aqueous mother liquors were acidified with dilute aqueous hydrochloric acid, extracted with chloroform and the gums obtained were triturated with a little ether to give further
quantities of product.

Yields, melting points, m.s. and analytical data are collected in Table 1. U.v. and $^1$H n.m.r. data are collected in Tables 2 and 3 respectively.

The ester (173b) gave, as colourless needles, 3-ethoxy-carbonyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (175b), $\nu_{\text{max}}$ 3300-2700 br (NH), 1725 and 1680 (CO), and 1620 (NHdef) cm$^{-1}$.

The nitrile (173d) afforded, as colourless plates, 3-cyano-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (175d), $\nu_{\text{max}}$ 3400-2800 br (NH), 2280 w (CN), 1685 (CO) and 1620 (NHdef) cm$^{-1}$.

The ester (174b) gave, as colourless needles, 3-ethoxy-carbonyl-5-methyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (176b), $\nu_{\text{max}}$ 1725 and 1680 (CO) cm$^{-1}$, without acidification.

(iii) In the Presence of Sodium Hydride

Solutions of the quinoxalinones [(173a-c) and (174a-d)] (O.O05 mol), in the minimum quantity of dry dimethylformamide (20-40 ml), were added at room temperature over 15 min to a vigorously stirred suspension of sodium hydride [(O.26g, O.011 mol) in the case of (173a-c), or (O.13g, O.0055 mol) in the case of (174a-d)] in dry dimethylformamide (5 ml). Stirring was continued at room temperature for a further 15 min. A solution of toluene-$p$-sulphonyl azide (2.Og, O.011 mol) in dry dimethylformamide (2. O ml) was added dropwise and the mixtures were stirred for 3 h
at room temperature. Precipitated solids were collected and combined with further crops, obtained by diluting the filtrates with water. The aqueous mother liquors were extracted with chloroform (A). The aqueous layers were then acidified with dilute aqueous hydrochloric acid and any solid products were filtered off. The aqueous mother liquors were extracted with chloroform (B).

Yields, melting points, m.s., and analytical data are collected in Table 1 and u.v. and $^1$H n.m.r. data in Tables 2 and 3 respectively.

Gums isolated from extracts (A) and (B) in the reaction of the quinoxalinone (173a) were shown by t.l.c. to be multicomponent mixtures.

The ester (173b) afforded (B), as colourless needles,

1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one-3-(N-toluene-p-sulphonyl)-carboxamide (175f), $\nu_{\text{max}}$ 3300-2500 br (NH), 1700 and 1670 (CO), and 1640 (NHdef) cm$^{-1}$.

3-Benzoyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (175c) (A), as colourless plates, $\nu_{\text{max}}$ 3300-2800 br (NH), 1680 and 1650 (CO), and 1620 (NHdef) cm$^{-1}$, and 3-(toluene-p-sulphonyl-amino) quinoxalin-2(1H)-one (178a) (B), $\nu_{\text{max}}$ 3100-2600 br (NH), 1680 (CO) and 1580 (NHdef) cm$^{-1}$, were isolated in the reaction of the quinoxalinone (173c).

The quinoxalinone (174a) yielded (B), as colourless needles,
1-methyl-3-(toluene-p-sulphonylamino)quinoxalin-2(1H)-one (178b),

\[ \text{v}_{\text{max}} 3150 \text{ (NH)}, 1700 \text{ and } 1650 \text{ (CO)}, \text{ and } 1600 \text{ (NHdef) cm}^{-1}. \]

The ester (174b) gave (B), as colourless platelets, 5-methyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one-3-(N-toluene-p-sulphonyl)-carboxamide (176f), \[ \text{v}_{\text{max}} 3300-2500 \text{ br (NH), 1700 and 1670 (CO), and 1640 (NHdef) cm}^{-1}. \]

The quinoxalinone (174c) gave (A), as colourless plates, 3-benzoyl-5-methyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (176c),

\[ \text{v}_{\text{max}} 1680 \text{ and } 1670 \text{ sh (CO) cm}^{-1}. \]

The triazoloquinoxalinone (176d) (85%) was prepared from the nitrile (174d).

(iv) In the Presence of Sodium Methoxide

To a solution of sodium (0.28g, 0.012 mol) in methanol (30 ml) containing the quinoxalinone (173a) (0.81g, 0.004 mol) at room temperature was added dropwise with stirring toluene-p-sulphonyl azide (1.57g, 0.008 mol) in methanol (5 ml). Stirring was continued at room temperature for 4 h and the insoluble solid was filtered off and acidified at room temperature with dilute aqueous hydrochloric acid to afford 3-acetyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (175a) (0.22g, 25%) (Melting point, m.s., and analytical data are collected in Table 1 and \(^1\text{H} \text{n.m.r. data in Table 3}). Work up of the reaction mother liquors by evaporation of the methanol, addition of water and extraction with
chloroform gave a dark gum (0.64g) which was shown by t.l.c. to be a multicomponent mixture.

(v) 5-Hydroxy-3-methoxycarbonyl-1,2,3-triazolo[1,5-a]-quinoxalin-4(5H)-one(179)

Dimethyl 1-(o-nitrophenyl)-1,2,3-triazole-4,5-dicarboxylate (163) (0.52g, 0.0018 mol) in ethanol (50 ml) afforded on hydrogenation over 10% palladium-charcoal a mixture of the product (179) and 3-methoxycarbonyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one (175j). The ester mixture was washed with saturated aqueous sodium hydrogen carbonate and the insoluble ester (175j) (40%), identical (i.r. spectrum) with a sample prepared later, was filtered off. Acidification of the sodium hydrogen carbonate extract with dilute aqueous hydrochloric acid afforded the product (179) (53%) m.p. 179°, M+260, (from aqueous dimethylformamide).

3.2. Reactions of 1,2,3-Triazolo[1,5-a]quinoxalinone Derivatives

(a) 1,2,3-Triazolo[1,5-a]quinoxalin-4(5H)-one-3-carboxylic Acid (175g) and its N-Methyl Derivative (176g)

(i) The triazoloquinoxalinones [(175b and j) and (176b)] (0.002 mol) in ethanol (10 ml) were heated under reflux with 2M aqueous sodium carbonate (5 ml) for 1 h. The ethanol was evaporated under reduced pressure and the aqueous mother liquors were acidified with dilute aqueous hydrochloric acid to yield the colourless acids
(175g) (85%), m.p. 283°, $\nu_{\text{max}}$ 2700-2300 br (OH), and 1730 and 1620 (CO) cm$^{-1}$, and (176g) (90%), m.p. 250°, $\nu_{\text{max}}$ 2800-2500 (OH), 1760 and 1620 (CO), which were not further purified.

(ii) The triazoloquinoxalinones [(175d and e) and (176d and e)] (0.001 mol) in ethanol (5 ml) were heated under reflux with 20% w/v aqueous potassium hydroxide (2.5 ml) for 3 h. The ethanol was evaporated under reduced pressure and the aqueous solutions were acidified with dilute aqueous hydrochloric acid to yield the colourless products (175g) and (176g) (82-96%), which were identical (m.p. and i.r. spectrum) to samples obtained in (i) above.

(iii) The triazoloquinoxalinones (175f) and (176f) (0.001 mol) were hydrolysed as described in (ii), with the modification that heating under reflux was continued for 17 h, to afford the acids (175g) and (176g) (90-95%), which were identical (m.p. and i.r. spectrum) to samples obtained in (i) above.

(iv) The triazoloquinoxalinone (176c) (0.30g, 0.001 mol) was warmed in glacial acetic acid (5 ml) containing 30% aqueous hydrogen peroxide (2.5 ml) at 50° for 48 h. The insoluble solid was filtered off and the filtrate was diluted with water and further solid was collected. The combined solids were stirred in dilute aqueous sodium hydroxide at room temperature for 0.5 h. The insoluble solid (A) was collected and the mother liquor was acidified with dilute aqueous hydrochloric acid to yield the acid
The i.r. spectrum of solid (A), \( v_{\text{max}} \) 1730 w and 1670 (CO) cm\(^{-1}\), indicated that it was a mixture of the phenyl ester (176i) and starting material (176c). The mixture was hydrolysed with 20% w/v aqueous potassium hydroxide as described in (ii) above. The solid hydrolysis product was stirred in saturated aqueous sodium hydrogen carbonate and the insoluble starting material (176c) (0.03g, 10%) (identical i.r. spectrum) was filtered off. The filtrate was acidified with dilute aqueous hydrochloric acid and the acid (176g) was collected (0.09g, 40%), m.p. 249\(^{0}\), i.r. spectrum identical with a sample prepared previously.

Treatment of the triazoloquinoxalinone (176a) with 30% aqueous hydrogen peroxide in glacial acetic acid, as described above, yielded only the acid (176g) (8%) m.p. 249\(^{0}\).

Similar treatment of the triazoloquinoxalinone (175c) gave the starting material (83%) (identified by its i.r. spectrum).

(b) 1,2,3-Triazolo[1,5-a]quinoxalin-4(5H)-one-3-carboxamide (175e) and its N-Methyl Derivative (176e)

The nitriles (175d) and (176d) (0.004 mol) were heated at 80\(^{0}\) in polyphosphoric acid (5 ml) for 3 h. The cooled solutions were diluted with water (50 ml) and the solids were collected to give (175e) as colourless plates, (95%) m.p. \( >350^{0}\) (from dimethylformamide), \( v_{\text{max}} \) 3400 - 3100 br (NH), 1680 (CO) and
1620 (NHdef) cm$^{-1}$, 
\[
\text{C}_{10}H_7N_5O_2 \text{ requires: } \quad \text{C, 52.4; H, 3.1; N, 30.6\%; M 229.}
\]
\[
\text{Found: } \quad \text{C, 52.2; H, 3.2; N, 30.4\%; M$^+$229.}
\]
and (176e) as colourless plates, (95\%) m.p. 317° (from dimethylformamide), $v_{\text{max}}$ 3500 - 3100 br (NH), 1710 and 1660 (CO), and 1620 (NHdef) cm$^{-1}$, 
\[
\text{C}_{11}H_9N_5O_2 \text{ requires: } \quad \text{C, 54.3; H, 3.7; N, 28.8\%; M 243.}
\]
\[
\text{Found: } \quad \text{C, 54.4; H, 3.9; N, 28.8\%; M$^+$243.}
\]

(c) 1, 2, 3-Triazolo[1, 5-a]quinoxalin-4(5H)-one (175h) and its N-Methyl Derivative (176h)

The acids (175g) and (176g) (O.02 mol) were heated under reflux in dimethylformamide (40 ml) for 0.5 h. Water was added to the refluxing solutions until they became turbid and the crystalline solids were collected from the cooled reaction mixtures to give (175h), as colourless prisms, (89\%) m.p. 284° (from aqueous dimethylformamide), $v_{\text{max}}$ 3200 - 2900 br (NH), 1690 (CO) and 1640 (NHdef) cm$^{-1}$, 
\[
\text{C}_{9}H_6N_4O \text{ requires: } \quad \text{C, 58.1; H, 3.3; N, 30.1\%; M 186.}
\]
\[
\text{Found: } \quad \text{C, 57.9; H, 3.3; N, 30.1\%; M$^+$186.}
\]
and (176h) as light yellow needles, (79\%) m.p. 254° (from aqueous dimethylformamide), $v_{\text{max}}$ 1670 (CO) cm$^{-1}$, 
\[
\text{C}_{10}H_8N_4O \text{ requires: } \quad \text{C, 60.0; H, 4.0; N, 28.0\%; M 200.}
\]
\[
\text{Found: } \quad \text{C, 60.4; H, 4.2; N, 27.9\%; M$^+$200.}
\]
(d) **Methylation of 1,2,3-Triazolo[1,5-a]quinoxalinones**

Solutions of the triazolquinoxalinones (175c, f and h) (O.002 mol) in the minimum quantity of dry dimethylformamide (5 ml) were added at room temperature over 15 min to a vigorously stirred suspension of sodium hydride (O.06 g, O.0022 mol) in dry dimethylformamide (1 ml). Stirring was continued at room temperature for a further 15 min. Methyl iodide (O.15 g, O.0022 mol) was added and the reaction mixtures were stirred at room temperature for 17 h. The precipitated solids were filtered off and combined with more material obtained by diluting the filtrates with water. The products (176 f and h) (85-87%) were identical (m.p. and i.r. spectrum) to samples obtained previously. Reaction of the ketone (175c) with methyl iodide and sodium hydride in dimethylformamide, as described before, afforded the triazolo-quinoxalinone (176h) (95%), identical (m.p. and i.r. spectrum) to a sample prepared before.

(e) **Attempted Reaction of the Ketone (176a) with Sodium Hypochlorite**

A solution of sodium hydroxide (0.74 g) in water (6 ml) was cooled in an ice-salt bath and treated with a slow stream of chlorine gas until the solution reached pH 7. Sodium hydroxide (0.14 g) in water (0.2 ml) was added to the solution which was then warmed to 55°. The ketone (176a) (0.25 g), O.001 mol) was added to the vigorously stirred mixture and the suspension was heated at 65° for
On cooling, sodium bisulphite (2.0g) in water (2.0 ml) was added dropwise to the suspension and the colourless starting ketone (176a) (identified by its m.p. and i.r. spectrum) (0.23g, 95%) was collected. Acidification of the filtrate afforded no further solid.

(f) **Attempted Cleavage of the Ketone (176a) with Ethanolic Potassium Hydroxide**

The ketone (176a) (0.25g, 0.001 mol) in ethanol (5 ml) was heated under reflux with 20% w/v aqueous potassium hydroxide (2.5 ml) for 17 h. The ethanol was evaporated under reduced pressure and the aqueous mother liquor was acidified with dilute aqueous hydrochloric acid to afford the starting ketone (identified by its i.r. spectrum) (0.21g, 88%).

(g) **Attempted Oxidation of the Ketone (176a) with Hydrogen Peroxide in Glacial Acetic Acid**

The ketone (176a) (0.25g, 0.001 mol) was warmed in glacial acetic acid (5 ml) containing 30% aqueous hydrogen peroxide (2.5 ml) at 50° for 17 h. The insoluble solid (A) (0.14g) was collected and the filtrate was diluted with water and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to afford the starting material (identified by its m.p. and i.r. spectrum) (0.06g, 25%). The solid (A), ν\text{max} = 3350 and 3200 - 2600 br (NH or OH), and 1640 (CO) cm\(^{-1}\), \(\text{T}[(\text{CD}_3)_2\text{SO}] 1.48 [1\text{H}, \text{d}(J 1\text{Hz}), \text{CH}]\),
1.50 - 2.58 (4H, m, ArH), 6.30 (3H, s, CH₃), and 8.16 [3H, d-
(J 1Hz), CH₃], had m.p. 228° and was reconverted into the ketone
(176a) by crystallisation from aqueous dimethylformamide and by
treatment with concentrated sulphuric acid. The solid (A) failed
to give a violet colour (liberation of iodine) when it was treated
with an acidified aqueous solution of potassium iodide.

(h) 3-Methoxycarbonyl-1,2,3-triazolo[1,5-a]quinoxalin-4(5H)-one
(175j)

The ester (179) (0.08g, 0.0003 mol) was heated under
reflux in 70% v/v aqueous ethanol (15 ml) with sodium dithionite
(O.08g) for 0.5 h, after which time more sodium dithionite (O.08g)
was added and heating under reflux was continued for a further 0.5 h.
The suspension was filtered hot, the filtrate was evaporated under
reduced pressure and the solid was collected with a little water to
give, as colourless needles, the ester (175j) (0.05g, 63%) m.p.
240° (from dimethylformamide), vₘₙₙₙₚ 3300 (NH), 1720 and 1690
(CO), and 1620 (NH def) cm⁻¹.

C₁₁H₈N₄O₃ requires: C, 54.1; H, 3.3; N, 22.9%; M 244.

Found: C, 53.9; H, 3.3; N, 23.0%; M⁺ 244.

3.3. Triazole Scission of 1,2,3-Triazolo[1,5-a]quinoxalinones
and Reactions of the Resultant Quinoxalinones

(a) 3-Acetoxyethylquinoxalin-2(1H)-one (180a) and its N-Methyl
Derivative (180b)
The acids (175g) and (176g) and the triazoloquinoxalinones (175h) and (176h) (0.005 mol) were heated under reflux in glacial acetic acid (30 ml) for 3 - 8 h. The glacial acetic acid was evaporated under reduced pressure and ether (30 ml) was added. The insoluble solids were filtered off to give the triazoloquinoxalinones (175h) and (176h) (25-40%), which were identical (m.p. and i.r. spectrum) to samples obtained before. The ether extracts were washed with saturated aqueous sodium hydrogen carbonate and evaporated to give the acetoxyquinoxalinones (50 - 72%), (180a), as light brown prisms, m.p. 183° (from ethyl acetate), \( \nu_{\text{max}} \) 3200-2600 br (NH), 1750 (OAc) and 1660 (CO) cm\(^{-1}\),

[C\(_{11}\)H\(_{10}\)N\(_2\)O\(_3\)]

requires: C, 60.5; H, 4.6; N, 12.8%; M 218.

Found: C, 60.4; H, 5.0; N, 12.5%; M\(^+\)218.

and (180b), as light brown prisms, m.p. 108° (from ethyl acetate), \( \nu_{\text{max}} \) 1740 (OAc) and 1660 (CO) cm\(^{-1}\),

[C\(_{12}\)H\(_{12}\)N\(_2\)O\(_3\)]

requires: C, 62.1; H, 5.2; N, 12.1%; M 232.

Found: C, 61.8; H, 5.2; N, 12.0%; M\(^+\)232.

The triazoloquinoxalinones (176 b and c) were recovered (identical i.r. spectrum) (94 - 100%) when they were heated under reflux in glacial acetic acid for 24 h.

(b) Quinoxaline-2,3(1H,4H)-dione (181a) and its N-Methyl Derivative (181b)

The quinoxalinones (180 a and b) (0.001 mol) were heated
with twice their weight of chromium trioxide in 70% v/v aqueous acetic acid (10 ml) at 100° for 1 h. The solvent was evaporated under reduced pressure and the resultant green gums were triturated with a little water to give the solid quinoxalinediones (88 - 95%) which were identical (m.p., mixed m.p. and i.r. spectra) to authentic samples.

3.4. Attempted Reaction of the Ester (175b) with Toluene-p-sulphonamide

The ester (175b) (0.26 g, 0.001 mol) in anhydrous dimethylformamide (6 ml) was added at room temperature over 15 min to a stirred suspension of sodium hydride (0.008 g, 0.003 mol) in anhydrous dimethylformamide (1.0 ml). Stirring was continued at room temperature for a further 15 min. Toluene-p-sulphonamide (0.34 g, 0.002 mol) in dimethylformamide (2.0 ml) was added and stirring was continued at room temperature for 2 h. The reaction mixture was diluted with water and dilute aqueous hydrochloric acid to give starting material (92%) m.p. 240° identified by its i.r. spectrum.

3.5. Attempted Reaction of the Quinoxalinone (173c) with Toluene-p-sulphonamide

Reaction of the ketone (173c) with toluene-p-sulphonamide as described above for the ester (175b) gave starting material (92%), identified by its i.r. spectrum.
3.6. **Hydrolysis of the Toluene-p-sulphonamide (178b)**

The quinoxalinone (178b) (0.64g, 0.002 mol) in glacial acetic acid (1.0 ml) was treated with concentrated sulphuric acid (1.5 ml) and the mixture was warmed at 100° for 1.5 h. The reaction mixture was poured on to ice and the insoluble solid was collected (0.21g) and crystallised from ethanol-glacial acetic acid to give a colourless solid (0.09g), m.p. 274°, which was identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample (178c).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>m.p. (°)</th>
<th>Formula</th>
<th>Azide with Quinoxalinones</th>
</tr>
</thead>
<tbody>
<tr>
<td>175a</td>
<td>25^d</td>
<td>266^f</td>
<td>C_{11}H_8N_4O_2</td>
<td>requires: C (%) 57.9 H (%) 3.5 N (%) 24.6 M 228</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 58.7 H (%) 3.8 N (%) 24.8 M^+228</td>
</tr>
<tr>
<td>175b</td>
<td>78^b</td>
<td>246^e</td>
<td>C_{12}H_10N_4O_3</td>
<td>requires: C (%) 55.8 H (%) 3.9 N (%) 21.7 M 258</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 55.3 H (%) 3.8 N (%) 21.9 M^+258</td>
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<tr>
<td>175c</td>
<td>41^c</td>
<td>251^f</td>
<td>C_{16}H_10N_4O_2</td>
<td>requires: C (%) 66.2 H (%) 3.5 N (%) 19.3 M 290</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 66.4 H (%) 3.7 N (%) 19.3 M^+290</td>
</tr>
<tr>
<td>178d</td>
<td>17^c</td>
<td>284^e</td>
<td>C_{15}H_{13}N_3O_3S</td>
<td>requires: C (%) 57.1 H (%) 4.2 N (%) 13.3 M 315</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 56.9 H (%) 4.2 N (%) 13.3 M^+315</td>
</tr>
<tr>
<td>175d</td>
<td>85^b</td>
<td>315^f</td>
<td>C_{10}H_5N_5O</td>
<td>requires: C (%) 56.9 H (%) 2.4 N (%) 33.2 M 211</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 56.3 H (%) 2.5 N (%) 32.7 M^+211</td>
</tr>
<tr>
<td>175f</td>
<td>63^c</td>
<td>304^f</td>
<td>C_{17}H_{13}N_5O_4S</td>
<td>requires: C (%) 53.3 H (%) 4.0 N (%) 17.6 M 383</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 53.3 H (%) 3.9 N (%) 18.2 M^+383</td>
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<tr>
<td>176a</td>
<td>25^a</td>
<td>231^e</td>
<td>C_{12}H_10N_4O_2</td>
<td>requires: C (%) 59.5 H (%) 4.2 N (%) 23.1 M 242</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: C (%) 59.9 H (%) 4.3 N (%) 23.4 M^+242</td>
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<tr>
<td>176b</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
<td>184&lt;sup&gt;e&lt;/sup&gt;</td>
<td>C_{13}H_{12}N_{4}O_{3}</td>
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<td></td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>183&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Found: 57.5 4.5</td>
<td>20.0</td>
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<tr>
<td>176c</td>
<td>75&lt;sup&gt;c&lt;/sup&gt;</td>
<td>204&lt;sup&gt;e&lt;/sup&gt;</td>
<td>C_{17}H_{12}N_{4}O_{2}</td>
<td>requires: 67.1 4.0</td>
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<td>78&lt;sup&gt;a&lt;/sup&gt;</td>
<td>276&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Found: 66.8 4.0</td>
<td>18.8</td>
</tr>
<tr>
<td>176d</td>
<td>78&lt;sup&gt;a&lt;/sup&gt;</td>
<td>276&lt;sup&gt;f&lt;/sup&gt;</td>
<td>C_{11}H_{7}N_{5}O</td>
<td>requires: 58.7 3.1</td>
</tr>
<tr>
<td></td>
<td>85&lt;sup&gt;c&lt;/sup&gt;</td>
<td>274&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Found: 58.6 3.2</td>
<td>31.3</td>
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<tr>
<td>176f</td>
<td>92&lt;sup&gt;c&lt;/sup&gt;</td>
<td>291&lt;sup&gt;f&lt;/sup&gt;</td>
<td>C_{18}H_{15}N_{5}O_{4}S</td>
<td>requires: 54.4 3.8</td>
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<tr>
<td></td>
<td>69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>268&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Found: 54.4 3.8</td>
<td>17.8</td>
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<tr>
<td>178b</td>
<td>69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>268&lt;sup&gt;e&lt;/sup&gt;</td>
<td>C_{16}H_{15}N_{3}O_{3}S</td>
<td>requires: 58.4 4.6</td>
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<tr>
<td></td>
<td></td>
<td>Found: 56.6 4.3</td>
<td>14.5</td>
<td>M+329</td>
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</tbody>
</table>

<p>| a Using piperidine as base. | b Using triethylamine. | c Using Sodium hydride. |
| d Using sodium methoxide. | e Crystallised from aqueous dimethylformamide. | f From dimethylformamide. |</p>
<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>log $\varepsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>175b</td>
<td>212, 222, 265, 323</td>
<td>4.36, 4.39, 4.00, 4.05</td>
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<tr>
<td>175h</td>
<td>220, 254, 307 inf, 315, 328sh</td>
<td>4.26, 4.00, 3.86, 3.92, 3.74</td>
</tr>
<tr>
<td>176a</td>
<td>228, 264, 328</td>
<td>4.39, 3.94, 4.05</td>
</tr>
<tr>
<td>176b</td>
<td>228, 265, 326</td>
<td>4.27, 3.87, 3.95</td>
</tr>
<tr>
<td>176h</td>
<td>223, 253, 306sh, 317, 328 inf</td>
<td>4.28, 4.08, 3.92, 3.98, 3.82</td>
</tr>
</tbody>
</table>
### Table 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>ArH</th>
<th>N-CH$_3$</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>175$^b$</td>
<td>1.30 - 2.86(m)</td>
<td></td>
<td>7.09$^e$</td>
</tr>
<tr>
<td>175b$^b$</td>
<td>1.62 - 2.88(m)</td>
<td></td>
<td>5.60(q), 8.63(t)$^d$</td>
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<tr>
<td>175h$^b$</td>
<td>1.62 - 2.74(m)</td>
<td></td>
<td>1.42$^f$</td>
</tr>
<tr>
<td>175j$^b$</td>
<td>1.38 - 2.80(m)</td>
<td></td>
<td>6.08</td>
</tr>
<tr>
<td>176a$^b$</td>
<td>1.30 - 2.88(m)</td>
<td>6.26</td>
<td>7.02$^e$</td>
</tr>
<tr>
<td>176b$^b$</td>
<td>1.50 - 2.62(m)</td>
<td>6.38</td>
<td>5.59(q), 8.64(t)$^d$</td>
</tr>
<tr>
<td>176c$^b$</td>
<td>1.42 - 2.65(m)</td>
<td>6.42</td>
<td></td>
</tr>
<tr>
<td>176d$^b$</td>
<td>1.42 - 2.25(m)</td>
<td>6.35</td>
<td></td>
</tr>
<tr>
<td>176e$^b$</td>
<td>1.42 - 2.25(m)</td>
<td>6.31</td>
<td></td>
</tr>
<tr>
<td>176f$^b$</td>
<td>1.40 - 2.60(m)</td>
<td>6.22</td>
<td>8.58$^g$</td>
</tr>
<tr>
<td>176h$^c$</td>
<td>1.30 - 2.84(m)</td>
<td>6.23</td>
<td>1.45$^f$</td>
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</table>

$^a$ Signals are sharp singlets unless otherwise designated.

$^b$ Measured in (CD$_3$)$_2$SO and $^c$ in CDCl$_3$. $^d$ J 7Hz.

$^e$ COCH$_3$. $^f$ 3-H. $^g$ CH$_3$ of toluene-$p$-sulphonyl.
Table 4

\(^1\text{H N.m.r. Signals (T) of 2-Substituted Quinoxalinones}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>ArH</th>
<th>N-CH(_3)</th>
<th>CH(_2)</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>178(^a)(^b)</td>
<td>1.43 - 2.72(m)</td>
<td>-</td>
<td>-</td>
<td>6.08(^e)</td>
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<tr>
<td>180(^a)(^c)</td>
<td>2.07 - 2.72(m)</td>
<td>-</td>
<td>4.68</td>
<td>7.76(^d)</td>
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<tr>
<td>180(^b)(^c)</td>
<td>2.06 - 2.76(m)</td>
<td>6.31</td>
<td>4.64</td>
<td>7.78(^d)</td>
</tr>
<tr>
<td>181(^b)(^b)</td>
<td>2.30 - 3.02(m)</td>
<td>6.51</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Signals are sharp singlets unless otherwise designated.

\(^b\) Measured in \((\text{CD}_3)_2\text{SO}\) and \(^c\) in \text{CDCl}_3\). \(^d\) OAc.

\(^e\) CH\(_3\) of toluene-p-sulphonyl.
CHAPTER 4

STUDIES ON THE SYNTHESIS AND REACTIVITY OF 1,2,3-TRIAZOLO[5,1-c]-1,2,4-TRIAZINE DERIVATIVES

DISCUSSION
\[
\begin{align*}
\text{NHCOCH}_3 \quad \text{2M HCl} \quad 90^\circ \quad 3h
\end{align*}
\]
(203) \[ \text{Ph} \ \text{NH}_2 \ \text{NHNHPh} \] \[ \text{HCO}_2\text{H} \rightarrow \text{Ph} \ \text{N} \ \text{N} \]

(205) \[ \text{H}_3\text{C} \ \text{NNN} \ \text{CH}_3 \] \[ \text{HCO}_2\text{H} \rightarrow \text{H}_3\text{C} \ \text{N} \ \text{N} \]

(207) \[ \text{H}_3\text{C} \ \text{NNN} \ ] \[ \text{HCO}_2\text{H} \rightarrow \text{O} \ \text{N} \ \text{N} \]

(209) \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \] \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \]

(210) \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \] \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \]

(211) \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \] \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \]

(212) \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \] \[ \begin{array}{c} \text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \end{array} \]
4.1. Introduction

The chemistry of 1,2,3-triazolo-1,2,4-triazine systems containing a bridgehead nitrogen atom [e.g. structures (157), (158), (193) and (194)] has not been investigated, although one report in the literature describes the formation of the 1,2,3-triazolo[1,5-b]-1,2,4-triazine (196), by acidic cleavage of the 1,5-dehydro-1,2,3-triazolo[1,2-a]-1,2,3-triazole (195). However, the unusual nature of this transformation and the lack of concrete chemical evidence makes the assigned structure (196) doubtful.

The synthesis and properties of the corresponding 1,2,4-triazolo-1,2,4-triazines [(197) - (199)] have been investigated, but the 1,2,4-triazolo[1,5-b]-1,2,4-triazine system (200) is, as yet, unknown. The 1,2,4-triazolo[4,3-b]-1,2,4-triazine system (202) has been studied in great detail since 3,4-diamino-1,2,4-triazole precursors (201) are readily available. 1,2,4-Triazolo-1,2,4-triazine derivatives [e.g. (204) and (206)] are generally prepared from a 4-aminotriazine [e.g. (203) → (204)] or a 3-hydrizinotriazine [e.g. (205) → (206)] respectively. In the case of an N-unsubstituted hydrizinotriazine, formation of the triazole ring takes place preferentially at the 2-position [e.g. (207) → (208)]. 1,2,4-Triazolo[3,4-c]-1,2,4-triazine derivatives (209) can be converted either by heat or by treatment with acid into the isomeric structures (210) by a process which is formally a Dimroth
\[
\begin{align*}
\text{PhCH}_2\text{CN} \quad &\rightarrow \quad \text{PhCH}_2\text{CN} \\
(R = H, \text{CH}_3) \quad &\rightarrow \quad \text{(213)} \\
\end{align*}
\]

\[
\begin{align*}
\text{H-N} \quad &\rightarrow \quad \text{H-N} \\
(30) \quad &\rightarrow \quad \text{(31)} \\
\end{align*}
\]
type rearrangement. The mechanism of a similar type of rearrangement of 1,2,4-triazolo[4,3-a] pyrimidines (211) has been elucidated by Rose.87

1,2,3-Triazolo[5,1-c]benzo-1,2,4-triazines have been prepared49 by the reaction of phenylacetonitrile with 2-azidonitrobenzenes in the presence of sodium methoxide. The products of these reactions have been shown to have the structure (213) rather than the linear structures (214), formed by subsequent Dimroth rearrangement of (213).88

Diazonium salts, derived from five-membered heterocycles, have been comparatively little studied.89 Of particular interest is the potential bifunctional reactivity of betaines of the type (216), which might provide the basis for a general route [(215) + (216) \rightarrow (217)] to fused 1,2,4-triazines. This route has previously been used to prepare pyrazolo[5,1-c]-1,2,4-triazines (219) from pyrazole-3-diazonium chloride (218).90 The readily available 5-amino-4-phenyl-1H-1,2,3-triazole (30) has been used to prepare 1,2,3-triazolo[1,5-a]pyrimidines (31), and it was expected that diazotisation of this amine (30) and subsequent coupling of the diazonium salt with active methylene compounds, would provide a synthetic route to the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system (157). Acid-catalysed triazole scission of this ring system would then provide a valuable method for the preparation of
synthetically important 1,2,4-triazine derivatives, which are otherwise available only by tedious synthetic routes.

4.2. **Synthesis of 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives**

The diazotisation of the amine (30) was smoothly effected in high yield using amyl nitrite in anhydrous methanolic hydrogen chloride. The diazonium salt (220) proved to be a relatively stable light yellow solid, which tended to turn red and slightly gummy on being stored at 0° for some time. Consequently, it was used in subsequent coupling reactions without purification.

Acetylacetone, ethyl acetoacetate, benzoylacetonitrile and malononitrile coupled with the diazonium salt (220), at room temperature and in the presence of sodium acetate, to give the 1,2,3-triazolo[5,1-c]-1,2,4-triazines (221 a-c and h) in high yield. On the other hand, ethyl cyanoacetate, benzoylacetonitrile and cyanoacetamide gave mixtures of the triazolotriazines (221f,g and i) and the intermediate hydrazones (223 c,e and f), the cyclised products precipitating directly from the reaction mixtures and the hydrazones being isolated on subsequent work-up. Under similar conditions, diethyl malonate, ethyl benzoylacete and dibenzoylmethane afforded the hydrazones (223 a,b and d) as sole products. Likewise, when the reaction mixtures from ethyl cyanoacetate and cyanoacetamide were stirred at room temperature for a short period the hydrazones (223 c and f) were the sole products. The
deaminated triazole (67a) was the only compound isolated when
the diazonium salt (220) was treated with aqueous ethanolic sodium
acetate alone or in the presence of malonic acid or benzyl methyl
ketone. The failure of these reactions demonstrates the requirement
of a moderately acidic methylene centre for successful coupling.

The hydrazones (223 a-f), heated under reflux in aqueous
ethanolic sodium acetate, were smoothly cyclised to the corresponding
triazolotriazines (221 d-g) and (222 a and b), demonstrating their
probable intermediacy in the reactions leading directly to triazolo-
triazine products. The hydrazone (223b) gave both possible
products (221d) and (222b), with the latter acidic product
predominating. Also, when the reaction mixtures from diethyl
malonate and benzoylacetonitrile were stirred for three hours at
room temperature and then heated under reflux the cyclised products
were obtained exclusively. However, when dibenzoylmethane was
treated in this way, it was recovered unchanged.

The hydrazones (223 a-f) were soluble in dilute aqueous
sodium hydroxide and were regenerated on acidification with dilute
aqueous hydrochloric acid, demonstrating the assigned structures,
and excluding the alternative, non-acidic structures (226) derived
by subsequent Dimroth rearrangement\(^9\) [(223) \(\rightleftharpoons\) (224) \(\rightleftharpoons\) (225)
\(\rightleftharpoons\) (226)] (Scheme 34). The presence of a free triazole NH-group
is also demonstrated by acetylation of the hydrazones (223 a and
c-e) to acetyl derivatives (223h-k) having characteristic i.r. and

Scheme 34
1H n.m.r. absorption. Thus, the i.r. absorption of the acetyl groups occurs at characteristically high frequencies (1760 - 1740 cm⁻¹) and the 1H n.m.r. absorption of the acetyl protons appears close to T7.2. However, the tautomeric nature of hydrogen linked to nitrogen in benzo-1,2,3-triazoles was demonstrated by Griess when he showed that the benzotriazole (228) was the common product of the deacylation of both benzotriazoles (227) and (229). Similarly, acetylation of the benzotriazole (230) affords a mixture of the isomeric acetyl derivatives (231) and (232). Therefore, it should be noted that the 1H-configurations depicted for the hydrazones (223 a-g) are purely arbitrary, as are the 1-acetyl structures (223 h-k) derived by acetylation. The corresponding 2H or 3H and 2-N-acetyl or 3-N-acetyl structures are equally likely. The attempted acetylation of the hydrazones (223b and f) resulted in decomposition.

4.3. Structure and Reactivity of 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives

The triazolo[5,1-c]triazines (221 a-i) are yellow to deep red crystalline solids which show no sign of diazo absorption (at 2500 - 2000 cm⁻¹) in i.r. spectra measured in the solid state. Their mass spectra exhibit abundant fragment ions at M⁺ - N₂, as well as a strong parent ion, confirming the presence of the fused 1,2,3-triazole nucleus.
(221a) \[ \text{CH}_3\text{CO} \quad \text{Ph} \text{NH}_2\text{NH}_2 \] \[ \text{Ph} \text{N} \equiv \text{N} \text{Ph} \]

(233) \[ \text{CH}_3\text{CO} \quad \text{Ph} \text{NH}_2\text{NH}_2 \] \[ \text{Ph} \text{N} \equiv \text{N} \text{Ph} \]

(234) \[ \text{CH}_3\text{CO} \quad \text{Ph} \text{NH}_2\text{NH}_2 \] \[ \text{Ph} \text{N} \equiv \text{N} \text{Ph} \]

(30) \[ \text{H} \text{N} \equiv \text{N} \text{Ph} \] \[ \text{NH}_2 \text{N} \equiv \text{N} \text{Ph} \] + \[ \text{CH}_3\text{N} \equiv \text{N} \text{CH}_3 \text{Ph} \]

Scheme 35

(221) \[ \text{R}_1 \text{N} \equiv \text{N} \text{Ph} \] \[ \text{R}_2 \text{N} \equiv \text{N} \text{Ph} \] \[ \text{R}_1 \text{N} \equiv \text{N} \text{Ph} \] \[ \text{R}_2 \text{N} \equiv \text{N} \text{Ph} \]

(235) \[ \text{R}_1 \text{N} \equiv \text{N} \text{Ph} \] \[ \text{R}_2 \text{N} \equiv \text{N} \text{Ph} \] \[ \text{R}_1 \text{N} \equiv \text{N} \text{Ph} \] \[ \text{R}_2 \text{N} \equiv \text{N} \text{Ph} \]

Scheme 36

(236) \[ \text{H} \text{N} \equiv \text{N} \text{Ph} \] \[ \text{H} \text{N} \equiv \text{N} \text{Ph} \] \[ \text{CH}_3 \text{N} \equiv \text{N} \text{CH}_3 \text{Ph} \]

(237) \[ \text{H} \text{N} \equiv \text{N} \text{Ph} \] \[ \text{H} \text{N} \equiv \text{N} \text{Ph} \] \[ \text{CH}_3 \text{N} \equiv \text{N} \text{CH}_3 \text{Ph} \]

(238) \[ \text{CH}_3 \text{N} \equiv \text{N} \text{CH}_3 \text{Ph} \]

(239a) \[ \text{CH}_3 \text{N} \equiv \text{N} \text{CH}_3 \text{Ph} \]

(239b) \[ \text{CH}_3 \text{N} \equiv \text{N} \text{CH}_3 \text{Ph} \]
\textbf{Scheme 37}
The angular configuration for the triazolotriazine (221a) was confirmed by reaction with phenylhydrazine to give the hydrazone (233) (Scheme 35). This reaction excludes the linear structure (234) [derived by subsequent Dimroth rearrangement of (221a)] which could not give rise to (233). The structure of the hydrazone was firmly established by its synthesis by condensation of the amine (30) with the known \(^94\) nitrosopyrazole (235) (Scheme 35). It follows that the triazolo[5, 1-c]triazine ring system (221) is stable to subsequent Dimroth rearrangement [(221) ⇄ (236) ⇄ (237)] (Scheme 36).

The scission of the triazine ring observed in the transformation [(221a) → (233)] appears to be a general process induced by carbonyl reagents (Scheme 37). Thus, the triazolotriazine (221a) reacted with hydrazine hydrate and hydroxylamine to yield the corresponding pyrazole (238) and isoxazole (239) derivatives respectively. In the former reaction a small amount of crystalline solid which may be the hydrazone (221k) was also isolated. However, there was insufficient material to allow full characterisation. The \(^1\text{H n.m.r.}\) spectrum of the isoxazole (239) indicates the presence of an equilibrium mixture of the cis (239a) and the trans (239b) isomers in the ratio of 2:1. The existence of geometric isomerism in the hydrazone (223) is also shown by the multiplicity in the \(^1\text{H n.m.r.}\) absorption of the methylene protons in the esters (223 a-c).
Scheme 38

(222a) $\xrightarrow{\text{OH}^-} (223g)$
Since only one product was isolated in the coupling reaction between the diazonium salt (220) and malonitrile and since the intermediate hydrazone is isomeric with the cyclised compound (221h), there was a problem in assigning the structure (221h). However, the ultra violet spectrum of the product (221h) was almost identical to that of the amide (221i), whose structure was confirmed by cyclisation of the hydrazone (223f). Unfortunately, attempts to further relate the nitrile (221h) to the amide (221i) by hydrolysis were unsuccessful. In polyphosphoric acid at 80° frothing occurred indicating the loss of nitrogen from (221h) but no organic material could be isolated from the reaction mixture. Also, the nitrile (221h) was recovered on attempted hydrolysis at room temperature with concentrated sulphuric acid.

The triazolotriazine (221a) proved to be unstable to strong base. Thus, the attempted cleavage of the acetyl group using 20% w/v ethanolic potassium hydroxide gave a black multicomponent tar. On the other hand, the acetyl compound (221a) was recovered in an attempted Dakin oxidation using hydrogen peroxide. The attempted hydrolysis of the ester (222a) with aqueous sodium hydroxide, methanolic potassium hydroxide or 2M aqueous sodium carbonate led in each case to a compound which was shown to be the ring-opened diacid (223g). The mechanism of this ring opening (Scheme 38) is similar to the earlier ring opening observed with
phenylhydrazine (Scheme 35). In contrast the ester (221b) was smoothly hydrolysed by aqueous sodium hydroxide to the acid (221j), with no complication of ring opening or decomposition. The acid (221j) proved to be thermally stable and neither decarboxylation nor rearrangement was observed when the acid was heated to its melting point or under reflux in dimethylformamide. The 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring system, at least in the case of the ester (221f), was also stable to ammonia at room temperature, the ester (221f) affording the amide (221i) under these conditions.

Methylation of the triazolotriazinone (222a) with methyl iodide in the presence of potassium carbonate afforded the N-methyl derivative (222c). However, methylation with methyl sulphate in aqueous sodium hydroxide gave a compound which showed only one carbonyl absorption in its i.r. spectrum (1740 cm\(^{-1}\)) but contained signals in its \(^1\)H n.m.r. spectrum due to two methyl groups. On the basis of this evidence, and the observed molecular formula, \(\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_3\), this product is formulated as 7-methoxy-6-methoxy-carbonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (221l).

4.4. **Triazole Scission of 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives**

In contrast to the scission of the triazine ring which occurs in the presence of carbonyl reagents and by analogy with the behaviour of 1,2,3-triazolo[5,1-c]benzo-1,2,4-triazines,\(^{33, 88}\) it
Scheme 39
was anticipated that scission of the triazole ring in 1,2,3-triazolo[5,1-c]-1,2,4-triazines would occur in acidic media. Thus, the triazolobenzotriazine (98) was cleaved in acetic acid alone, or containing acetyl chloride, acetyl bromide or sodium dithionite to give the acetoxybenzyl (240), the chlorobenzyl (244), the bromobenzyl (245) or the benzyl (243) benzotriazine derivatives respectively (Scheme 39). In aqueous acetic acid containing chromium trioxide or in aqueous sulphuric acid, the benzoyl (242) or the hydroxybenzyl (241) derivatives are likewise obtained (Scheme 39). In the present studies, the 1,2,3-triazolo[5,1-c]-triazine derivatives were found to undergo similar acid catalysed triazole scission.

Heated under reflux in glacial acetic acid, the triazolotriazines (221a,c, and e-i) and (222b) were smoothly converted into the corresponding acetoxybenzyltriazines (246b and d-i) and (246c). In general, the reaction mixtures were very dark and the products were purified by column chromatography. In the case of the nitrile (221h), chromatography of the gummy product over alumina resulted in hydrolysis to the corresponding amide (246i). However, using silica the cyano compound (246h) was isolated.

Scission of the acid (221j) afforded a product which was shown by its $^1$H n.m.r. spectrum to be the unsubstituted triazine (246a), formed by decarboxylation of the initially formed triazine acid (246i). Also, scission of the ester (221b) gave a crude product,
the $^1$H n.m.r. spectrum of which indicated that it was the triazine ester (246c). However, after purification by column chromatography, decarbethoxylation had occurred and the product triazine (246a) was identical to that isolated in the scission of the acid (221j). The facile decarboxylation of the triazine acid (246 l) contrasts with the behaviour of the parent acid (221j) which resisted thermal decomposition. Acetic acid scission of the ester (222a) afforded a gum which was shown by its $^1$H n.m.r. spectrum to be a mixture of the initially formed triazine ester (247b) and the decarbethoxylated triazine (247a). Like the triazinone (247c), the triazinones (247 a and b) were strongly acidic, being soluble in saturated aqueous sodium hydrogen carbonate and adsorbing irretrievably on both alumina and silica, thereby precluding their separation.

The triazines (246 a and b) were viscous, light yellow gums which resisted attempted crystallisation and failed to give solid derivatives (picrate or dinitrophenylhydrazone). The triazines (246 d-i) and the triazinone (247c) were colourless low melting solids.

In accord with the assigned structures, hydrolysis of the acetoxybenzyltriazines (246i) and (246d) with aqueous sodium carbonate or aqueous sodium bicarbonate gave the corresponding alcohols (249b) and (249a). However, similar treatment of the
triazine (246a) gave dark multicomponent gums. The α-hydroxy-benzyl structure for the alcohol (249b) was established by manganese dioxide oxidation to the ketone (251), albeit in low yield. However, the attempted oxidation of the triazine (246b) with chromium trioxide in 70% aqueous acetic acid at room temperature led to the recovery of the starting material and at 100° afforded a multicomponent tar. As can be judged from the frequency of multicomponent, tarry products in their reactions, the 1,2,4-triazine derivatives appear to be very sensitive both to basic and oxidising conditions. The 5-methyl derivatives seem to be especially sensitive, whereas the 5-amino derivatives are more stable.

When the triazolotriazines (221 a, b, e and f) were heated under reflux in a mixture of acetyl chloride and acetic acid, the products were gums whose t.l.c. and 1H n.m.r. spectra were consistent with mixtures of the corresponding acetoxybenzyl and chlorobenzyl scission products. However, only in the case of the amino-ester (221f) could the chlorobenzyltriazine (248) be isolated from the mixture by column chromatography. The reaction of the triazolotriazines (221 b and e) with acetyl bromide in glacial acetic acid gave black gums, the t.l.c. of which showed several components. Also, the triazolotriazine (221a) on treatment with 20% v/v aqueous sulphuric acid, 2M aqueous hydrochloric acid or with chromium trioxide in 70% aqueous acetic acid likewise afforded only
multicomponent gums. These reactions contrast with those of
the benzotriazine system (see before) and reflect the greater
instability either of the triazolotriazine ring system or of the
product triazines. Heated under reflux in glacial acetic acid
containing sodium dithionite, the triazolotriazine (221c) afforded
the α-acetoxybenzyltriazine (246d). In an attempt to displace an
intermediate diazonium group, the triazolotriazine (221i) was
heated under reflux in glacial acetic acid containing hypophosphorus
acid but was recovered unchanged. The former reaction
demonstrates the greater resistance to reduction of an α-acetoxy-
benzyl-1,2,4-triazine compared with an α-acetoxybenzylbenzo-
1,2,4-triazine. However, catalytic hydrogenolysis of the
amino-ester (246f) occurred smoothly to give the benzyltriazine
(250a). The attempted hydrogenolysis of the amino-amide (246i),
on the other hand, was unsuccessful and hydrogenation of the ketone
(246b) gave a multicomponent mixture.

As further proof of structure, it was hoped to degrade a
1,2,3-triazolo[5,1-c]-1,2,4-triazine to a 1,2,4-triazine derivative
whose constitution could be established by unambiguous synthesis.
With this objective, synthetic routes to 3-benzyl-1,2,4-triazines
were investigated. Atkinson has described three synthetic
methods leading to 1,2,4-triazines: namely (a) the condensation
of acylhydrazides with dicarbonyl compounds in acetic acid
containing ammonium acetate [cf. Scheme 40 (i)]; (b) the
Scheme 40

Scheme 41
condensation of acylhydrazides with dicarbonyl compounds with 
preliminary isolation of the 1,2-diketone monoacylhydrazone, 
followed by ring closure with ammonia under pressure [cf. (ii)] ;
and (c) dehydrogenation of dihydrotetrazines, prepared by 
condensation of an α-acylaminoketone with hydrazine, followed by 
ring closure [cf. (iii)] . A more recent synthetic route to 1,2, 
4-triazine derivatives involves the condensation of amidrazones 
with α-dicarbonyl compounds [cf. (iv)] .

Using the conditions described by Atkinson, an attempt 
was made to synthesise 3-benzyl-5-phenyl-1,2,4-triazine (250b) 
from phenylglyoxal and phenylacetohydrazide. Chromatography of 
the multicomponent mixture obtained allowed the isolation of 3-
benzyl-6-phenyl-1,2,4-triazine (250c). In contrast the condensation 
of phenylacetamidrazone hydrochloride with phenylglyoxal, in the 
presence of triethylamine, gave the isomeric triazine (250b) along 
with the 1,2,4-triazole (256). Neunhoeffer has shown 
[cf. (252) - (255)] that the 1H n.m.r. absorption of H-6 in a 5-
substituted 1,2,4-triazine occurs at lower field than H-5 in a 6-
substituted 1,2,4-triazine. It follows that the isomeric 3-benzyl-
1,2,4-triazines have the structures (250 b and c) respectively.

Triazole scission of the ester (221d) would be expected to 
occur with decarbethoxylation of the initially formed triazine (246m) 
to give the triazine (246k). Catalytic hydrogenation of the triazine 
(246k) would then yield the triazine (250b) (Scheme 41) , already
Scheme 42

(i) \[
\begin{align*}
\text{H}_2\text{NOC} & \quad \xrightarrow{1. \text{Ac}_2\text{O}} \quad \xrightarrow{2. \text{HO}} \quad \text{CH}_3
\end{align*}
\]

(ii) \[
\begin{align*}
\text{H}_2\text{NOC} & \quad \xrightarrow{\text{HCO}_2\text{H}} \quad \xrightarrow{\text{Ac}_2\text{O}} \quad \text{H}_2\text{NOC}
\end{align*}
\]

(iii) \[
\begin{align*}
\text{H}_2\text{NOC} & \quad \xrightarrow{(\text{EtO})_2\text{CO}} \quad \xrightarrow{\text{EtO}^\ominus} \quad \text{O}
\end{align*}
\]

(iv) \[
\begin{align*}
\text{Cl} & \quad \text{Ph} & \quad \text{guanidine} & \quad \text{H}_2\text{NOC} & \quad \text{Ph}
\end{align*}
\]

(v) \[
\begin{align*}
\text{EtO}_2 & \quad \text{CH}_3 & \quad \text{guanidine} & \quad \text{H}_2\text{NOC} & \quad \text{CH}_3
\end{align*}
\]
synthesised from phenylacetamidrazone and phenylglyoxal.

Unfortunately, the ester (221d) was formed in very low yield from the cyclisation of the hydrazone (223b) and consequently lack of material prevented the study of its stepwise degradation to the triazine (250b).

Many synthetic methods, generally involving acylation with subsequent cyclisation [cf. Scheme 42 (i) - (iii)], have been developed for the cyclisation of pyrazine or triazine amino-amides to pteridines or azapteridines respectively. In an alternative route to these compounds, guanidine has been used to displace an amino group or a chloro group in pyrazines or triazines to effect the required cyclisation [cf. Scheme 42 (iv) and (v)]. It was therefore of interest to study the potential of the 5-amino-triazines (246i) and (250a) as intermediates in such syntheses of azapteridines. The amino-amide (246i) reacted with acetic anhydride in the presence of concentrated sulphuric acid to give the monoacetyl derivative (246j), but attempts to effect the cyclisation of this compound in aqueous sodium hydroxide led only to black decomposition products, presumably due to the instability of the triazine ring in (246j) to strong base. When heated under reflux with ethyl acetate in the presence of sodium ethoxide, the amino-amide (246i) gave, not an azapteridine derivative but rather, the benzoyltriazine (251), identical to the product obtained by manganese dioxide oxidation of the corresponding α-hydroxybenzyl
derivative (249b). Formation of the ketone (251) is presumably the result of oxidation of the alcohol (249b) in the basic reaction medium. The amino-amide (246i) was recovered from the attempted reaction with formic acid in the presence of acetic anhydride. The amino-ester (250a), when heated under reflux in methanol in the presence of guanidine, using the conditions of Taylor, afforded a black multicomponent oil from which no recognisable product could be isolated.
CHAPTER 5

STUDIES ON THE SYNTHESIS AND REACTIVITY OF 1, 2, 3-TRIAZOLO[5, 1-c]-1, 2, 4-TRIAZINE DERIVATIVES

EXPERIMENTAL
5.1. Synthesis of 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives

N.B. For general notes on experimental procedure, see page 30.

(a) (i) 5-Amino-4-phenyl-1H-1,2,3-triazole (30), prepared by the method of Sutherland and Tennant\(^\text{11}\), had m.p. 125\(^\circ\) (from water) (lit.\(^\text{11}\) 125\(^\circ\)).

(ii) Benzoylacetonitrile, prepared by the method of Gabriel and Eschenbach\(^\text{106}\) had m.p. 72\(^\circ\) (from ethanol) (lit.\(^\text{106}\) 79\(^\circ\)).

(b) 4-Phenyl-1H-1,2,3-triazole-5-diazonium chloride (220)

A solution of the aminotriazole (30) (29.0 g, 0.17 mol) in methanol (500 ml) was saturated at 0\(^\circ\) with dry hydrogen chloride. Amyl nitrite (23.0 g, 0.19 mol) was added dropwise to the solution stirred at 0\(^\circ\) and stirring was continued at 0\(^\circ\) for 1.5 h. The diazonium salt (220) (80%), m.p. 149\(^\circ\), was filtered off, combined with a second crop obtained by concentrating the solution to approximately half volume, and was used without further purification.

(c) General Method for the Preparation of the Triazolo[5,1-c]-triazines (221 a-c, and f-i) and the Hydrazones (223 a-f)

Solutions of the active methylene compounds (0.007 mol) and anhydrous sodium acetate (0.8 g) in water (2.0 ml) and ethanol (5.0 ml) were cooled to 0\(^\circ\) and then stirred and treated dropwise during 15 min with a solution of the diazonium salt (220)
(1.4 g, 0.0065 mol) in ethanol (25 ml) and water (25 ml). The mixtures were stirred in the melting ice bath for 17 h. Precipitated solid products (A) were filtered off. The ethanol was removed from the filtrate under reduced pressure and the aqueous mother liquors were extracted with chloroform to give, after trituration with a little ether, products (B).

Yields, melting points, m. s. and analytical data are collected in Table 5, and u. v. data in Table 8.

6-Acetyl-7-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (221a) was obtained (A), as orange-brown prisms, \( \nu_{\text{max}} \) 1700 (CO) cm\(^{-1}\), \( \Upsilon[(\text{CD}_3)_2\text{SO}] \) 1.66-2.68 (5H, m, ArH), 7.20 (3H, s, CH\(_3\)), and 7.29 (3H, s, Ac), from acetylacetone. No hydrazone was isolated (B).

6-Ethoxycarbonyl-7-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (221b) was obtained (A), as orange-brown prisms, \( \nu_{\text{max}} \) 1720 (CO) cm\(^{-1}\), \( \Upsilon(\text{CF}_3\cdot\text{CO}_2\text{H}) \) 1.50 - 2.45 (5H, m, ArH), 5.20 [2H, q (J 7 Hz), CH\(_2\)], 6.87 (3H, s, CH\(_3\)), and 8.47 [3H, t (J 7 Hz), CH\(_3\)], from ethyl acetoacetate. No intermediate hydrazone was isolated (B).

6-Benzoyl-7-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (221c) was obtained (A), as orange brown prisms, \( \nu_{\text{max}} \) 1680 (CO) cm\(^{-1}\), \( \Upsilon(\text{CF}_3\cdot\text{CO}_2\text{H}) \) 1.50 - 2.75 (1OH, m, ArH), and 7.17 (3H, s, CH\(_3\)), from benzoylacetone. No hydrazone was
was isolated (B).

7-Amino-6-cyano-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-
triazine (221h) was obtained (A), as maroon needles, \( \nu_{\text{max}} \) 3400, 3300 and 3150 (NH), and 1640 (NH def) cm\(^{-1}\), from malonitrile. No hydrazone was isolated (B).

7-Amino-6-ethoxycarbonyl-3-phenyl-1,2,3-triazolo[5,1-c]-
1,2,4-triazine (221e) was obtained (A), as red needles, \( \nu_{\text{max}} \) 3450 and 3350 (NH), 1720 (CO) and 1610 (NH def) cm\(^{-1}\), \( T[(CD_3)_2SO] \)
1.70 - 2.78 (5H, m, ArH), 5.53[2H, q(J 7Hz), \( CH_2 \)], and 8.60 
[3H, q(J 7Hz), \( CH_2 \)], from ethyl cyanoacetate. The intermediate 
ethy1 cyanoglyoxylate 2-(4-phenyl-1H-1,2,3-triazol-5-yl) hydrazone 
(223c), \( \nu_{\text{max}} \) 3300 - 2800 br (NH), 2300 w (CN) and 1700 (CO) 
cm\(^{-1}\), was also isolated (B).

7-Amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-
6-carboxamide (221i) was obtained (A), as red needles, \( \nu_{\text{max}} \) 3450 and 3300 (NH), 1680 (CO) and 1590 (NH def) cm\(^{-1}\), from cyano-
acetamide. The intermediate, 2-oxocynoacetamide 2-(4-phenyl-
1H-1,2,3-triazol-5-yl) hydrazone (223f), as red needles, \( \nu_{\text{max}} \) 
3350-2800 br (NH), 2300 w (CN) and 1690 (CO) cm\(^{-1}\), was also isolated (B).

7-Amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-
triazine (221g) was obtained (A), as maroon plates, \( \nu_{\text{max}} \) 3500 and 
3400 (NH), 1670 (CO) and 1600 (NH def) cm\(^{-1}\), from benzoyl-
acetonitrile. The intermediate phenylglyoxal onitrile 2-(4-phenyl-1H-1,2,3-triazol-5-yl) hydrazone (223e), was also obtained (B), as a yellow solid, $\nu_{\text{max}}$ 3300-2700 br (NH), 2300 w (CN) and 1650 (CO) cm$^{-1}$.

Diethyl mesoxalate 2-(4-phenyl-1H-1,2,3-triazol-5-yl) hydrazone (223a) was obtained (A), as a yellow solid, $\nu_{\text{max}}$ 3400 and 3200 - 2500 br (NH), and 1690 and 1660 (CO) cm$^{-1}$, $\tau[(\text{CD}_3)_2\text{SO}]$ 2.12 - 2.62 (5H, m, ArH), 5.54 - 5.88 (4H, m, CH$_2$), and 8.63 - 8.84 (6H, m, CH$_3$), from diethyl malonate.

Ethyl benzoylglyoxalate 2-(4-phenyl-1H-1,2,3-triazol-5-yl) hydrazone (223b) was obtained (A), as yellow plates, $\nu_{\text{max}}$ 3400 - 3100 br (NH), and 1690 and 1660 (CO) cm$^{-1}$, $\tau[(\text{CD}_3)_2\text{SO}]$ 2.10 - 2.78 (1OH, m, ArH), 5.82 - 6.12 (2H, m, CH$_2$), and 8.96 [3H, t (J 7Hz), CH$_3$], from ethyl benzoylacetate.

1,3-Diphenylpropane-1,2,3-trione 2-(4-phenyl-1H-1,2,3-triazol-5-yl) hydrazone (223d) was obtained (A), as yellow plates, $\nu_{\text{max}}$ 3300 - 2600 br (NH), and 1660 and 1650 sh (CO) cm$^{-1}$, from dibenzoylmethane. 4-Phenyl-1H-1,2,3-triazole (67a) (32%), m.p. 145$^\circ$ (lit. 107 145$^\circ$), $\nu_{\text{max}}$ 3200 - 2800 br (NH) cm$^{-1}$, $\tau($CDCl$_3$) 2.03 (1H, s, 5-H) and 2.08 - 2.64 (5H, m, ArH), was also isolated (B).

Treatment of the diazonium salt (220) with aqueous ethanolic sodium acetate, as described above, alone or in the presence of
malonic acid, or benzyl methyl ketone yielded 4-phenyl-1H-1,2,3-
triazole (67a) (90-98%).

(d) Base Catalysed Cyclisation of the Hydrazones (223 a-f) to the
Triazolo[5,1-c]triazines (221 d-g, and i) and (222 a and b)

The hydrazones (223 a-f) (0.01 mol) and anhydrous sodium
acetate (1.6 g, O.02 mol) in water (20 ml) and ethanol (150 ml)
were heated under reflux for 1.5 h. On cooling the crystalline
products were collected. The ethanol was evaporated from the
filtrates by evaporation under reduced pressure and the aqueous
mother liquors were extracted with chloroform to yield further
products. Filtrates by evaporation under reduced pressure and
the aqueous mother liquors were extracted with chloroform to
yield further products. Yields, melting points, m.s. and analytical
data are collected in Table 6 and u.v. data in Table 8.

The triazolo[5,1-c]triazines (221e and i) were formed
from the hydrazones (223c and f).

In the case of the hydrazone (223e) the triazolo[5,1-c]triazine
(221g) was obtained (30%) together with unreacted hydrazone (223e)
(56%).

6-Benzoyl-3,7-diphenyl-1,2,3-triazolo[5,1-c]-1,2,4-
triazine (221f) was obtained, as red prisms, \( \nu_{\text{max}} \) 1680 (CO) cm\(^{-1}\),
from the hydrazone (223d).

In the case of the hydrazones (223 a and b), no solid resulted
from the cooled reaction mixtures. The ethanol was removed from
the mixtures by evaporation under reduced pressure and non-acidic
material (A) was extracted with chloroform. The aqueous
solutions were acidified with dilute aqueous hydrochloric acid and
the products (B) were filtered off.

6-Ethoxycarbonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-
triazin-7 (4H)-one (222a) was obtained (B), as yellow-brown plates,
$\nu_{\text{max}} = 3200 - 2700 \text{ br (NH), and 1740 and 1680 (CO) cm}^{-1}$,
$\delta[(\text{CD}_3)_2\text{SO}] 2.00 - 2.64 (5\text{H, m, ArH}, 5.55 [2\text{H, q(J }7\text{Hz), CH}_2]$, 
and 8.64 [3H, t(J 7Hz) CH$_3$], from the hydrazone (223a).

6-Benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazin-7
(4H)-one (222b), was obtained (B), as yellow-green plates, $\nu_{\text{max}}$
3300 - 2800 br (NH), and 1700 and 1680 (CO) cm$^{-1}$, together with
(A) 6-ethoxycarbonyl-3,7-diphenyl-1,2,3-triazolo[5,1-c]-1,2,4-
triazine (221d), as red needles, $\nu_{\text{max}}$ 1740 (CO) cm$^{-1}$ from the
hydrazone (223b).

(c) Acetylation of the Hydrazones (223 a-f)

The hydrazones (223 a-f) (0.001 mol) in acetic anhydride
(2.0 ml) were warmed at 100$^\circ$ for 5 min. The acetic anhydride
was evaporated off under reduced pressure and the resultant gums
were triturated with a little ether to yield the solid acetyltriazoles
(223 h-k). Yields, melting points, m.s. and analytical data are
collected in Table 7.
Diethyl mesoxalate 2-(1-acetyl-4-phenyl-1,2,3-triazol-5-yl) hydrazone (223h), as a yellow solid, $\nu_{\text{max}}$ 1740 (Ac), 1720 and 1670 (CO) cm$^{-1}$, $\tau$(CDCl$_3$) 2.14 - 2.62 (5H, m, ArH), 5.54 - 5.82 (4H, m, CH$_2$), 7.21 (3H, s, Ac), and 8.57 - 8.79 (6H, m, CH$_3$), was prepared from the hydrazone (223a).

Ethyl cyanoglyoxalate 2-(1-acetyl-4-phenyl-1,2,3-triazol-5-yl) hydrazone (223i) was isolated, as a yellow solid, $\nu_{\text{max}}$ 2300 w (CN), 1740 (Ac) and 1700 (CO) cm$^{-1}$, $\tau$(CDCl$_3$) 2.10 - 2.64 (5H, m, ArH), 5.59[2H, q(J 7Hz), CH$_2$], 7.18(3H, s, Ac), and 8.59[3H, t(J 7Hz), CH$_3$], from the hydrazone (223d).

1,3-Diphenylpropane-1,2,3-trione 2-(1-Acetyl-4-phenyl-1,2,3-triazol-5-yl) hydrazone (223j) was prepared, as a yellow solid, $\nu_{\text{max}}$ 1750 (Ac), and 1660 and 1650 sh (CO) cm$^{-1}$, $\tau$(CDCl$_3$) 1.90 - 2.68 (15H, m, ArH), and 7.20(3H, s, Ac), from the hydrazone (223d).

Phenylglyoxalonitrile 2-(1-acetyl-4-phenyl-1,2,3-triazol-5-yl) hydrazone (223k) was isolated, as a yellow solid, $\nu_{\text{max}}$ 2250 w (CN), 1750 (Ac) and 1650 (CO) cm$^{-1}$, $\tau$(CDCl$_3$) 1.92 - 2.90(10H, m, ArH), and 7.17(3H, s, Ac), from the hydrazone (223c).

The attempted acetylation of the hydrazones (223b and f), as described above, yielded only black tarry material.

(f) Direct Synthesis of the Triazolo[5,1-c]triazoines (221 f and g)
and (222a)

Solutions of the active methylene compounds (0.007 mol) and anhydrous sodium acetate (1.6 g) in water (2.0 ml) and ethanol (5.0 ml) were cooled to 0° and then stirred and treated dropwise with a solution of the diazonium salt (220) (1.4 g, 0.0065 mol) in ethanol (25 ml) and water (25 ml). The mixtures were stirred in the melting ice bath for 3 h and were then heated under reflux for 1.5 h. On cooling the solid products were collected. Evaporation of the ethanol from the filtrate under reduced pressure and extraction of the aqueous mother liquors with chloroform gave small quantities of gums which were shown by t.l.c. to be multi-component mixtures. The triazolo[5,1-c]triazine (221g) (49%) m.p. 212° (from aqueous dimethylformamide) was obtained from benzoylacetonitrile. Starting material (84%) was recovered from the attempted reaction with dibenzoylmethane. In the case of diethyl malonate the insoluble solid obtained when reaction was complete was the sodium salt of the product. The salt was acidified with dilute aqueous hydrochloric acid and the solid was collected and combined with a further crop obtained by acidifying the reaction mother liquors with dilute aqueous hydrochloric acid to give the triazol[4]triazine (222a) m.p. 167° (from ethanol-glacial acetic acid).

5.2. Reactions of Triazolo[5,1-c]triazine Derivatives
(a) 3,5-Dimethylpyrazol-4-one (4-phenyl-1H-1,2,3-triazol-5-yl) hydrazone (238)

The triazolotriazine (221a) (0.50g, 0.002 mol) in methanol (20 ml) containing 85% hydrazine hydrate (0.5 ml) was heated under reflux for 1.5 h. On cooling the insoluble hydrazone (221k) was filtered off (13%), m.p. 228°C (from ethanol). The original methanol mother liquor was evaporated under reduced pressure to afford the yellow pyrazole (238) (0.44g, 84%), as yellow needles, m.p. 218°C (from ethanol), $\nu_{\text{max}}$ 3300 - 2400 br (NH), and 1590 cm$^{-1}$ (NH def) cm$^{-1}$. $\delta [(CD_3)_2SO]$ 1.79 - 2.70 (5H, m, ArH), and 7.48 (6H, s, CH$_3$). $\text{C}_{13}\text{H}_{11}\text{N}_7$ requires: C, 58.4; H, 4.9; N, 36.7%; M 265. Found: C, 58.3; H, 4.9; N, 36.7%; M$^+$ 265.

(b) 4-(4-Phenyl-1H-1,2,3-triazol-5-ylazo)-3,5-dimethyl-1-phenylpyrazole (233)

The triazolotriazine (221a) (0.50g, 0.002 mol) in methanol (20 ml) containing freshly distilled phenylhydrazine (0.22g, 0.002 mol) was heated under reflux for 3 h. The methanol was evaporated under reduced pressure to give the pyrazole (233) (0.67g, 100%), as yellow needles, m.p. 196°C (from ethanol), $\nu_{\text{max}}$ 3200 - 2500 br (NH), and 1580 cm$^{-1}$ (NH def) cm$^{-1}$. $\delta (\text{CF}_3\cdot \text{CO}_2\text{H})$ 1.80 - 2.48 (1OH, m, ArH), 7.07 (3H, s, CH$_3$), and 7.20 (3H, s, CH$_3$).
C_{19}H_{11}N_{7} \text{ requires: } C, 66.5; H, 5.0; N, 28.6\%; M 343.

\textbf{Found: } C, 66.5; H, 5.0; N, 28.6\%; M^{+} 343.

(c) 4-(4-Phenyl-1H-1,2,3-triazol-5-ylazo)-3,5-dimethylisoxazole (239)

Solutions of the triazolotriazine (221a) (0.50g, O.002 mol) in methanol (20 ml) and hydroxylamine hydrochloride (O.13g, O.002 mol) in water (1.0 ml), neutralised with sodium acetate, were mixed and heated under reflux for 1.5 h. The methanol was evaporated under reduced pressure and the product (0.46g, 85\%) was collected, as a yellow solid, m.p. 187° (from ethanol), ν_{max} 3150 (NH) and 1600 (NHdef) cm^{-1}, T(CF_{3}.CO_{2}H) 1.64 - 2.40 (5H, m, ArH), 7.92 (1H, s), 8.10 (2H, s), 8.33 (2H, s), and 8.44 (1H, s).

C_{13}H_{12}N_{6}O \text{ requires: } C, 58.2; H, 4.5; N, 31.3\%; M 248.

\textbf{Found: } C, 58.2; H, 4.4; N, 31.0\%; M^{+} 248.

(d) \textbf{Attempted Cleavage of the Ketone (221a) with Ethanolic Potassium Hydroxide}

The ketone (221a) (0.25g, O.001 mol) in ethanol (10 ml) containing 20\% w/v aqueous potassium hydroxide (10 ml) was heated under reflux for 0.75 h. The ethanol was evaporated under reduced pressure and the aqueous solution was acidified with dilute aqueous hydrochloric acid and extracted with chloroform to yield a black gum (0.21g).
(e) **Attempted Oxidative Cleavage of the Ketone (221a)**

The ketone (221a) (O. 50g, O. 002 mol) was stirred at room temperature for 17 h in 1M aqueous sodium hydroxide (5 ml) containing 3% aqueous hydrogen peroxide (O. 25 ml). The insoluble starting material (identified by its i.r. spectrum) was filtered off (86%). Acidification of the filtrate with dilute aqueous hydrochloric acid and extraction of the acidic solution with chloroform yielded a gum (O. 03g) which was shown by t.l.c. to be a multicomponent mixture.

(f) **Hydrolysis of the Esters (221b) and (222a)**

The esters (221b) and (222a) (O. 001 mol) were heated under reflux in 1M methanolic potassium hydroxide (50 ml) for 1.0h. The methanol was evaporated under reduced pressure and the aqueous solution was acidified with dilute aqueous hydrochloric acid to yield the acids, (221j) (93%), m.p. 179° (from ethanol-acetic acid), \( \nu_{\text{max}} \) 3700-3300 br (OH), and 1740 and 1720 sh (CO) cm\(^{-1}\).

\[
\text{C}_{12}\text{H}_{9}\text{N}_5\text{O}_2 \quad \text{requires: C, 56.5; H, 3.5; N, 27.4%; M 255.}
\]

\[
\text{Found: C, 57.0; H, 3.5; N, 27.6% M}^+ 255.
\]

and (223g) (81%), m.p. 234° (from ethanol-light petroleum), \( \nu_{\text{max}} \) 3700 - 3300 br (OH), 1680 (CO), and 1620 (NH def) cm\(^{-1}\), \( T[(\text{CD}_3)_2\text{SO}] \) 1.94 - 2.74 (m, ArH).
C_{11}H_{9}N_{5}O_{4}.H_{2}O requires:  C, 48.0; H, 3.3; N, 25.5%; M 257.

Found:  C, 48.1; H, 3.3; N, 25.6%; M^+257.

Hydrolysis of the ester (223a) with 2M aqueous sodium carbonate and 2M aqueous sodium hydroxide afforded the acid (223g), identical (m.p. and i.r. spectrum) to that obtained before.

Attempted decarboxylation of the acid (221j) by heating under reflux in dimethylformamide for 0.5h, followed by dilution of the reaction mixture with water, led to the starting acid (77%).

Attempted Esterification of the Hydrazone Acid (223g)

The acid (223g) (0.28g, 0.001 mol) in ethanol (10 ml) containing concentrated sulphuric acid (1.0 ml) was heated under reflux for 6.0h. On cooling no solid resulted and the ethanol was partially evaporated under reduced pressure. The remainder of the solution was poured on to ice (30g) and the solution was extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield a yellow oil (0.28g) which was shown by t.l.c. to be a multicomponent mixture.

(g) Methylation of the Triazolotriazinone (222a)

6-Ethoxycarbonyl-4-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one (222c)

The ester (222a) (1.14g, 0.004 mol) in anhydrous acetone (150 ml) was heated under reflux on a boiling water bath with
methyl iodide (0.4 g) and anhydrous potassium carbonate (0.8 g) for 3.0 h. The mixture was evaporated and water (20 ml) was added to the resultant cake. The aqueous solution was extracted with chloroform to give the N-methyl derivative (222c) (0.60 g, 50%), as orange plates, m.p. 195° (from ethanol-glacial acetic acid), $v_{\text{max}}$ 1740 sh and 1700 (CO) cm$^{-1}$, $T(\text{CD}_3\text{SO})$ 1.72 - 2.61 (5H, m, ArH), 5.50 [2H, q (J 7 Hz) CH$_2$], 5.54 (3H, s, CH$_3$), and 8.61 [3H, t (J 7 Hz) CH$_3$].

$\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_3$ requires: C, 56.2; H, 4.4; N, 23.4%; M 299.  

Found: C, 56.2; H, 4.5; H, 23.8%; M$^+$ 299.

Acidification of the aqueous layer with dilute aqueous hydrochloric acid gave the starting triazolotriazine (222a) (0.42 g, 37%) (identified by its i.r. spectrum).

6-Methoxycarbonyl-7-methoxy-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (2211)

The ester (222a) (0.29 g, 0.001 mol) in 10% w/v aqueous sodium hydroxide (10 ml) containing dimethyl sulphate (0.75 ml) was shaken at room temperature for 5 h. The precipitated product (2211) was collected (0.14 g, 49%), as yellow plates, m.p. 175° (from ethanol-glacial acetic acid), $v_{\text{max}}$ 1740 (CO) cm$^{-1}$, $T(\text{CF}_3\text{CO}_2\text{H})$ 1.72 - 2.41 (5H, m, ArH), 5.55 (3H, s, CH$_3$), and 5.71 (3H, s, CH$_3$).

$\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_3$ requires: C, 54.7; H, 3.9; N, 24.6%; M 285.
Found:  C, 54.3; H, 4.0; N, 24.8%; M+ 285.

The filtrate, on extraction with chloroform, afforded an unidentified yellow oil (0.10g).

(h) **Attempted Transformations of the Triazolotriazines (221f)**

and (221h) into the amide (221i)

(i) The nitrile (221h) (0.23g, 0.001 mol) was warmed at 80° in polyphosphoric acid (5 ml) for 3 h and the cooled solution was poured into water (20 ml). Extraction with chloroform afforded no material. The aqueous solution was neutralised with sodium hydrogen carbonate and re-extraction with chloroform again afforded no material.

(ii) The nitrile (221h) (0.23g, 0.001 mol) was stirred in concentrated sulphuric acid (1 ml) at room temperature for 1 h. The solution was poured onto ice (5g) and the solid was collected (0.21g) and shown by its i.r. spectrum to be starting material.

(iii) The ester (221f) (0.27g, 0.001 mol) in dimethylformamide (3 ml) was saturated at 0° with ammonia and the solution was left at room temperature for 24 h. The crystalline amide (221i) (0.09g, 38%), which was identical (m.p., mixed m.p. and i.r. spectrum) to an authentic sample, was filtered off. Work up of the mother liquor by dilution with water gave a red solid (0.06g), m.p. 218°, which was a mixture of the starting ester (221f) and the product amide (221i).

(i) **Independent Synthesis of 4-(4-Phenyl-1H-1,2,3-triazol-5-ylazo)-3,5-dimethyl-1-phenylpyrazole (233)**
3,5-Dimethyl-4-nitroso-1-phenyl-pyrazole (235), prepared by the method of Wolff\(^94\) had m.p. 93\(^\circ\) (from ethanol) lit.\(^94\) 94\(^\circ\).

A mixture of nitrosopyrazole (235) (1.0g, 0.005 mol) and the aminotriazole (30) (0.8g, 0.005 mol) in glacial acetic acid (20 ml) was stirred at room temperature for 48 h. The reaction mixture was poured into water (200 ml) and the aqueous solution was extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate to afford a dark gum (1.14g) which was chromatographed over alumina to give on elution with 50\% toluene-light petroleum the starting pyrazole (0.11g, 11\%), m.p. 93\(^\circ\) (identified by its i.r. spectrum), and on further elution with toluene, the product (233) (0.19g, 11\%), which was identical (m.p., mixed m.p. and i.r. spectrum) to the sample prepared previously.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>m.p.(°)</th>
<th>Formula</th>
<th>C(%)</th>
<th>H(%)</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>221a</td>
<td>90</td>
<td>210(^a)</td>
<td>(\text{C}<em>{13}\text{H}</em>{11}\text{N}_{5}\text{O})</td>
<td>61.7</td>
<td>4.4</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 61.3</td>
<td>4.3</td>
<td>27.8</td>
</tr>
<tr>
<td>221b</td>
<td>90</td>
<td>174(^a)</td>
<td>(\text{C}<em>{14}\text{H}</em>{13}\text{N}<em>{5}\text{O}</em>{2})</td>
<td>59.3</td>
<td>4.6</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 59.3</td>
<td>4.7</td>
<td>24.4</td>
</tr>
<tr>
<td>221c</td>
<td>90</td>
<td>157(^a)</td>
<td>(\text{C}<em>{18}\text{H}</em>{13}\text{N}_{5}\text{O})</td>
<td>68.6</td>
<td>4.2</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 69.1</td>
<td>4.2</td>
<td>22.7</td>
</tr>
<tr>
<td>221h</td>
<td>98</td>
<td>202(^b)</td>
<td>(\text{C}<em>{11}\text{H}</em>{7}\text{N}_{7})</td>
<td>55.7</td>
<td>3.0</td>
<td>41.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 55.7</td>
<td>3.0</td>
<td>42.1</td>
</tr>
<tr>
<td>221f</td>
<td>38</td>
<td>224(^a)</td>
<td>(\text{C}<em>{13}\text{H}</em>{12}\text{N}<em>{6}\text{O}</em>{2})</td>
<td>54.9</td>
<td>4.2</td>
<td>29.5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 54.9</td>
<td>4.2</td>
<td>29.0</td>
</tr>
<tr>
<td>223c</td>
<td>61</td>
<td>149(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221i</td>
<td>72</td>
<td>245(^b)</td>
<td>C(_{11})H(_9)N(_7)O</td>
<td>requires: 51.8 3.5 38.4 M 255</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
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<td>---------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 51.3 3.5 38.8 M(^+)255</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>223f</td>
<td>24</td>
<td>175(^c)</td>
<td>C(_{11})H(_9)N(_7)O</td>
<td>requires: 51.8 3.5 38.4 M 255</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 53.2 4.3 37.8 M(^+)255</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221g</td>
<td>4</td>
<td>214(^b)</td>
<td>C(<em>{17})H(</em>{12})N(_6)O</td>
<td>requires: 64.6 3.8 26.6 M 316</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 64.6 3.9 26.7 M(^+)316</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>223e</td>
<td>93</td>
<td>155(^c)</td>
<td>C(<em>{17})H(</em>{12})N(_6)O</td>
<td>requires: 64.6 3.8 26.6 M 316</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 64.7 4.1 26.2 M(^+)316</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>223a</td>
<td>96</td>
<td>110(^c)</td>
<td>C(<em>{15})H(</em>{17})N(_5)O(_4)</td>
<td>requires: 54.4 5.2 21.1 M 331</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 54.2 5.0 21.7 M(^+)331</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>223b</td>
<td>97</td>
<td>150(^c)</td>
<td>C(<em>{19})H(</em>{17})N(_5)O(_3)</td>
<td>requires: 62.8 4.7 19.3 M 363</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 62.8 4.6 19.5 M(^+)363</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>223d</td>
<td>65</td>
<td>149(^c)</td>
<td>C(<em>{22})H(</em>{17})N(_5)O(_2)</td>
<td>requires: 69.9 4.3 17.7 M 395</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 69.8 4.3 17.8 M(^+)395</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Crystallised from ethanol-glacial acetic acid

\(^b\) from aqueous dimethylformamide

\(^c\) from ethanol-light petroleum

\(^d\) Cyclised on attempted crystallisation
Table 6

Triazolo[5,1-c]triazines (221 e-g and i) and (222 a and b) Obtained by Base Catalysed Cyclisation of Hydrazones (223 a-f)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>m.p. (°)</th>
<th>Formula</th>
<th>C(%)</th>
<th>H(%)</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>221e</td>
<td>90</td>
<td>224°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221i</td>
<td>95</td>
<td>245°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221g</td>
<td>30</td>
<td>214°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221f</td>
<td>95</td>
<td>204°</td>
<td>C_{23}H_{15}N_{5}O</td>
<td>requires: 73.2</td>
<td>4.0</td>
<td>18.6 M 377</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 73.0</td>
<td>3.9</td>
<td>19.0 M^{+} 377</td>
</tr>
<tr>
<td>222a</td>
<td>89</td>
<td>167°</td>
<td>C_{13}H_{11}N_{5}O_{3}</td>
<td>requires: 54.7</td>
<td>3.9</td>
<td>24.6 M 285</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 54.8</td>
<td>3.9</td>
<td>24.1 M^{+} 285</td>
</tr>
<tr>
<td>222b</td>
<td>95</td>
<td>202°</td>
<td>C_{17}H_{11}N_{5}O_{2}</td>
<td>requires: 64.3</td>
<td>3.5</td>
<td>22.1 M 317</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 63.8</td>
<td>3.4</td>
<td>22.3 M^{+} 317</td>
</tr>
<tr>
<td>221d</td>
<td>2.5</td>
<td>147°</td>
<td>C_{19}H_{15}N_{5}O_{2}</td>
<td>requires: 66.1</td>
<td>4.4</td>
<td>20.3 M 345</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: 66.1</td>
<td>4.3</td>
<td>20.7 M^{+} 345</td>
</tr>
</tbody>
</table>

a Crystallised from ethanol-glacial acetic acid  
b from aqueous dimethylformamide
<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield(%)</th>
<th>m.p.(°)</th>
<th>Formula</th>
<th>C(%)</th>
<th>H(%)</th>
<th>N(%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>223g</td>
<td>57</td>
<td>112(^a)</td>
<td>C(<em>{17}H</em>{19}N_5O_5)</td>
<td>54.7</td>
<td>5.1</td>
<td>18.8</td>
<td>M+373</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>requires: 54.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found: 54.5</td>
<td>5.0</td>
<td>19.0</td>
<td>M+373</td>
<td></td>
</tr>
<tr>
<td>223h</td>
<td>64</td>
<td>117(^a)</td>
<td>C(<em>{15}H</em>{14}N_6O_3)</td>
<td>55.2</td>
<td>4.3</td>
<td>25.8</td>
<td>M+326</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>requires: 55.1</td>
<td>4.2</td>
<td>26.2</td>
<td>M+326</td>
<td></td>
</tr>
<tr>
<td>223i</td>
<td>52</td>
<td>125(^a)</td>
<td>C(<em>{25}H</em>{19}N_5O_3)</td>
<td>68.6</td>
<td>4.4</td>
<td>16.0</td>
<td>M+437</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>requires: 63.8</td>
<td>4.0</td>
<td>16.6</td>
<td>M+437</td>
<td></td>
</tr>
<tr>
<td>223j</td>
<td>78</td>
<td>160(^a)</td>
<td>C(<em>{19}H</em>{14}N_6O_2)</td>
<td>63.7</td>
<td>4.0</td>
<td>23.4</td>
<td>M+358</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>requires: 63.8</td>
<td>4.0</td>
<td>23.2</td>
<td>M+358</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Crystallised from ethyl acetate-light petroleum
<table>
<thead>
<tr>
<th>Compound</th>
<th>λ max (nm)</th>
<th>log ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>221a</td>
<td>222, 260, 305 inf, 400</td>
<td>4.06, 4.35, 3.65, 2.95</td>
</tr>
<tr>
<td>221b</td>
<td>220, 262, 301 inf, 404</td>
<td>4.06, 4.44, 4.00, 3.13</td>
</tr>
<tr>
<td>221c</td>
<td>222 inf, 260, 402</td>
<td>4.07, 4.41, 3.18</td>
</tr>
<tr>
<td>221d</td>
<td>253, 295, 426</td>
<td>4.32, 4.21, 3.50</td>
</tr>
<tr>
<td>221e</td>
<td>220, 281, 450</td>
<td>4.14, 4.28, 2.94</td>
</tr>
<tr>
<td>221f</td>
<td>215 inf, 260, 285 inf, 426</td>
<td>4.21, 3.53, 4.33, 3.59</td>
</tr>
<tr>
<td>221g</td>
<td>225, 271, 301 inf, 450</td>
<td>4.23, 4.42, 4.28, 2.62</td>
</tr>
<tr>
<td>221h</td>
<td>223, 270 sh, 282, 475</td>
<td>4.17, 4.32, 4.34, 2.63</td>
</tr>
<tr>
<td>221i</td>
<td>223, 278, 434</td>
<td>4.25, 4.41, 3.17</td>
</tr>
<tr>
<td>222a</td>
<td>217, 265, 370</td>
<td>4.11, 4.49, 3.77</td>
</tr>
<tr>
<td>222b</td>
<td>219, 261, 382</td>
<td>4.14, 4.50, 3.41</td>
</tr>
<tr>
<td>223a</td>
<td>220, 258, 339</td>
<td>4.06, 4.07, 4.09</td>
</tr>
<tr>
<td>246d</td>
<td>224, 264</td>
<td>4.14, 4.21</td>
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<tr>
<td>246f</td>
<td>220, 244, 318</td>
<td>4.02, 4.12, 3.82</td>
</tr>
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<td>220, 245, 321</td>
<td>4.02, 4.08, 3.75</td>
</tr>
<tr>
<td>250a</td>
<td>219, 244, 318</td>
<td>4.00, 4.10, 3.83</td>
</tr>
</tbody>
</table>
5.3. **Triazole Scission of 1,2,3-Triazolo[5,1-c]-1,2,4-triazines**

(a) **3-(a-Acetoxybenzyl)-1,2,4-triazines (246a-i)**

The triazolotriazines (221 a-c, and e-j) and (222 a and b) (0.005 mol) were heated under reflux in glacial acetic acid (50 ml) for 5-24 h. The glacial acetic acid was evaporated under reduced pressure and chloroform was added. The chloroform solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give the products which were dark gums or solids.

Yields, melting points, m.s., and analytical data are collected in Table 9 and u.v. data in Table 8.

(i) The gum obtained from the triazolotriazine (221a) was purified by dry column chromatography in ether over alumina to give **3-(a-acetoxybenzyl)-6-acetyl-5-methyl-1,2,4-triazine (246b)**,

\[
\nu_{\text{max}} \text{ (thin film) } 1745 \text{ (C.OAc)} \text{ and } 1705 \text{ (CO) } \text{ cm}^{-1}, \ \tau(\text{CDCl}_3) \ 2.35 - 2.90 \ (5H, \text{ m, ArH}), \ 3.17 \ (1H, \text{ s, CH}), \ 7.24 \ (3H, \text{ s, CH}_3), \ 7.26 \ (3H, \text{ s, CH}_3), \ \text{and} \ 7.80 \ (3H, \text{ s, OAc}).\\
\]

The triazine (246b) failed to give a dinitrophenylhydrazone or a picrate derivative.

(ii) The triazolotriazine (221b) gave without purification **3-(a-acetoxybenzyl)-6-ethoxycarbonyl-5-methyl-1,2,4-triazine (246c)**,

\[
\nu_{\text{max}} \text{ (thin film) } 1730 \text{ br (CO and C.OAc)}, \ \tau(\text{CDCl}_3) \ 2.30 - 2.82 \ (5H, \text{ m, ArH}), \ 3.12 \ (1H, \text{ s, CH}), \ 5.54 \ [2H, q(\text{J 7Hz}) \ CH_2], \ 7.27 \ (3H, \text{ s, CH}_3), \ 7.70 \ (3H, \text{ s, OAc}), \ \text{and} \ 8.60 \ [3H, t(\text{J 7Hz}) \ CH_3].\\
\]

(iii) The gums from the compounds (221b) and (221j) were
purified by dry column chromatography in ether over alumina to afford 3-(a-acetoxybenzyl)-5-methyl-1,2,4-triazine (246a), \( \nu_{\text{max}} \) (thin film) 1730 (OAc cm\(^{-1}\)), \( \delta(\text{CDCl}_3) \) 1.10 (1H, s, CH), 2.30-2.85 (5H, m, ArH), 3.15 (1H, s, CH), 7.57 (3H, s, CH\(_3\)), and 7.84 (3H, s, OAc).

(iv) The gum from compound (221c) was purified by chromatography in 1:1 toluene-ether over alumina to give 3-(a-acetoxybenzyl)-6-benzoyl-5-methyl-1,2,4-triazine (246d), \( \nu_{\text{max}} \) 1740 (OAc) and 1670 (CO) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 1.99 - 2.70 (1OH, m, ArH), 3.07 (1H, s, CH), 7.37 (3H, s, CH\(_3\)), and 7.76 (3H, s, OAc).

(v) The crude solid obtained from the compound (221f) was washed with a little ether and crystallised to yield 3-(a-acetoxybenzyl)-5-amino-6-ethoxycarbonyl-1,2,4-triazine (246f), \( \nu_{\text{max}} \) 3450, 3250 and 3200 (NH), 1730 (OAc), 1700 (CO) and 1620 (NH\(_{\text{def}}\)) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 2.10 (1H, br, NH), 2.37 - 2.75 (5H, m, ArH), 3.32 (1H, s, CH), 4.04 (1H, br, NH), 5.55[2H, q(J 7Hz) CH\(_2\)], 7.80 (3H, s, OAc), and 8.58[3H, t(J 7Hz), CH\(_3\)].

(vi) The triazolotriazine (221e) gave a solid which was washed with a little ether and purified by crystallisation to give 3-(a-acetoxybenzyl)-6-benzoyl-5-phenyl-1,2,4-triazine (246c), \( \nu_{\text{max}} \) 1725 (OAc) and 1680 (CO) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 1.84 - 2.71 (15H, m, ArH), 3.31 (1H, s, CH), and 7.80 (3H, s, OAc).

(vii) The solid obtained from the triazolotriazine (221g) was
purified by dry column chromatography in ether over alumina to
give 3-(α-acetoxybenzyl)-6-benzoyl-5-amino-1,2,4-triazine (246g),
\( \nu_{\text{max}} \) 3450 and 3200 (NH), 1730 (C\_OAc) and 1680 (CO) cm\(^{-1}\),
\( \tau(\text{CDCl}_3) \) 1.66 (1H, br, NH), 1.88 - 2.80 (1OH, m, ArH), 3.26
(1H, s, CH), 3.40 (1H, br, NH), and 7.78 (3H, s, OAc).

(viii) The gum obtained from the triazolotriazine (221h) was
purified by chromatography in toluene over silica to give 3-(α-
acetoxybenzyl)-5-amino-6-cyano-1,2,4-triazine (241h), \( \nu_{\text{max}} \) 3350 and 3250 (NH), 2280 w (CN), 1730 (C\_OAc) and 1640 (NH\_def),
\( \tau(\text{CDCl}_3) \) 2.40 - 2.86 (5H, m, ArH), 3.34 (1H, s, CH), 3.48
(2H, br, NH), and 7.82 (3H, s, OAc).

(ix) The triazolotriazine (221i) gave a solid which was purified by
chromatography in ether over alumina to give 3-(α-acetoxybenzyl)-
5-amino-1,2,4-triazine-6-carboxamide (246i), \( \nu_{\text{max}} \) 3500 - 3100
br (NH), 1720 (C\_OAc), 1680 (CO) and 1610 (NH\_def) cm\(^{-1}\),
\( \tau(\text{CDCl}_3) \) 1.50 (1H, br, NH), 2.16 (1H, br, NH), 2.40 - 2.62
(5H, m, ArH), 3.33 (1H, s, CH), 3.64 (2H, br, NH), and 7.80
(3H, s, OAc).

(x) The sodium hydrogen carbonate extract from the reaction of
the triazolotriazine (222b) was acidified with dilute aqueous
hydrochloric acid and extracted with chloroform to give 3-(α-
acetoxybenzyl)-6-benzoyl-1,2,4-triazin-5(2H)-one (247c), \( \nu_{\text{max}} \) 1740 (C\_OAc) and 1680 (CO) cm\(^{-1}\), \( \tau(\text{CDCl}_3) \), 2.02 - 2.92
(10H, m, ArH), 3.40 (1H, s, CH), and 7.92 (3H, s, OAc).

(xi) The crude gum from the ester (222a) proved to be a mixture of 3-(α-acetoxybenzyl)-6-ethoxycarbonyl-1,2,4-triazin-5(2H)-one (247b) and the decarbethoxylated triazine 3-(α-acetoxybenzyl)-1,2,4-triazin-5(2H)-one (247a), \( \nu_{\text{max}} \) 1740 br (C.OAc) and 1720 (CO) cm\(^{-1}\), \( \tau(\text{CDCl}_3) \) 2.13 (s, CH), 2.30 - 2.84 (5H, m, ArH), 3.40 (br, CH), 5.52 [q(J 7Hz), CH\(_2\)] and 8.59 [t(J 7Hz), CH\(_3\)]. The gum was totally soluble in saturated aqueous sodium hydrogen carbonate and was regenerated on acidification with dilute aqueous hydrochloric acid. The gum adsorbed irretrievably on alumina or silica on attempted separation by column chromatography.

(b) 5-Amino-3-(α-chlorobenzyl)-6-ethoxycarbonyl-1,2,4-triazine (248)

The triazolotriazine (221e) (1.32g, 0.005 mol) was heated under reflux with acetyl chloride (12.5 ml) in glacial acetic acid (17.5 ml) for 4.0h. The mixture was evaporated under reduced pressure, chloroform was added, and the solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated under reduced pressure to give a light coloured gum. Chromatography in 1:1 toluene-ether over alumina afforded the chlorotriazine, as a colourless solid, (0.44g, 30%), m.p. 110\(^{\circ}\) (from benzene-light petroleum), \( \nu_{\text{max}} \) 3400, 3300 and 3200 (NH), 1695 (CO) and 1630 (NH def) cm\(^{-1}\), \( \tau(\text{CDCl}_3) \) 2.08 (1H, br, NH), 2.28 - 2.86 (5H, m,
ArH), 3.44 (1H, br, NH), 3.79 (1H, 5, CH), 5.54 [2H, q(J 7 Hz), CH₂], and 8.61 [3H, b(J 7 Hz) CH₃].

\[
\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_2\text{Cl} \text{ requires: } C, 53.3; H, 4.4; N, 19.2\%; M 292. \\
\text{Found: } C, 53.6; H, 4.5; N, 19.2\%; M^+ 292.
\]

(c) The Attempted Scission of the Triazolotriazines (221b and f) to 3-(α-Bromobenzyl)-1,2,4-triazines

The triazolotriazines (221b and f) (0.001 mol) were heated under reflux with acetyl bromide (2.5 ml) in glacial acetic acid (3.5 ml) for 4.0 h. The mixture was evaporated under reduced pressure, chloroform was added, and the solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield black gums, which were shown by t.l.c. to be multicomponent mixtures.

(d) The Attempted Scission of the Triazolotriazines (221c and i) to 3-Benzyl-1,2,4-triazines

(i) The triazolotriazine (221c) (0.29g, 0.001 mol) in glacial acetic acid (20 ml) was heated under reflux with sodium dithionite (0.62g) for 17 h. The solution was filtered hot and evaporated under reduced pressure. Chloroform was added to the resultant gum and the solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated under reduced pressure to give the acetoxytriazine (246d) (0.32g, 91%) m.p. 125°, identical (i.r. spectrum) to a sample obtained before.
(ii) A solution of the triazolotriazine (221i) (0.27g, 0.001 mol) in ethanol (30 ml) and glacial acetic acid (5.0 ml) was heated under reflux with hypophosphorus acid (0.6 ml) for 3.0h. The mixture was evaporated under reduced pressure, chloroform was added and the solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated under reduced pressure to afford the starting material (84%) (identified by its i.r. spectrum).

(e) **The Attempted Scission of 1,2,3-Triazolo-[5,1-c]-1,2,4-triazines to 3-(a-Hydroxybenzyl)-1,2,4-triazines**

(i) The triazolotriazine (221a) (0.25g, 0.001 mol) in glacial acetic acid (20 ml) was heated under reflux with 20% w/v aqueous sulphuric acid (5 ml) for 1.5h. The dark solution was concentrated, diluted with water and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a black tar (0.23g) which was shown by t.l.c. to be a multicomponent mixture.

(ii) The triazolotriazine (221a) (0.25g, 0.001 mol) in ethanol (38 ml) was heated under reflux with 2M aqueous hydrochloric acid (2ml) for 6h. The ethanol was evaporated under reduced pressure, water was added and the aqueous solution was extracted with chloroform to give a yellow oil (0.27g) which was shown by t.l.c. to be a multicomponent mixture.

(f) **The Attempted Scission of the Ketone (221a) to 6-Acctyl-3-**
benzoyl-5-methyl-1,2,4-triazine

The triazolotriazine (221a) (0.50g, 0.002 mol) in 70% v/v aqueous acetic acid (40 ml) containing chromium trioxide (1.2g) was heated on a boiling water bath for 2.0h. The solvent was removed under reduced pressure and water was added. The aqueous solution was extracted with chloroform and the extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a dark gum (0.49g) which was shown by t.l.c. to be a multicomponent mixture.

5.4. Reactions of 1,2,4-Triazines

(a) Catalytic Hydrogenation of 3-(a-Acetoxybenzyl)-1,2,4-triazines

The acetoxybenzyltriazines (246a, e and i) (0.002 mol) were hydrogenated in ethanol over 10% palladium-charcoal.

(i) In the case of the triazine (246e) evaporation of the filtered mixture gave 5-amino-3-benzyl-6-ethoxycarbonyl-1,2,4-triazine (250a) (90%) m.p. 110° (from benzene-light petroleum), $\nu_{\text{max}}$ 3400, 3300, and 3200 (NH), 1695 (CO) and 1630 (NH def) cm$^{-1}$, $\delta$(CDCl$_3$) 2.30 (1H, br, NH), 2.58 - 2.86 (5H, m, ArH), 3.96 (1H, br, NH), 5.56[2H, q(J 7Hz), CH$_2$], 5.82 (2H, s, CH$_2$), and 8.59[3H, t(J 7Hz) CH$_3$].

C$_{13}$H$_{14}$N$_4$O$_2$ requires: C, 60.5; H, 5.5; N, 21.7%; M 258.

Found: C, 60.4; H, 5.2; N, 21.6%, M$^+$ 258.
(ii) The acetoxybenzyltriazine (246i) gave starting material (82%) (identified by its i.r. spectrum).

(iii) The filtered mixture from the acetoxybenzyltriazine (246b) was evaporated to afford a gum (0.42g) which was shown by t.l.c. to contain at least five components.

(b) 3-(α-Hydroxybenzyl)-1,2,4-triazines

(i) The acetoxybenzyltriazines (246 b, d and i) (0.001 mol) in ethanol (10 ml) were heated under reflux with 1M aqueous sodium carbonate (5 ml) for 0.5h. The ethanol was evaporated under reduced pressure, water was added and the aqueous solutions were extracted with chloroform. Evaporation of the chloroform extracts afforded the products.

5-Amino-3-(α-hydroxybenzyl)-1,2,4-triazine-5-carboxamide

(249b) (98%) m.p. 103° (from benzene), ν\(\text{max} \) 3600-2050 br (NH and OH), 1690 (CO) and 1630 (NH def) cm\(^{-1}\), \(\text{T(CF}_3\text{CO}_2\text{H}) \) 0.14 (1H, br, NH), 1.59 (1H, br, NH), 1.93 (1H, br, NH), 2.35 (1H, br; NH), 2.55 (5H, s, ArH), and 3.94 (1H, s, CH), was prepared from the acetoxybenzyltriazine (246i).

\(\text{C}_{11}\text{H}_{11}\text{N}_5\text{O}_2\) requires: C, 53.9; H, 4.5; N, 28.6% ; M 245.

\(\text{Found: C, 54.2; H, 4.7; N, 26.1%; M}^+\text{245.}\)

The acetoxytriazines (246a and d) afforded black gums which were shown by t.l.c. to be multicomponent mixtures.

(ii) The acetoxybenzyltriazines (246b and d) were treated with
saturated aqueous sodium hydrogen carbonate under the conditions described in (a) above and the mixtures were worked up as before.

The acetoxybenzyltriazine (246d) afforded 6-benzoyl-3-(a-hydroxybenzyl)-5-methyl-1,2,4-triazine (249a) (91%), $v_{\text{max}}$ (thin film) 3700 - 3150 br (OH) and 1670 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 1.98 - 2.86 (1OH, m, ArH), 3.84 (1H, s, CH), and 7.37 (3H, s, CH$_3$).

The acetoxybenzyltriazine (246a) afforded a low yield of a black gum which could not be characterised.

(c) The Attempted Oxidation of the Triazines (246b) and (249b) to Benzoyltriazines

(i) 5-Amino-3-benzoyl-1,2,4-triazine-6-carboxamide (25i)

A solution of the hydroxybenzyltriazine (249b) (0.25g, O.001 mol) in acetone (10 ml) was heated under reflux on a boiling water bath with activated manganese dioxide (1.0g) for 2.0h. The solution was filtered hot and the residue was washed with hot acetone. The combined acetone filtrate and washings were evaporated to give the benzoyltriazine (251) (0.05g, 20%) m.p. 222° (from ethanol-light petroleum), $v_{\text{max}}$ 3500 - 3100 br (NH), 1680 (CO) and 1630 (NH$_{\text{def}}$) cm$^{-1}$, $\delta$(CF$_3$.CO$_2$H) O.97 (1H, br, NH), 1.56 - 1.76 (2H, m, ArH), 1.85 (1H, br, NH), 2.05 - 2.44 (3H, m, ArH), and 2.52 (2H, br, NH).

$\text{C}_{11}\text{H}_{9}\text{N}_{5}\text{O}_2$ requires: C, 54.3; H, 3.7; N, 28.8%; M 243.

Found: C, 54.3; H, 3.7; N, 28.6%; M$^+$ 243.
(ii) A solution of the acetoxybenzyltriazine (246b) (0.15 g) in 70% aqueous acetic acid (10 ml) containing chromium trioxide (0.30 g) was stirred at room temperature for 48 h. Water (10 ml) was added and the aqueous solution was extracted with chloroform which was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a yellow gum (0.13 g) which was shown by its 1H n.m.r. spectrum to be the starting triazine.

The gum (0.13 g) in 70% aqueous acetic acid (10 ml) containing chromium trioxide (0.30 g) was heated at 100° for 0.5 h. Work up as above gave a black tar (0.07 g) which was shown by t.l.c. to be a multicomponent mixture.

(d) The Attempted Conversion of the Aminotriazines (246i) and (250a) into 7-Azapteridine Derivatives

5-Acetamido-3-(1-acetoxybenzyl)-1,2,4-triazine-6-carboxamide (246j)

(i) The acetoxybenzyltriazine (246i) (0.58 g, 0.002 mol) was stirred in acetic anhydride (3 ml) containing concentrated sulphuric acid (0.3 ml) for 4.0 h. Ice (20 g) was added and the aqueous solution was extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield the acetamidotriazine (246j) (0.60 g, 92%) m.p. 111° (from benzene), $\nu_{\text{max}}$ 3450 and 3300 (NH), 1720 and 1700 (CO), and 1620 (NH def) cm$^{-1}$, $\tau$(CDCl$_3$) 2.78 (1H, br, NH),
2.36 - 2.70 (6H, m, ArH and NH), 3.32 (1H, s, CH), 3.90 (1H, br, NH), 7.50 (3H, s, N-Ac), and 7.77 (3H, s, OAc).

\[ \text{C}_{15}^\text{H}_{13}^\text{N}_{5}^\text{O}_{4} \text{ requires: } C, 54.7; N, 4.6; N, 21.3\%; M 329. \]

\[ \text{Found: } C, 54.6; H, 4.8; N, 21.5\%; M^+ 329. \]

(ii) The acetamidotriazine (246j) (0.68g, 0.002 mol) was stirred in 2M aqueous sodium hydroxide (2.0 ml) for 5 min. The solution was extracted with chloroform to remove non-acidic material and the aqueous layer was acidified with glacial acetic acid. The supernatant liquor was decanted from a black gum (0.61g) which could not be solidified by trituration and was shown by t.l.c. to be a multicomponent mixture.

(iii) The acetoxybenzyltriazine (246i) (0.58g, 0.002 mol) was treated with a solution of sodium (0.23g, 0.01 mol) in absolute ethanol (20 ml) and the mixture was heated under reflux with ethyl acetate (1.6 ml) for 22h. The ethanol was evaporated under reduced pressure and the resultant cake was acidified with aqueous acetic acid and the product was collected and crystallised to yield the benzoyltriazine (251) (0.39g, 85%) m.p. 218° identical (mixed m.p. and i.r. spectrum) with a sample prepared above.

(iv) The acetoxybenzyltriazine (246i) (0.58g, 0.002 mol) was heated under reflux in a mixture of acetic anhydride (4.0 ml) and formic acid (4.0 ml) for 2.0h. The mixture was evaporated under reduced pressure and the resultant gum was solidified by
treatment with a little ether to yield the starting material (98\%) (identified by its i.r. spectrum).

(v) The ester (250a) (0.52g, 0.002 mol) was heated under reflux in methanol (20 ml) containing guanidine hydrochloride (0.38g, 0.004 mol) and sodium (0.093g, 0.004 mol) for 17 h. The methanol was evaporated under reduced pressure and the residue was heated under reflux in dimethylformamide for 0.5h. The solution was filtered hot to remove inorganic material and no solid resulted on cooling. The dimethylformamide was evaporated under reduced pressure to give a dark red gum (0.43g) which was shown by t.l.c. to be a multicomponent mixture.

5.5. Synthesis of the 1,2,4-Triazines (250 b and c)

(a) The Attempted Synthesis of 3-Benzyl-5-phenyl-1,2,4-triazine (250b)

(i) A solution of phenylglyoxal (2.85g) and phenylacethyldrazide (3.20g) in glacial acetic acid (31.5 ml) was heated under reflux with ammonium acetate (16.25g) for 8h. The cooled solution was poured into water and the aqueous solution was extracted with chloroform to give a black gum (3.04g). Trituration of the gum with ether yielded phenylacetamide (0.71g) (identified by its i.r. spectrum) as an insoluble solid. The gum isolated from the evaporated filtrate was chromatographed over alumina. Elution with 1:1 toluene-light petroleum yielded 3-benzyl-6-phenyl-1,2,
4-triazine (25Oc) (0.10g, 2%) m.p. 132° (from benzene light petroleum), \( T(\text{CDCl}_3) 1.14 \) (1H, s, CH), 1.84 - 2.82 (1OH, m, ArH), and 5.54 (2H, s, CH\(_2\)).

\[
\text{C}_{16}\text{H}_{13}\text{N}_3 \quad \text{requires:} \quad \text{C, 77.7; H, 5.3; N, 17.0\%; M 247.}
\]

\[
\text{Found:} \quad \text{C, 77.7; H, 5.1; N, 17.3\%, M}^+\text{247.}
\]

Further elution with toluene gave an unidentified solid (0.40g, 8%) m.p. 132° (from benzene), \( \nu_{\text{max}} \) 3200 - 2800 br, (NH), and 1620 (NHdef) cm\(^{-1}\), \( T(\text{CDCl}_3) 1.06 \) - 2.80 (1OH, m, ArH), and 5.34 (2H, s, CH\(_2\)).

\[
\text{C}_{16}\text{H}_{12}\text{N}_2\text{O} \quad \text{requires:} \quad \text{C, 77.4; H, 4.9; N, 11.2\%; M 248.}
\]

\[
\text{Found:} \quad \text{C, 77.2; H, 4.9; N, 11.2\%; M}^+\text{248.}
\]

Further elution with 1:1 toluene-ether gave a second unidentified solid (0.24g, 4%) m.p. 201° (from benzene-light petroleum), T(1.10 - 2.90 (1OH, m, ArH), 2.35 (1H, s, CH) and 7.22 (3H, s, CH\(_3\)).

\[
\text{C}_{18}\text{H}_{14}\text{N}_4 \quad \text{requires:} \quad \text{C, 75.5; H, 4.9; N, 19.6\%; M 286.}
\]

\[
\text{Found:} \quad \text{C, 75.3; H, 4.9; N, 19.5\%; M}^+\text{286.}
\]

(ii) Phenylacetamidrazone hydrochloride, prepared by the method of Hilgetag\(^1\), had m.p. 132° (lit.\(^1\) 107° 134°).

(iii) A solution of phenylacetamidrazone hydrochloride (0.95g) and phenylglyoxal (0.65g) in methanol (15.0 ml) was heated with triethylamine (0.5g) at 50° for 1.0h. The methanol was evaporated and the resultant gum was chromatographed over alumina. Elution
with toluene yielded the product (250b) (0.41 g, 33%) m.p. 70°
(from benzene-light petroleum), \( \delta (\text{CDCl}_3) \) O. 56 (1H, s, CH), 1.86 - 
2.86 (1OH, m, ArH), and 5.57 (2H, s, CH\(_2\)).

\( \text{C}_{16}\text{H}_{13}\text{N}_3 \) requires: C, 77.7; H, 5.3; N, 17.0%; M 247.

Found: C, 78.0; H, 5.2; N, 17.0%; M\( ^+ \) 247.

Further elution with ether afforded 3-benzyl-1,2,4-triazole (256)
(O.30 g, 37%) m.p. 93° (from benzene-light petroleum) (lit.\(^8\)
94°), \( \nu_{\text{max}} \) 3200 - 2400 br (NH), and 1580 (NH\text{def}) cm\(^{-1}\),
\( \delta (\text{CDCl}_3) \) 2.16 (1H, s, CH), 2.76 (5H, s, ArH), and 5.89 (2H, s,
CH\(_2\)).

\( \text{C}_{9}\text{H}_9\text{N}_3 \) requires: C, 67.9; H, 5.7; N, 26.4%; M 159.

Found: C, 68.0; H, 5.5; N, 26.8%; M\( ^+ \) 159.
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<th>H(%)</th>
<th>N(%)</th>
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<td>4.1</td>
<td>25.5</td>
<td>M&lt;sup&gt;+&lt;/sup&gt; 269</td>
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</table>
Isolated as a yellow viscous gum.

Crystallised from benzene-light petroleum.

From benzene.

From ethanol.
CHAPTER 6

APPROACHES TO THE SYNTHESIS OF 1,2,3-TRIAZOLE-
1,2,4-TRIAZOLE AND 1,2,3-TRIAZOLE[1,5-b]-1,2,4-
TRIAZINE DERIVATIVES

DISCUSSION
Scheme 43
6.1. Introduction

The 1,2,3-triazolo[5,1-c]-1,2,4-triazole (159) and 1,2,3-triazolo[1,5-b]-1,2,4-triazole (160) ring systems have not, as yet, been prepared. Diazo tautomers (2) of fused 1,2,3-triazole systems (1) have not been observed\(^8,9,11,34\) although the intermediacy of a diazo tautomer has been suggested in the Dimroth rearrangement of the triazolopyrimidinone (155)\(^34\) (cf. page 17). Investigation of the triazolotriazole systems (159) and (160) is, therefore, of special interest since it might be expected that the increased strain inherent in two fused five membered rings would lead to their existence almost entirely in the open-chain diazo form.

It was hoped that reaction of a hydrazinotriazole (257) or a 1,5-diaminotriazole (258) with acylating agents would lead to the triazolotriazole systems (159) and (160). For example, acylating agents have been used\(^109,110\) to prepare 1,2,4-triazolo[4,3-b]-1,2,4-triazole derivatives from 3,4-diamino-1,2,4-triazoles (259). Thus prolonged reaction of (259a) with acetic anhydride\(^109\) gave the triazolotriazole (260a) and reaction of (259b) with benzoyl chloride, in the presence of pyridine, afforded the triazolotriazole (260b). The triazolotriazole (260b) was also the product\(^111\) of the oxidation of the benzylidene derivative (261) with lead tetraacetate (Scheme 43). In addition, reaction of the triazoles (257) and (258) with dicarbonyl compounds might afford derivatives of the hitherto unknown 1,2,3-triazolo[5,1-c]-1,2,4-triazine (157)
and 1,2,3-triazolo[1,5-b]-1,2,4-triazine (158) ring systems (cf. page 54). An investigation of synthetic routes to and reactions of the triazoles (257) and (258) was, therefore, undertaken. It should also be noted that the triazoles (257) and (258) are Dimroth isomers related by the potential rearrangement process [(257)⇌(258)]. Consequently, it is possible that the synthesis of one triazole could lead to the synthesis of all four ring systems [(157)-(160)].

The possible synthetic routes to the 5-hydrazino-1H,1,2,3-triazole (257) are outlined in Scheme 44. Displacement of the thiomethyl group or chloride ion from the triazoles (265) and (263) respectively by hydrazine would be expected to lead directly to the triazole (257). Acid hydrolysis of a hydrazone (223) or reduction of the diazonium salt (220) might also afford the desired triazole (257). Reaction of an amidrazone [(266); R - electron withdrawing] with toluene-p-sulphonyl azide could give either the hydrazino-triazole (257) or the isomeric diaminotriazole (258). Other synthetic routes to the 1,5-diaminotriazole (258) are outlined in Scheme 45. Again, displacement of chloride ion from the 1-aminotriazole (267) with ammonia might be expected to afford the triazole (258).

6.2. Synthesis of 5-Thiomethyltriazoles

The displacement of thiomethyl groups by hydrazine is well known in the synthesis of hydrazino heterocycles and
thiomethyl heterocycles are readily prepared from the corresponding thiols by methylation. Triazole thiols (264) have been prepared\(^\text{113}\) in low yield in a somewhat dangerous cycloaddition reaction involving an isothiocyanate and diazomethane. However, this synthesis has been superseded by that of Regitz\(^\text{53, 54}\) involving diazo transfer from toluene-\(p\)-sulphonyl azide to the active methylene centre of the thioamide (132) (cf. page 15 and Scheme 20). Ethyl malonate monothioamide was, therefore, prepared\(^\text{114}\). In our hands, the thioamide, which was shown to be pure by its\(^1\)H n.m.r. spectrum, was found to have a melting point considerably lower than that quoted by Erlenmeyer.\(^\text{114}\) The reaction of ethyl malonate monothioamide with toluene-\(p\)-sulphonyl azide afforded a product whose spectral properties are consistent with the triazolethiol (273a). Also, methylation\(^\text{115}\) of the thiol (273a) smoothly afforded the thiomethyltriazole (273b). The mechanism of the formation of the triazolethiol (273a) (Scheme 46) involves the intermediacy of the hydroxytriazole (292) (cf. page 28 and Scheme 32). However, preliminary reaction of the thiomethyltriazole (273b) with hydrazine hydrate at room temperature afforded two products whose\(^1\)H n.m.r. spectra indicated that the thiomethyl group had not been displaced. The preparation of ethyl malonate monothioamide was not readily reproducible and this precluded further investigation of this route.
Scheme 47
6.3. **Synthesis of Chlorotriazoles**

The chlorination of 5-hydroxy-1,2,3-triazoles is simply effected using phosphorus pentachloride\(^1\)\(^1\)\(^6\), and yields the corresponding chlorotriazole. Reaction of the chlorotriazole with hydrazine may be expected to occur readily to give the hydrazino-triazole (257).

The known 5-chlorotriazoles (274a and b) were prepared in the expectation that the hydrazinotriazoles of the type (293) initially produced in the reaction with hydrazine hydrate, could be made to undergo Dimroth rearrangement to give the 1-amino-5-anilinotriazoles (279a and b) (Scheme 47). Heated under reflux in ethanol containing hydrazine hydrate, the chlorotriazole (274a) resisted reaction. However, reaction in hydrazine hydrate itself proceeded smoothly to give, not the hydrazinotriazole (295a), but the Dimroth isomer (279a), whose structure follows from its reaction with dicarbonyl compounds to give 1,2,3-triazolo[1,5-b]-1,2,4-triazine derivatives (see later).

Similar reaction of the ester (274b) afforded a multicomponent black tar. The 1-aminotriazolotriazole (279a) gave a benzylimide derivative (283a) on reaction with benzaldehyde and a diacetyl derivative on brief treatment with acetic anhydride. However, reaction of (279a) with acylating agents did not lead to the expected 1,2,3-triazolo[1,5-b]-1,2,4-triazole derivatives. Prolonged reaction with acetic anhydride or formic acid led in both cases to
multicomponent gums. Also, the attempted base catalysed cyclisation of the diacetyl derivative (282a) gave a low yield of a compound, the $^1$H n.m.r. of which indicated that it was the monoacetyl derivative (282b), but lack of material prevented its characterisation. Reaction of the amine (279a) with triethyl orthoformate gave the ethoxymethylene derivative (283f) but attempted cyclisation with potassium hydroxide gave a viscous multicomponent gum. The attempted oxidative cyclisation of the benzylidene derivative (283a) with manganese dioxide gave a gum from which no recognisable products could be separated by column chromatography. In the presence of lead tetraacetate the benzylidene derivative (283a) gave a multicomponent tar. The hydrazone (223d), on oxidation with manganese dioxide, gave a mixture of at least three components, which could not be separated by column chromatography over silica, and over alumina, reaction occurred on the column, elution giving only multicomponent mixtures.

The reactions of the amine (279a) with dicarbonyl compounds proved to be more successful. Thus, reaction with glyoxylic acid hydrate in glacial acetic acid, afforded an orange multicomponent gum, but in methanol in the presence of concentrated sulphuric acid, a yellow solid, whose spectral properties were consistent with the methyl ester (283b), was isolated. Schiff's base formation had occurred with concomitant esterification in the presence of
concentrated sulphuric acid. Similarly, reaction with ethyl pyruvate gave the ester (283c) but reaction with benzoylformic acid occurred without esterification to give the acid (283d). The ester (283e) was formed by reaction of the amine (279a) with ethyl benzoylformate. Attempted cyclisation of the ester (283b), by heating under reflux in ethanolic sodium ethoxide, aqueous ethanolic sodium carbonate or in xylene, dimethylformamide, or 2-ethoxy-ethanol, led to black multicomponent gums. However, cyclisation occurred in low yield when the ester (283b) was heated under reflux in ethanol containing piperidine, and more efficiently by stirring the ester (283b) in methanol containing piperidine, to give the 1,2,3-triazolo[1,5-b]-1,2,4-triazinone (284a). Also, using the last conditions, the esters (283c and e) gave the corresponding cyclic products (284b and c), but the acid (283d) was recovered after similar treatment.

Attempted scission of the triazolotriazinone (284a) in glacial acetic acid, gave a black multicomponent oil.

Because of the limitations inherent in 1-amino-5-anilino-triazoles as triazolotriazole precursors, attention was turned to the synthesis of the unsubstituted compounds (257) or (258), and therefore to 5-hydroxy-1H-1,2,3-triazoles the initial starting materials. (cf. Schemes 44 and 45). Although 5-hydroxytriazoles (270) exist in equilibrium with the diazo tautomer, it is known that phosphorus pentachloride induces cyclisation prior to
chlorination.

The amide (270a) was prepared by the method of Dimroth using phenyl azide and malonamide in the presence of sodium ethoxide. The same product (270a) was also isolated, in high yield, in the diazo transfer reaction of malonamide with toluene-p-sulphonyl azide. The mechanism of these two reactions is outlined in Scheme 48, aniline or toluene-p-sulphonamide being the reaction by-products. Acetylation of the amide (270a) gave a diacetyl derivative, which decomposed on attempted crystallisation to yield a monoacetyl derivative and then the starting triazole. The structures (271a and b) are tentatively assigned to the acetyl derivatives. Hydrolysis of the amide (270a) afforded, on acidification, a colourless solid which was shown, by burning, to be a salt. Attempted acidification of this salt, by heating under reflux in dilute aqueous hydrochloric acid, was unsuccessful.

Chlorination of the triazole (270a) with phosphorus pentachloride in phosphoryl chloride gave a low yield of a colourless product, whose i.r. spectrum contained cyano absorption indicating that it was the chloro-nitrile (274c). Also, chlorination using the milder chlorination procedure of reaction with phosphoryl chloride in the presence of N, N-diethylaniline gave a higher yield of this compound which on standing quickly became dark and tarry and could not be further characterised.

Diazo transfer from toluene-p-sulphonyl azide to ethyl
malonamate was also investigated as a route to the hydroxytriazole ester (27Of). In the presence of sodium ethoxide, the diazo-amide (27Ob) was isolated in high yield and in the presence of piperidine, the known diazo-ester (27Of) was the product. In the ionic medium, the mechanism of the reaction is, as described for ethyl malonate monothioamide (Scheme 46). In this case, the triazole is not isolated indicating that, under these conditions, the diazo tautomer (27Ob) is the thermodynamically more stable species.

The mechanism in Scheme 49 is proposed to account for the formation of the diazo-ester (27Of). Again, toluene-p-sulphonamide is isolated as a by-product, formed as the anion by elimination from the intermediate (294). The diazo-amide (27Ob), on attempted crystallisation from a variety of solvents, gave a second compound whose structure has not, as yet, been elucidated.

In a further attempt to synthesise the ester (27Of), the reaction of ethyl malonamate with phenyl azide in the presence of sodium ethoxide was investigated. The diazo-amide (27Oc) was isolated and this was not the expected product since the reaction of methyl malonamate with phenyl azide in the presence of sodium methoxide is reported to give the diazo-ester (27Og) (Scheme 50). The intermediate (295) affords the product in each case by displacement of ethoxide ion and aniline respectively. The difference in the products isolated must reflect either a solvent
Scheme 51

\[
\begin{align*}
&\text{NC} \xrightarrow{\text{R, CH}_2\text{N}_2} \text{CONH}_2 \\
&\text{PhCH}_2\text{CONH}_2 + \text{PhN}_3 \rightarrow \text{Ph\text{N}_\text{Ts}} \quad \text{Ph\text{N}_\text{Ts}} \\
&\text{PhCH}_2\text{CONH}_2 + \text{PhN}_3 \rightarrow \text{Ph\text{N}_\text{Ts}} \quad \text{Ph\text{N}_\text{Ts}}
\end{align*}
\]

(295) \quad \begin{array}{c}
R \\
\text{a} \quad \text{CONH}_2 \\
\text{b} \quad \text{CN}
\end{array}

(296):
effect or the ease of displacement of ethoxide ion compared with methoxide ion. Hydrolysis of the amide (270e) gave a highly insoluble acid which could not be characterised directly or in the form of its sodium salt.

The reaction of toluene-$p$-sulphonyl azide with cyanoacetamide was investigated in the hope that the cyanotriazole (270k) could be prepared. At $0^\circ$ the dark impure product (275a) was isolated from a black reaction mixture but, at $-10^\circ$, the product triazole (275a) was obtained smoothly and in high yield. The structure of (275a) follows from the fact that it gives an acetyl derivative, the acetyl protons of which absorb at $7.7.2$ characteristic of a $1$-$N$-acetyl-$1,2,3$-triazole. Hydrolysis of the amide (275a) afforded the acid (275h) and reduction of (275a) with sodium in liquid ammonia resulted in desosylation to give the known ketone (275e). To confirm the probable mechanism (Scheme 51) of the reaction of toluene-$p$-sulphonyl azide with cyanoacetamide the known reaction with malononitrile was repeated, affording the nitrile (275c). The $1$-toluene-$p$-sulphonyl-$1,2,3$-triazole intermediate (296) is destabilised by the electron withdrawing group at the $1$-position, leading to Dimroth rearrangement to the products (275a and c) (Scheme 51).

5-Hydroxy-$4$-phenyl-$1H$-$1,2,3$-triazole (270h) has been prepared previously, albeit in low yield, by the condensation of phenyl azide with phenylacetamide. Begtrup has also
\[
\text{PhCH}_2\text{N}_3 + \text{PhCH} = \text{CO}_2\text{Et} \rightarrow \text{PhCH}_2\text{N} = \text{N} - \text{Ph} \\
\text{PhCH} = \text{CO}_2\text{Et} \rightarrow \text{PhCH}_2\text{N} = \text{N} - \text{Ph} \\
\overset{(297)}{\text{CO}_2\text{Et}}
\]
found that 1-benzyl-5-hydroxy-4-phenyl-1,2,3-triazole (270i) is formed, in reasonable yield, from benzyl azide and diethyl 2-phenylmalonate although it is known that benzyl azide, unlike phenyl azide, does not react with ethyl phenylacetate itself. Reaction proceeds via decarbethoxylation of the intermediate triazolone (297). It is known that the triazolone (298) can be hydrolysed to the required triazole (270h), but the synthesis of (298) is viable only on a very small scale. It was, therefore, hoped to exploit these findings by investigating the synthesis of the triazolone (298) and thence the triazole (270h) from the reactions of toluene-p-sulphonyl azide and phenyl azide with the 2-phenyl esters (276a-c).

Under normal transfer conditions (O°), toluene-p-sulphonyl azide does not react with a methylene centre activated only by a single carbonyl group and a phenyl group. Confirmation of this observation was found in the fact that phenylacetamide was recovered from the attempted reaction with toluene-p-sulphonyl azide in the presence of sodium ethoxide. Therefore, in an attempt to promote reaction, ethyl phenylacetate was heated under reflux in ethanol with toluene-p-sulphonyl azide. Unfortunately, other than decomposition of the azide, no reaction was observed, ethyl phenylacetate being recovered. The esters (276a-c) were prepared and their reactions with toluene-p-sulphonyl
azide were investigated. Multicomponent mixtures were isolated from the reactions of the esters (276a and b) with toluene-\(\text{p}\)-sulphonyl azide but the amide (276c) gave a low yield of a colourless solid, as well as starting amide (276c). This colourless solid decomposed to multicomponent oils on attempted crystallisation. Similar behaviour has been described\(^ {124}\) for the triazolone (298). However, insufficient material was isolated to permit the attempted hydrolysis [(298)\(\rightarrow\) (27Oh)].

Since viable synthetic routes to 5-hydroxytriazoles suitable for chlorination were not available, this synthetic approach to the hydrazinotriazole (257) and the diaminotriazole (258) was not continued further.

6.4. **Synthesis of 5-Hydrazino-1H-1,2,3-triazoles**

It is well known\(^ {129}\) that acid hydrolysis of a hydrazone readily leads to regeneration of the parent hydrazine. Since the hydrazone (223a) was readily available, having been prepared from the diazonium salt (220) and diethyl malonate (cf. Chapter 4), it was of interest to attempt its cleavage to the hydrazine (275a) in dilute acid. The hydrazone (223a) was recovered on attempted reaction with anhydrous ethereal hydrochloric acid and it afforded a multicomponent gum on hydrolysis with dilute aqueous hydrochloric acid.

Diazonium salts may be reduced\(^ {130}\) to the corresponding
hydrazines using sodium sulphite. However, the reaction of the diazonium salt (220) with sodium sulphite gave only a dark red multicomponent gum. On the other hand, when the diazonium salt (220) was reduced with sulphur dioxide in aqueous ethanol, the product was the triazole (67a) formed by reductive deamination of the diazonium salt. An attempt to condense the intermediate hydrazine (257a) in situ with formic acid, thus leading to triazolotriazole formation, gave a low yield of an, as yet, unidentified solid.

However, the hydrazine (257a), produced in situ by sulphur dioxide reduction of the diazonium salt (220), when condensed with dicarbonyl compounds, gave 1, 2, 3-triazolo[5, 1-c]-1, 2, 4-triazine derivatives, in moderate to low yield. Glyoxal, biacetyl, benzil, methylglyoxal and phenylglyoxal afforded the triazolotriazines (285a-e) respectively, the deaminated triazole (67a) also being isolated in each case. A similar reaction with glyoxylic acid gave only multicomponent gums. However, the red gum obtained in the reaction with ethyl pyruvate was shown by t.l.c. to be a two component mixture which, when heated under reflux in aqueous ethanolic sodium acetate, gave the triazole (67a) and, on acidification, the triazolotriazinone (286). Reaction with ethyl benzoylformate also led to a red gum, which, on treatment with ethanolic sodium acetate, gave the deaminated triazole (67a) and a compound identical to that obtained in the reaction with
Scheme 52

(257a) \[ \rightleftharpoons \] \[ (RCO)_2 \] \[ \rightleftharpoons \] \[ (285) \]

(258a) \[ \rightleftharpoons \] \[ (RCO)_2 \] \[ \rightleftharpoons \] \[ (299) \]
\[
\text{HN-} \quad \text{N} \quad \text{Ph} \quad \overset{\text{SO}_2}{\rightarrow} \quad \text{HN-} \quad \text{N} \quad \text{Ph} \\
\downarrow \quad \text{(EtO}_2\text{C})_2\text{CH}_2 \quad \downarrow \quad \text{(EtO}_2\text{C})_2\text{CO} \\
\text{(220a)} \quad \text{Scheme 53} \quad \text{(222a)}
\]

\[
\text{HN-} \quad \text{N} \quad \text{Ph} \quad \overset{\text{SO}_2}{\rightarrow} \quad \text{HN-} \quad \text{N} \quad \text{Ph} \\
\downarrow \quad \text{CH}_3\text{CHCO}_2\text{H} \quad \downarrow \quad \text{(CH}_3\text{CO})_2 \\
\text{(220a)} \quad \text{Scheme 54} \\
\text{H}_3\text{CO-C} \quad \text{CH}_3 \\
\text{CO}_2\text{H} \quad \overset{\text{H}_2\text{O}}{\rightarrow} \quad \text{(285b)}
\]
formic acid (see above).

The assigned structure of the triazolotriazines (285a-e) 
and (286) had to be confirmed because of the possibility that the 
hydrazinotriazole (257a), produced initially in situ, had undergone 
rearrangement to the 1,5-diaminotriazole (258a) prior to 
condensation, thus giving isomeric triazolo[1,5-b]triazine 
derivatives (299) (Scheme 52). The reaction with diethyl mesox-
alate was, therefore, investigated since the triazolo[5,1-c]-
triazinone produced, should be identical to the compound (222a) 
obtained from the coupling reaction of the diazonium salt (220) 
with diethyl malonate (Scheme 53) (cf. Chapter 4). The red gum 
isolated in the reaction, on treatment with piperidine, gave the 
deaminated triazole (67a) and a low yield of the triazolo[5,1-c]-
triazinone (222a). To confirm this finding, the diazonium salt 
(220) was coupled with methylacetoacetic acid, using the 
conditions of Stevens. The triazolotriazine isolated in high 
yield, was identical to that obtained in the reaction of diazonium 
salt (220) with biacetyl, in the presence of sulphur dioxide 
(Scheme 54). Since the triazolo[5,1-c]triazine configuration has 
been established for the compounds (221) and (222) (see page 59 
and Scheme 35), the reaction of the diazonium salt (220) with 
dicarbonyl compounds in the presence of sulphur dioxide must 
afford derivatives of the 1,2,3-triazolo[5,1-c]-1,2,4-triazine ring
The triazolotriazines (285 b, c and e) underwent triazole scission in glacial acetic acid to give the gummy α-acetoxybenzyl-triazines (287 a, b and d). The triazine (285d) was recovered after treatment with glacial acetic acid and was decomposed on heating under reflux in glacial acetic acid containing concentrated hydrochloric acid, in an attempt to promote scission. On attempted hydrogenolysis the α-acetoxybenzyltriazine (287d) was recovered and the α-acetoxybenzyltriazine (287c) afforded the gummy dihydrotriazine (288) which was reconverted into the triazine (287c) using manganese dioxide.

6.5. Synthesis of 1-Amino-5-hydroxy-1,2,3-triazoles

Two synthetic routes to 1-amino-5-hydroxy-1,2,3-triazoles (cf. Scheme 45) were investigated: the reaction of a triazole or diazo ester with hydrazine; and the reaction of a suitable hydrazide with toluene-p-sulphonyl azide or phenyl azide. The first method has been used by Curtius\textsuperscript{132} to synthesise 1-amino-5-hydroxy-1,2,3-triazole-4-(N-toluene-p-sulphonyl) carboxamide (277b). This reaction was repeated and the amide (277b) was isolated in low yield, along with a solid, not reported by Curtius, whose analytical data were not consistent with an isomer of (277b).

An attempt was made to extend this reaction to the esters (270d) and (278)\textsuperscript{48} in an attempt to obtain the corresponding 1-
\[
\begin{align*}
\text{(300)} & \quad \text{CONNHNNH}_2 \\
\text{RCOX} & \quad \text{(301)}
\end{align*}
\]
aminotriazoles (277). Reaction of the ester (270d) with hydrazine hydrate led, on acidification, to recovery of the starting ester, even after prolonged treatment. However, the ester (278) gave a compound which was shown to be the hydrazide (275e) formed from the intermediate Dimroth isomer (275i). The hydrazide is therefore stable to further rearrangement to the required 1-amino-5-hydroxy-1,2,3-triazole system. Satisfactory analytical data could not be obtained for the hydrazide (275e), but acetylation gave a compound whose analysis is consistent with the diacetyl derivative (275f). The $^1$H n.m.r. spectrum of (275f) contained a singlet at approximately $\tau 7.2$, indicating the presence of a 1-N-acetyl group. The presence of a hydrazide group was confirmed by diazotisation to give an unstable azide (275j), which detonated on heating and decomposed on attempted crystallisation. Since the 3H-tautomer (300) is a possible structure for the compound (275e), it seemed worthwhile to attempt its cyclisation to give the 1,2,3-triazolo[1,5-d]-1,2,4-triazine ring system (301). However, attempted reaction with triethyl orthoformate in the presence of acetic anhydride afforded a black multicomponent tar and reaction with urea at 200° under nitrogen gave a black multicomponent solid.

The diazo transfer reaction from toluene-p-sulphonyl azide to malonamic acid hydrazide gave, on acidification, a
triazole which seemed to be either isomer (277a) or (270j).
Reaction of malonamic acid hydrazide with phenyl azide also gave this product. Hydrolysis of the product produced a salt which could not be converted into the free acid by acidification. The triazole (277a) or (270j) with benzaldehyde or glyoxylic acid, in the presence of concentrated sulphuric acid, reacted to give the hydrazones (281a and b) respectively, the latter product being unstable to crystallisation, affording a colourless, unidentified solid. Since ring opening to the diazo tautomer occurred simultaneously with condensation, these reactions proved unhelpful in assigning a structure (277a) or (270j) to the triazole product. Also, attempted detosylation of the 1-aminotriazole (277b) with sodium in liquid ammonia to give the amide (277a) yielded no identifiable product.

Cyanoacethydrazide, on reaction with toluene-\(p\)-sulphonyl azide gave the hydrazide (275d) which on hydrolysis gave the acid (275h), but in common with the hydrazide (275e) satisfactory analytical data could not be obtained for (275d). The mechanism of formation of the hydrazide (275d) is identical to that shown for the amide (275a) formed from cyanoacetamide (cf. page 113 and Scheme 51).

The attempted condensation reaction between phenyl azide and phenylacethydrazide, using the conditions of Begtrup, led
$\text{RCH}_2\text{CN} \rightarrow \text{RCH}_2\text{C}^\text{OEt} \rightarrow \text{RCH}_2\text{C}^\text{NHNHCHO}$

$(302)$  $(303)$  $(304)$

$\text{NH}_2\text{CH}_2\text{R}$

$(306)$

$	ext{NH}_2\text{C}^\text{HCl}$

$(305)$

Scheme 55
to recovery of the starting hydrazide, along with an unidentified solid, derived by dimerisation of phenylacethyldrazide with loss of hydrazine.

6.6. **Synthesis of 1,5-Diamino-1,2,3-triazoles**

The diazo transfer reaction of ethyl malonamate with toluene-p-sulphonyl azide, in the presence of piperidine, affords in high yield ethyl 2-diazomalonamate (cf. page 112). Diazo transfer from toluene-p-sulphonyl azide to a methylene amidrazone derivative, therefore, would be expected to afford either a 5-hydrazino-1H-1,2,3-triazole (257) (cf. Scheme 44) or a 1,5-diamino-1,2,3-triazole (258) (cf. Scheme 45).

Methylene amidrazone derivatives can be prepared from substituted acetonitrile derivatives (302) by formation of the iminoether (303) and its subsequent reaction with formhydrazide to give the formylamidrazone (304), followed by acid hydrolysis to the amidrazone hydrochloride (305)\(^{108}\) (Scheme 55). The 1,2,4-triazole (306) is also formed in the last stage.

Phenylacetamidrazone hydrochloride (281) had been prepared earlier and it was found to give a multicomponent oil on attempted reaction with toluene-p-sulphonyl azide, in the presence of sodium hydride. Therefore, the amidrazone hydrochloride (280c), more suited to the diazo transfer reaction, was synthesised. The known iminoether (280a) was prepared from
ethyl cyanoacetate and used immediately without purification. (If left at 0° in a desiccator, the colourless iminoether became deep yellow). Reaction of the iminoether with formhydrazide proceeded smoothly to give the formylamidrazone (280b) in high yield. Hydrolysis of the formylamidrazone (280b) with hydrochloric acid gave, in reasonable yield, the amidrazone hydrochloride (280c), along with a compound whose properties are consistent with the 1,2,4-triazole hydrochloride [(306); R = CO$_2$Et].

In the presence of piperidine, the diazo transfer reaction from toluene-$p$-sulphonyl azide to the active methylene centre of the amidrazone (280c) afforded the diamine (279c). The 1,5-diamine structure of the ester (279c) was confirmed by its conversion into a benzyldene derivative (289a), which on treatment with acetic anhydride gave a monoacetyl derivative (289b) whose structure is consistent with its $^1$H n.m.r. spectrum. The formylamidrazone (280b) failed to react with toluene-$p$-sulphonyl azide in the presence of piperidine but in the presence of sodium hydride a highly insoluble product was isolated. On attempted crystallisation from dimethylsulphoxide this compound decomposed to a multi-component mixture.

Attempted triazolo[1,5-b]triazole formation by heating the 1,5-diamine (279c) in formic acid or acetic anhydride led to inseparable mixtures. Also, heated under reflux in triethyl orthoformate, the 1,5-diamine gave the ethoxymethylene
derivative (289f) which, on attempted cyclisation with acetic anhydride in the presence of phosphoric acid, gave a black multi-component tar.

On treatment with dicarbonyl compounds in ethanol in the presence of acetic acid, the 1,5-diamine (279c) gave high yields of the 1,2,3-triazolo[1,5-b]-1,2,4-triazines (290a–e) and (291b and c). Since the triazolotriazines, although colourless solids, were highly fluorescent in u.v. light, it was simple to monitor these reactions by t.l.c., thereby judging the optimum reaction time. The orientation shown for the triazolotriazines (290d and e) and (291b and c) are based on the assumption that the 1-amino group in the compound (279c) is more basic than the 5-amino group. However, confirmation of this assignment must await the degradation of one of these molecules to a known triazine derivative. In the reaction of the diamine (279c) with ethyl pyruvate, the insoluble product (291b) and the highly soluble, low melting intermediate (289d) were isolated. On attempted crystallisation the hydrazone (289d) precipitated as a gum, but its structure follows from its cyclisation to the triazolotriazinone (291b), in the presence of piperidine. Heated under reflux in the presence of glyoxylic acid hydrate, the diamine (279c) gave the acid (289c) which was recovered on attempted cyclisation with piperidine. Reaction in methanol in the presence of concentrated sulphuric acid failed to
occur with simultaneous esterification (cf. page 109), the acid (289c) again being isolated. However, in the presence of concentrated sulphuric acid, the diamine (279c) with biacetyl gave the gummy hydrazone (289e), which, on treatment with piperidine, afforded the triazolotriazine (290b). It should be noted that, although the triazolotriazines (290 a-e) and (291 b and c) were formed in the presence of glacial acetic acid, no triazole scission was observed. This must be due to the well known (see page 25) stabilising effect of a carbonyl group at the 3-position of a fused 1,2,3-triazole derivative.

Attempted hydrolysis of the ester (290a) with aqueous ethanolic sodium carbonate afforded a black tar and in the presence of aqueous ethanolic sulphuric acid, the ester (290d) was recovered unchanged. The degradation of the triazolo[1,5-b]-triazine derivatives, therefore, must await further experimental work.
CHAPTER 7

APPROACHES TO THE SYNTHESIS OF 1,2,3-TRIAZOLE-1,2,4-TRIAZOLE AND 1,2,3-TRIAZOLE[1,5-b]-1,2,4-TRIAZINE DERIVATIVES

EXPERIMENTAL
Preparation of Starting Materials

Toluene-$p$-sulphonyl azide$^{77}$ and phenyl azide$^{134}$ were prepared by the methods described in Organic Synthesis.

Ethyl malonate monothioamide, prepared by the method of Erlenmeyer,$^{114}$ had m.p. 28° (lit.,$^{114}$ 79°).

Ethyl malonamate, prepared by the method of Gupta,$^{135}$ had m.p. 50° (from ethanol) (lit.$^{135}$, 50°).

Diethyl 2-phenylmalonate (276a), prepared by the method described in Organic Synthesis,$^{126}$ had b.p. 150-152°/8 mm (lit.$^{126}$, 158-162°/10 mm).

Ethyl 2-phenylcyanoacetate (276b), prepared by the method of Nelson and Cretcher,$^{127}$ had b.p. 144-146°/8 mm (lit.$^{127}$, 145°/7 mm).

Ethyl 2-phenylmalonamate (276c), prepared by the acid hydrolysis of the nitrile (276b) using concentrated sulphuric acid, had m.p. 150° (from ethanol-light petroleum) (lit.$^{128}$, 152°).

Ethyl benzoylformate was obtained as an oil by the esterification of benzoylformic acid using ethanol in the presence of concentrated sulphuric acid and was used without purification.

Phenylacethydrazide, prepared by the method of Curtius,$^{136}$ had m.p. 115° (from aqueous ethanol) (lit.$^{136}$, 116°).

Cyanoacethydrazide, prepared by the method of von Rothenburg,$^{137}$ had m.p. 115° (from ethanol) (lit.$^{137}$, 115°).
Malonamic acid hydrazide, prepared by the method of Bulow and Bozenhardt, had m.p. 126° (from ethanol) (lit., 127°).

N.B. For general notes on experimental procedures, see page 30.

7.1. **Synthesis of 5-Hydroxytriazoles**

(a) Solutions of malonamide (2.5 g, 0.025 mol) in absolute ethanol (50 ml) and sodium (0.58 g, 0.025 mol) in absolute ethanol (30 ml) were mixed, cooled to 0° and treated dropwise with stirring with a solution of toluene-p-sulphonyl azide (4.9 g, O.025 mol) in absolute ethanol (20 ml). The mixture was stirred in the melting ice bath for 2.0 h. The insoluble salt was collected, dissolved in the minimum quantity of hot water, cooled, and acidified with concentrated hydrochloric acid to afford 5-hydroxy-1H-1,2,3-triazole-4-carboxamide (270a) (2.6 g, 84%), m.p. 186° (from water) (lit., 196° and 187° identical (m.p. and i.r. spectrum) to a sample prepared from phenyl azide and malonamide by the method of Dimroth. The ethanol mother liquor was evaporated and the residue was treated with water and acidified with concentrated hydrochloric acid to yield toluene-p-sulphonamide (0.82 g) m.p. 127° (from water) (lit., 139°).

The triazole (270a) (1.28 g, O.01 mol) was heated at 100° in acetic anhydride (2.0 ml) for 5 min. The acetic anhydride
was evaporated under reduced pressure and trituration of the resultant gum with a little ether afforded the diacetyl derivative (271a) (2.05g, 97%) m.p. 105°, \( \nu_{\text{max}} \) 3400 and 3200 (NH), 1780 (Ac), 1690 (CO) and 1620 (NH def) cm\(^{-1}\), \( T [(\text{CD}_3)_2\text{SO}] \) 1.78 (1H, s, br, NH), 2.16 (1H, s, br, NH), 7.21 (3H, s, N.Ac), and 7.60 (3H, s, O.Ac). The diacetylated triazole (1.06g, 0.005 mol) on attempted crystallisation from ethanol gave a colourless crystalline monoacetyl derivative (271b) (0.34g, 40%) m.p. 139°, \( \nu_{\text{max}} \) 3350 and 3200 br (NH), 1750 (Ac), 1690 and 1660 cm\(^{-1}\), \( T [(\text{CD}_3)_2\text{SO}] \) 2.22 (1H, s, br, NH), 2.34 (1H, s, br, NH), and 7.34 (3H, s, Ac). On evaporation of the ethanol filtrate a second colourless solid (0.30g, 47%) m.p. 178° was collected using a little ether and this was identical (i.r. spectrum) to the starting triazole (270a).

(b) Phenylacetamide was recovered (70%) on attempted reaction with toluene-p-sulphonyl azide using the above conditions.

c) Reaction of diethyl malonate, ethyl malonamate, or ethyl malonate monothioamide, with toluene-p-sulphonyl azide, as described in (a) above, gave the products described below. Work up of the mother liquors as in method (a) gave more product but no toluene-p-sulphonamide was isolated.

Diethyl malonate gave 2-diazo-(N-toluene-p-sulphonyl) malonamate (272) (94%) m.p. 85° (from water) \( (litr., 85^\circ) \).

Ethyl malonate monothioamide afforded 5-mercapto-1H-
1, 2, 3-triazole-4-(N-toluene-p-sulphonyl) carboxamide (273a)
(58%) m.p. 205° (from ethanol-acetic acid), \( \nu_{\text{max}} \) 3450 and 3300 \( \text{cm}^{-1} \) (\( \text{NH} \)), 1680 (CO) and 1600 (NH\( \text{def} \)) cm\(^{-1} \).

\[
\text{C}_{10}\text{H}_{10}\text{N}_{4}\text{O}_{3}\text{S}_{2}
\]
requires: C, 40.3; H, 3.4; N, 18.8; S, 21.5%;

\[
\text{M} 298.
\]

\[
\text{Found: } \text{C}, 40.2; \text{H}, 3.4; \text{N}, 18.8; \text{S}, 21.7%;
\]

\[
\text{M}^{+} 298.
\]

Ethyl malonamate yielded 2-diazo-(N-toluene-p-sulphonyl) malonamide (270b) (85%) m.p. 142°, \( \nu_{\text{max}} \) 3700-3200 br (\( \text{NH} \)), 2150 (\( ^{\dagger} \text{N} \)), 1680 and 1650 (CO), and 1615 (NH\( \text{def} \)) cm\(^{-1} \), \( \text{M}^{+} 217 \).

On attempted crystallisation (from toluene, ethanol, glacial acetic acid, dimethylformamide or water) the amide changed to an unidentified colourless solid, m.p. 230° (from ethanol), \( \nu_{\text{max}} \) 3500 and 3250 (\( \text{NH} \)), 2180 (\( ^{\dagger} \text{N} \)) and 1630 cm\(^{-1} \).

\[
\text{Found: } \text{C}, 39.5; \text{H}, 3.0; \text{N}, 18.0; \text{M}^{+} 217.
\]

(d) Ethyl phenylacetate (0.82g, O.005 mol) and toluene-p-sulphonyl azide (1.0g; O.005 mol) were added to a solution of sodium (O.23g, O.01 mol) in methanol (10 ml). The mixture was heated under reflux for 20h. On cooling no solid separated and the methanol was removed under reduced pressure. Water (10 ml) was added to the resultant cake and the aqueous solution was extracted with ether to give a colourless liquid (0.70g), identical (i.r. spectrum) to an authentic sample of ethyl phenylacetate. Acidification of the aqueous mother liquor gave no
material.

(e) Cyanoacetamide was reacted with toluene-p-sulphonyl azide using the conditions of method (a) with the modification that the reaction was carried out at -10°. As in (b) further product was obtained on work up of the mother liquor and no toluene-p-sulphonamide was isolated. The product was 5-(toluene-p-sulphonylamino)-1H-1,2,3-triazole-4-carboxamide (275a) (50%) m.p. 215° (from water), $v_{\text{max}}$ 3500, 3400 and 3200 (NH), 1650 (CO) and 1600 (NH def) cm$^{-1}$.

$C_{10}H_{11}N_5O_3S$ requires: C, 42.7; H, 3.9; N, 24.9%; M 281.

Found: C, 42.8; H, 3.9; N, 24.8%, M$^+$ 281.

Acetylation of the triazole (275a) using the procedure described in (a) afforded 1-acetyl-5-(toluene-p-sulphonylamino)-1,2,3-triazole-4-carboxamide (275b) (94%) m.p. 182° (from acetic anhydride), $v_{\text{max}}$ 3500, 3400 and 3300 (NH), 1770 (Ac), 1690 and 1670 (CO), and 1600 (NH def) cm$^{-1}$, $\delta$ [(CD$_3$)$_2$SO] 2.40 [2H, d(J 8Hz), ArH], 2.55 [2H, d (J 8Hz), ArH], 7.29 (3H, s, N.Ac), and 7.59 (3H, s, CH$_3$).

$C_{12}H_{13}N_5O_4S$ requires: C, 44.6; H, 4.1; N, 21.7%; M 323.

Found: C, 44.6; H, 4.2; N, 20.9%; M$^+$ 323.

Malononitrile similarly gave 4-cyano-5-(toluene-p-sulphonylamino)-1H-1,2,3-triazole (275c) (12%) m.p. 187° (from water) (lit., 190°), $v_{\text{max}}$ 3150 (NH) and 2300 w (CN) cm$^{-1}$. 
Reactions of Toluene-p-sulphonyl Azide with Diethyl 2-
Phenylmalonate (276a), Ethyl 2-Phenylcyanoacetate (276b)
and Ethyl 2-Phenylmalonamate (276c).

(f) Solutions of the esters (276 a-c) (0.025 mol) in absolute
ethanol (50 ml) were treated with a solution of sodium (0.58 g,
0.005 mol) in absolute ethanol (30 ml). The mixtures were cooled
to 0° and treated dropwise with stirring with a solution of toluene-
p-sulphonyl azide (4.9 g, 0.025 mol) in absolute ethanol (20 ml).
The mixtures were stirred in the melting ice bath for 2. Oh, and
were then evaporated. The resultant cakes were treated with
water and the aqueous solutions were extracted with ether (A),
acidified with concentrated hydrochloric acid and extracted with
ether (B).

In the case of the ester (276a) liquids (4.97 g) and (0.81 g)
were isolated from extracts (A) and (B) respectively and were
shown by t.l.c. to be multicomponent mixtures.

The ester (276b) gave liquids (2.58 g) and (3.96 g) from the
extracts (A) and (B) respectively which were shown by t.l.c. to
be multicomponent mixtures.

In the reaction of the ester (276c) extract (A) gave starting
material (40%) (identified by t.l.c. and its i.r. spectrum) and
acidification of the aqueous mother liquor gave an unidentified solid (1.30g), \( \nu_{\text{max}} \) 3400 (NH), and 1725 and 1690 (CO) cm\(^{-1}\).

The attempted crystallisation of the solid from ethanol or from benzene gave a gum which was shown by t.l.c. to be multicomponent.

\[(g) \quad 1,4\text{-Diphenyl-5-hydroxy-1,2,3-triazole (27Oc), prepared by the method of Dimroth,}^{116} \text{ had m.p. } 145^\circ \text{ (lit., } 151^\circ) \text{ and was used without further purification.} \]

\[4\text{-Ethoxycarbonyl-5-hydroxy-1-phenyl-1,2,3-triazole (27Od), prepared by the method of Dimroth,}^{140} \text{ had m.p. } 73^\circ \text{ (from water) (lit., } 74^\circ) \text{ and was isolated as the diazo tautomer ethyl 2-diazo-(N-phenyl)-malonamate (27Od).} \]

\[5\text{-Hydroxy-1-phenyl-1,2,3-triazole-4-carboxamide (27Oe)} \]

Phenyl azide (11.9g, 0.1 mol) was added to a solution of sodium (2.3g, 0.1 mol) in absolute ethanol (25 ml) containing ethyl malonamate (13.1g, 0.1 mol) and the mixture was heated on a boiling water bath for 0.5h. The mixture was cooled and the insoluble salt was filtered off, dissolved in the minimum quantity of hot water, cooled and acidified with concentrated hydrochloric acid. The solid was collected and crystallised from aqueous dimethylformamide to give 2-diazo-(N-phenyl)-malonamide (27Oe) (17.2g, 86%), \( \nu_{\text{max}} \) 3400 and 3300 (NH), 2150 (\( \text{N} \equiv \text{N} \)), 1670 and 1650 sh (CO), and 1600 and 1570 (NH def) cm\(^{-1}\).
C_{9}H_{8}N_{4}O_{2} \text{ requires: } C, 52.9; H, 4.0; N, 27.4\%; M 204.

\text{Found: } C, 52.9; H, 4.1; N, 27.3\%; M^+ 204.

\text{(g) Reaction of Phenyl Azide with Ethyl 2-Phenylmalonamate (276c)}

Ethyl 2-phenylmalonamate (4.02 g, 0.02 mol) and phenyl azide (2.40 g, 0.02 mol) were heated under reflux with a solution of sodium (0.46 g, 0.02 mol) in absolute ethanol (25 ml) for 17 h. The ethanol was evaporated under reduced pressure and water and ether were added to the resultant cake. An insoluble solid was filtered off and acidified with dilute aqueous hydrochloric acid to give 1,4-diphenyl-5-hydroxy-1,2,3-triazole (276c) (0.50 g, 10%) m.p. 144°. The aqueous layer was acidified with concentrated hydrochloric acid to give phenylacetamide (0.24 g, 7%) m.p. 156°. The ether extract afforded the starting amide (276c) (2.97 g) m.p. 150°, identified by its i.r. spectrum.

\text{(h) 4-Ethoxycarbonyl-5-hydroxy-1H-1,2,3-triazole (276f)}

Ethyl malonamate (3.27 g, 0.025 mol) in absolute ethanol (50 ml) was stirred and treated dropwise with piperidine (4.25 g, 0.05 mol) followed by a solution of toluene-\text{"p"}-sulphonyl azide (4.90 g, 0.025 mol) in absolute ethanol (20 ml). Stirring was continued at room temperature for 1.0 h. No insoluble solid was present. The mixture was evaporated under reduced pressure, water (30 ml) was added and the aqueous solution was extracted with chloroform.
The extract was washed with dilute aqueous hydrochloric acid and evaporated to give the colourless ethyl 2-diazomalonamate tautomer \((270\text{f})\) (3.81 g, 97%) m.p. 143° (from ethanol) \((\text{lit.}, 146°)\), \(\nu_{\text{max}}\) 3400, 3300 sh and 3200 (NH), 2150 (\(\text{N} \equiv \text{N}\)), 1700 and 1660 (CO) \(\text{cm}^{-1}\), \(\tau\) (CDCl\(_3\)) 2.50 (1H, br, NH), 3.64 (1H, br, NH), 5.70 [2H, q(J 7Hz), CH\(_2\)] and 8.68 [3H, t(J 7Hz), CH\(_3\)].

\[
C_9H_7N_3O_3 \text{ requires: C, 38.2; H, 4.5; N, 26.7%; M 157.}
\]

\[
\text{Found: C, 38.4; H, 4.6; N, 26.7%; M}^+ 157.
\]

The aqueous layer was acidified with concentrated hydrochloric acid to give toluene-p-sulphonamide (3.04 g, 71%).

7.2. Chlorination of 5-Hydroxytriazales

(a) 5-Chloro-1,4-diphenyl-1,2,3-triazole \((274\text{a})\), prepared by the method of Dimroth\(^{116}\) had m.p. 140° (from ethanol) \((\text{lit.}, 137°)\).

5-Chloro-4-ethoxycarbonyl-1-phenyl-1,2,3-triazole \((274\text{b})\), prepared by the method of Lieber et al\(^{117}\) had m.p. 82° (from ethanol) \((\text{lit.}, 82° \text{ and } 87° 140°)\).

(b) The Attempted Chlorination of 5-Hydroxy-1H-1,2,3-triazole-4-carboxamide \((270\text{a})\)

(i) The amide \((270\text{a})\) (0.26 g, 0.002 mol) in phosphoryl chloride (2.5 ml) containing phosphorus pentachloride (0.42 g) was heated at 100° for 1.0 h. The phosphoryl chloride was distilled from the reaction mixture under reduced pressure and the residue was
poured on to ice. The aqueous mixture was extracted with ether to give a pale brown solid (O.10g), m.p. 122°, \( \nu_{\text{max}} \) 3400-2500 \( \text{br} \) (NH), 2300 \( \text{w} \) (CN) and 1600 (NH def) cm\(^{-1}\).

(ii) The amide (270a) (1.30g, O.01 mol) was treated with phosphoryl chloride (8.7 ml) and redistilled diethylaniline (2.1 ml). The mixture was left at room temperature for 20 min and then heated at 135° (oil bath) for 2 h. The solvent was removed under reduced pressure and the resultant dark gum was treated with ice and extracted with ether. The ether extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to afford a pale brown solid (O.61g) m.p. 114°, identical (i.r. spectrum) to the compound obtained in (i) above. On standing for a few days solids from the above reactions became black and were not purified further.

7.3. The Attempted Synthesis of 1-Amino-5-hydroxy-1,2,3-triazoles

(a) (i) Solutions of malonamic acid hydrazide (2.93g, O.025 mol) in absolute ethanol (50 ml) and sodium (O.58g, O.025 mol) in absolute ethanol (30 ml) were mixed, cooled to 0° and treated dropwise with stirring with a solution of toluene-p-sulphonyl azide (4.9g, O.025 mol) in absolute ethanol (20 ml). The mixture was stirred in the melting ice bath for 2 Oh. The insoluble salt was collected, dissolved in the minimum quantity of hot water, cooled
and acidified with hydrochloric acid to yield 1-Amino-5-hydroxy-1,2,3-triazole-4-carboxamide (277a) (1.22g, 34%) m.p. 178° (from water), $v_{\text{max}}$ 3400, 3300 and 3250 (NH), 2850-2300 br (OH), 1670 (CO) and 1590 (NH def) cm$^{-1}$.

$C_{3}H_{5}N_{5}O_{2}$ requires: C, 25.2; H, 3.5; N, 48.9%; M 143.

Found: C, 25.5; H, 3.5; N, 44.4%; M$^{+}$ 143.

The ethanol mother liquor was evaporated and the residue was treated with water and acidified with concentrated hydrochloric acid to yield toluene-$p$-sulphonamide (2.17g).

(ii) The reaction of malonamic acid hydrazide with phenyl azide, using the method of Dimroth$^{38}$ afforded the triazole (277a) (62%) m.p. 175°, identical (i.r. spectrum) to the product (277a) obtained in (i) above.

(b) Cyanoacethydrazide was reacted with toluene-$p$-sulphonyl azide using the conditions of (a) (i) above, with the modification that the reaction was carried out at -10°. Further product was obtained on work up of the mother liquor and no toluene-$p$-sulphonamide was isolated. The product was 5-(toluene-$p$-sulphonylamino)-1H-1,2,3-triazole-4-carbohydrazide (275d) (38%) m.p. 259° (from dimethylformamide-glacial acetic acid), $v_{\text{max}}$ 3300 and 3200-2600 br (NH), 1680 (CO) and 1580 (NH def) cm$^{-1}$.

$C_{10}H_{12}N_{6}O_{3}$S requires: C, 46.5; H, 4.1; N, 28.4%; M 296.

Found: C, 46.3; H, 4.7; N, 25.0%; M$^{+}$ 296.
(c) Reaction of the Esters (27Od), (272) and (278) with Hydrazine Hydrate

(i) 5-Amino-4-ethoxycarbonyl-1-phenyl-1,2,3-triazole (278), prepared by the method of Dimroth, had m.p. 126° (from ethanol-glacial acetic acid) (lit., 126°).

(ii) The ester (278) (4.64g, 0.02 mol) in ethanol (75 ml) containing hydrazine hydrate (3.0 ml) was heated under reflux for 17 h. The ethanol was evaporated under reduced pressure, dilute aqueous hydrochloric acid was added and the colourless 5-anilino-1H-1,2,3-triazole-4-carbohydrazide (275e) was filtered off (4.11g, 79%) (i.r.

\[ \text{C}_{9}\text{H}_{10}\text{N}_{6}\text{O} \text{ requires: C, 49.5; H, 4.6; N, 38.5%; M 218.} \]

\[ \text{Found: C, 54.9; H, 5.6; N, 32.0%; M} + 218. \]

The triazole (275e) was acetylated using the procedure described before giving a diacetylated derivative (275f) (89%) m.p. 181° (from ethyl acetate-acetic anhydride) \( \nu_{\text{max}} \text{ 3300 (NH), 1750 (Ac), 1700 (CO) and 1600 (NH def) cm}^{-1} \), \( \delta [(\text{CO}_3)_2\text{SO 2.30 - 3.12 (5H, m, ArH), 6.60 (1H, br, NH), 7.24 (3H, s, N.Ac) and 8.02 (3H, s, Ac).} \]

\[ \text{C}_{13}\text{H}_{14}\text{N}_{6}\text{O}_3 \text{ requires: C, 51.7; H, 4.7; N, 27.8%; M 302.} \]

\[ \text{Found: C, 51.8; H, 4.6; N, 27.9%; M} + 302. \]

(iii) The ester (27Od) was recovered unchanged (87%) (i.r.
spectrum) on attempted reaction with hydrazine as described in (ii).

(iv) The ester (272) (2.47g, 0.01 mol) in ethanol (75 ml) containing hydrazine hydrate (1.88g, 0.03 mol) was heated under reflux for 0.5h. The ethanol was evaporated under reduced pressure and the resultant gum was triturated with ethanol-ether to afford a colourless salt which was acidified at room temperature with dilute aqueous sulphuric acid to afford the product (277b) (0.8g, 32%) m.p. 163° (from ethanol) (lit. 164°).

The ethanol-ether mother liquors were evaporated to a gummy solid which was treated with dilute aqueous hydrochloric acid. Extraction of the aqueous solution led to a gum which gave on trituration with ether a colourless solid (0.6g, 16%) m.p. 181° (from ethanol-glacial acetic acid), $v_{\text{max}}$ 3400 - 3100 br (NH), 2150 (N=N), 1680 (CO) and 1620 (NH def) cm$^{-1}$.

Found: C, 46.7; H, 4.6; N, 20.7%; M$^+$ 364.

(d) Reaction of Phenyl Azide with Phenylacethyldrazide

A mixture of phenylacethyldrazide (3.9g) and phenyl azide (3.1g) was added to a suspension of sodium ethoxide (1.77g) in absolute ethanol (15 ml). The dark solution was heated under reflux on a boiling water bath for 6h. The ethanol was evaporated under reduced pressure, water was added to the resultant cake and the aqueous solution was extracted with chloroform to give
starting phenylacethydrazide (1.62g) identified by its i.r. spectrum.
The aqueous layer was acidified with concentrated hydrochloric acid and the colourless solid was collected and combined with further material obtained by extracting the acidic filtrate with chloroform (total 1.97g). The unidentified product had m.p. 243° (from glacial acetic acid), $v_{\text{max}}$ 3200 (NH) and 1600 (NH def) cm$^{-1}$.

$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$ requires: C, 71.6; H, 6.0; N, 10.4%; M 268.

Found: C, 71.5; H, 5.9; N, 10.6%; M$^+$268.

7.4. The Synthesis of 1, 5-Diamino-1,2,3-triazoles

(a) 1-Amino-5-anilino-4-phenyl-1,2,3-triazole (279a)

(i) The chlorotriazole (274a) (40.9g, 0.16 mol) was heated under reflux with hydrazine hydrate (250 ml) for 17 h. The mixture was evaporated under reduced pressure, dilute aqueous hydrochloric acid was added and the insoluble solid was collected, combined with further material isolated by extracting the acidic filtrate with chloroform, and crystallised to give the product (279a), as colourless needles, (30.4g, 71%) m.p. 140° (from ethanol-benzene), $v_{\text{max}}$ 3300 and 3250 (NH), 1630 w, 1600 and 1590 (NH def) cm$^{-1}$.

$\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_{1\frac{1}{2}}\text{C}_6\text{H}_6$ requires: C, 70.1; H, 5.9; N, 24.0%; M 251.

Found: C, 70.1; H, 6.1; N, 24.1%; M$^+$251.

(ii) The attempted reaction of the chlorotriazole (274a) with
hydrazine hydrate in ethanol afforded only unchanged starting material (90%).

(b) The attempted reaction of the chlorotriazole (274b) with hydrazine hydrate as described above (i) yielded only a black intractable gum.

(c) (i) **Ethyl malonate iminoether (280a)** was prepared by the method of Pinner \(^{133}\) and was used immediately without further purification.

(ii) **Ethyl (1-N-Formylamidrazono) acetate (280b)**

A solution of formhydrazide (24.0g) in anhydrous ethanol (400 ml) was treated with the iminoether (280a) (63.0g) and the solution was left at 0° for 17 h. The colourless crystalline product was filtered off and combined with more product obtained by evaporating the mother liquor (total 64.0g) m.p. 109° (from ethanol), \( \nu_{\text{max}} \) 3400 and 3250 (NH), 1720 and 1670 (CO), and 1630 - 1550 br (NH def) cm\(^{-1}\), \( T (\text{CDCl}_3) 1.57 \) and 4.10 (3H, br, NH), 2.05 and 2.32 (1H, CH), 5.84 [2H, q(J 7Hz), CH\(_2\)], 6.72 and 6.83 (2H, CH\(_2\)) and 8.74 [3H, t(J 7Hz), CH\(_3\)].

\[ \text{C}_6\text{H}_{11}\text{N}_3\text{O}_3 \] requires: C, 41.6; H, 6.4; N, 24.3%; M 173.

**Found:** C, 41.6; H, 6.4; N, 24.2%; M\(^+\) 173.

(iii) **Ethyl amidrazonoacetate hydrochloride (280c)**

The formylamidrazone (270b) (50.0g) was stirred in anhydrous 1.5M ethereal hydrochloric acid (500 ml) for 17 h.
The ether was evaporated under reduced pressure and anhydrous ethanol (400 ml) was added. The insoluble hydrochloride was filtered off (29.0g) m.p. 194°, νₚₙ₆₃ 3300 - 2400 (NH) cm⁻¹.

The ethanol of the filtrate was concentrated to approximately 30 ml and anhydrous ether was added until the solution became turbid. The solution was cooled to 0° and the colourless crystalline product was collected (19.2g, 35%) m.p. 112°, νₚₙ₆₃ 3400 - 2500 br (NH), and 1720, 1700, 1670 and 1630 sh cm⁻¹, 7 [(CD₃)₂SO] 1.03 (1H, s, br, NH), 3.46 (1H, s, br, NH), 5.90 [2H, q(J 7Hz), CH₂], 6.28 (2H, s, CH₂), and 8.85 [3H, t(J 7Hz), CH₃].

(iv) 1,5-Diamino-4-ethoxycarbonyl-1,2,3-triazole (279c)

The amidrazone hydrochloride (270c) (18.1g, 0.1 mol) in absolute ethanol (400 ml) was treated dropwise with stirring at 0° with piperidine (18.7g, 0.22 mol) followed by toluene-₃-sulphonyl azide (43.3g, 0.22 mol) and stirring was continued at 0° for 2 h. The reaction mixture was filtered to afford the product (279c) (13.4g, 78%) m.p. 110° (from ethanol), νₚₙ₆₃ 3500 and 3400 - 3100 br (NH), 1690 (CO), and 1650 and 1610 (NH def) cm⁻¹, 7 (CDCl₃) 4.85 (4H, br, NH), 5.61 [2H, q(J 7Hz), CH₂], and 8.60 [3H, t(J 7Hz), CH₃].

C₅H₉N₅O₂ requires: C, 35.1; H, 5.3; N, 40.9%; M 171.

Found: C, 35.2; H, 5.4; N, 40.9%; M⁺ 171.
Work up of the mother liquors by evaporating to a cake and acidifying with glacial acetic acid afforded no further product. Toluene-\(p\)-sulphonamide was not isolated.

(v) The attempted reaction of the formylamidrazone (27Ob) with toluene-\(p\)-sulphonyl azide in the presence of piperidine using the conditions described above gave only toluene-\(p\)-sulphonamide (95\%) m.p. 125\°.

(vi) The Attempted Reaction of the Formylamidrazone (27Ob) with Toluene-\(p\)-sulphonyl Azide in the Presence of Sodium Hydride

The formylamidrazone (27Ob) (1.73g; 0.01 mol) in dry dimethylformamide (10 ml) was added at room temperature over 15 min. to a vigorously stirred suspension of sodium hydride (0.011 mol) in dry dimethylformamide (2.0 ml). Stirring was continued for a further 15 min. and toluene-\(p\)-sulphonyl azide (2.17g, 0.011 mol) in dry dimethylformamide (2.0 ml) was added dropwise. Stirring was continued at room temperature for a further 2 h, the insoluble salt (A) was filtered off and the filtrate was diluted with water and acidified with dilute aqueous hydrochloric acid affording no solid. Salt (A) was stirred in aqueous acetic acid for 0.5 h and the free compound was collected (0.9g). Attempted crystallisation of this highly insoluble material from dimethylformamide led to black decomposition products.
(d) The Attempted Reaction of Phenylacetamidrazono with
Toluene-p-sulphonyl azide
Phenylacetamidrazono treated with toluene-p-sulphonyl
azide in the presence of sodium hydride as described (c) (vi) above,
and dilution of the reaction mixture with water gave an oil which
was shown by t.l.c. to be a multicomponent mixture.

(e) The Attempted Reduction of 4-Phenyl-1H-1,2,3-triazole-
5-diazonium chloride (220) to 5-Hydrazino-4-phenyl-1H-
1,2,3-triazole (257a).

(i) A solution of sodium hydroxide (0.5g) and sodium bisulphite
(1.1g) in water (5.0 ml) was treated with a few drops of phenol-
phthalein indicator. Small amounts of sodium bisulphite (total
0.1g) were added until the colour was just discharged. A further
portion of sodium bisulphite (0.1g) was added followed by a
solution of the diazonium salt (220) in concentrated hydrochloric
acid (0.5 ml), water (2.0 ml) and methanol (1.0 ml). Frothing
occurred and a red gum precipitated. The mixture was warmed
at 65° for 0.5h, allowed to cool, and acidified with concentrated
hydrochloric acid. The acidic mixture was heated at 100° for 6h.
Work up of the reaction mixture gave no identifiable material.

(ii) The diazonium salt (220) (1.05g, 0.005 mol) was added
slowly to 80% v/v aqueous ethanol (50 ml) saturated at 0° with
sulphur dioxide. The solution was resaturated at 0° with sulphur
dioxide and was left at room temperature for 17 h. The ethanol was evaporated under reduced pressure and the aqueous solution was extracted with chloroform to give a red gum (0.72) which on trituration with a little ether gave a cream coloured solid (0.32 g) m.p. 147° (lit. 107° 145°) which was identical (i.r. spectrum) to the deaminated triazole (67a).

(f) The Attempted Hydrolytic Cleavage of the Hydrazone (224a)

(i) A solution of the hydrazone (224a) (0.66 g) in anhydrous ether (100 ml) was saturated at 0° with anhydrous hydrogen chloride. The solution was left at room temperature for 24 h and the ether was evaporated to afford a red gum which was treated with water and chloroform. Evaporation of the chloroform layer yielded the starting hydrazone (identified by its i.r. spectrum). The aqueous layer was neutralised with concentrated aqueous ammonia and extracted with chloroform to give an unidentified yellow gum (0.02 g).

(ii) A solution of the hydrazone (224a) (0.66 g) in ethanol (10 ml) containing 1M aqueous hydrochloric acid (5.0 ml) was heated under reflux for 0.5 h. No solid crystallised from the reaction mixture on cooling and the ethanol was evaporated under reduced pressure. The residual aqueous solution was extracted with chloroform to afford the starting hydrazone (0.62 g) (identified by its i.r. spectrum). Prolonging the reaction for 17 h gave on work up of the reaction
mixture an impure, unidentified, gummy solid.

7.5. Miscellaneous Reactions of Triazoles

(a) Reaction of 5-Hydroxy-1H-1,2,3-triazole-4-carboxamide
(270a) with Ethyl Acetoacetate

The amide (270a) (0.34 g, 0.002 mol) was heated under reflux with ethyl acetoacetate (0.30 g, 0.002 mol) in glacial acetic acid (10 ml) for 4 h. The glacial acetic acid was evaporated under reduced pressure and the resultant gum was triturated with ethanol-ether to afford a colourless solid (0.27 g) m.p. 180° (from ethanol-light petroleum), v_{max} 3600-3200 br (NH or OH), 1760 (CO), and 1720 - 1580 br cm^{-1}, τ[CD_{3}]_{2}SO 2.48 (2H, s, br, NH), 2.60 (2H, s, br, NH), 4.86 (1H, s, CH), and 7.90 (3H, s, CH_{3}).

Found: C, 37.5; H, 4.9; N, 17.1%; M+117.

When the reaction was carried out in ethanol in the presence of piperidinede work up led to the recovery (90%) of the starting triazole (270a) (identified by its i.r. spectrum).

(b) Reactions of 5-(Toluene-p-sulphonylamino)-1H-, 1,2,3-
triazole-4-carboxamide (275a)

(i) Reductive Detosylation with Sodium in Liquid Ammonia

A suspension of the triazole (275a) (1.14 g, 0.004 mol) in liquid ammonia (20 ml) was stirred and treated with small pieces of sodium (total 0.5 g) until the green colour produced initially became permanent. Ammonium chloride was added until the
reaction mixture became colourless and the ammonia was allowed
to evaporate at room temperature. Water (20 ml) was added to
the resultant cake and the solution was adjusted to pH6 by the
addition of glacial acetic acid. The aqueous solution was
evaporated under reduced pressure and the cake was leached with
hot ethanol. Evaporation of the ethanol extract gave a colourless
solid which was triturated with a little water to yield 5-amino-1H-
1,2,3-triazole-4-carboxamide (275g) (0.40g, 70%) m.p. 223°
(from water) (lit., 225°).

(ii) The amide (275a) (0.28g, 0.001 mol) was heated under
reflux with 100% hydrazine hydrate (10 ml) for 17 h. The mixture
was evaporated under reduced pressure, water was added and the
solution was adjusted to pH6 using dilute aqueous hydrochloric
acid. The aqueous solution was concentrated under reduced
pressure and the colourless hydrazide (275d) was collected (0.09g,
31%), identical (i.r. spectrum) to a sample prepared before.

(c) Reactions of 5-Anilino-1H-1,2,3-triazole-4-carboxyhydrazide
(275e)

(i) To a stirred solution of the hydrazide (275e) (1.00g, 0.005
mol) in glacial acetic acid (40 ml) at 5° C was added dropwise a
solution of sodium nitrite (0.43g) in water (2.0 ml). Stirring
was continued at 5° for 1.0 h and the mixture was then diluted with
water (60 ml) and extracted with chloroform. The chloroform
extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated under reduced pressure to yield the yellow azide (275j) (0.26g, 23%) m.p. 134°, $\nu_{\text{max}}$ 3400 - 3100 br (NH), 2100 (-N=N=N), 1660 (CO) and 1600 (NH def) cm$^{-1}$, which decomposed on attempted crystallisation from ethanol.

(ii) The hydrazide (275e) (0.60g, 0.03 mol) was heated under reflux in acetic anhydride (5.0 ml) containing triethyl orthoformate (5.0 ml) for 1.0h. The mixture was evaporated under reduced pressure to give a black gum (0.84g) which was shown by t.l.c. to be a multicomponent mixture.

(iii) The hydrazide (275e) (0.40g, 0.002 mol) and urea (0.12g, 0.002 mol) were heated together under nitrogen at 200° for 1.0h. A black solid resulted which was shown by t.l.c. to be a multicomponent mixture.

(d) Reactions of 1-Amino-5-hydroxy-1,2,3-triazole-4-(N-toluene-p-sulphonyl) carboxamide (277b)

The N-toluene-p-sulphonamide (277b) was treated with sodium in liquid ammonia as described before for the amide (275a). Work up of the mixture failed to give organic material.

(e) Reactions of 1-Amino-5-hydroxy-1,2,3-triazole-4-carboxamide (277a)

The aminotriazole (277a) (0.29, 0.002 mol) in methanol (5.0 ml) was treated with concentrated sulphuric acid (1.0 ml) and
water (1.0 ml) followed by a solution of benzaldehyde (0.21g, 0.002 mol) or glyoxylic acid hydrate (0.18g, 0.002 mol) in methanol (5.0 ml). The reaction mixtures were stirred at room temperature for 5 mins and the precipitated solids were filtered off to give respectively benzyldiene-2-diazooxamic acid hydrazide (0.39g, 85%) (281a), as colourless needles, m.p. 205° (from ethanol), $\nu_{\text{max}}$ 3400 and 3200 - 2400 br (NH), 2150 ($\equiv\equiv\equiv\equiv N$), 1650 (CO) and 1580 (NHdef) cm$^{-1}$.

$\text{C}_5\text{H}_9\text{N}_5\text{O}_2$ requires: C, 51.9; H, 3.9; N, 30.3%; M 231.

**Found:** C, 52.2; H, 4.1; N, 30.6%; M$^+$ 231.

and the diazo-hydrazone (281b) (0.34g, 85%), $\nu_{\text{max}}$ 3300 and 3150 (NH), 2800 - 2400 br (OH), 2150 ($\equiv\equiv\equiv\equiv N$), 1700, 1680 and 1650 (CO), and 1600 (NHdef) cm$^{-1}$, Attempted crystallisation from ethanol-glacial acetic acid resulted in partial decomposition of the compound (281b).

(f) **Methylation of the Mercaptotriazole (273a)**

The triazole (273a) (2.0g, 0.0066 mol) in 10% w/v aqueous sodium hydroxide (30 ml) and ethanol (3.0 ml) was treated with methyl iodide (0.8 ml) and the mixture was stirred at room temperature for 2 h, and acidified with dilute aqueous hydrochloric acid. The aqueous solution was decanted from the precipitated gum which was solidified by trituration with a little ether. The aqueous mother liquor was extracted with chloroform to give
further solid. The combined solids were crystallised from ethanol-light petroleum to give the thiomethyltriazole (273b) (1.82g, 89%)
m.p. 187° (from ethanol-light petroleum), $v_{\text{max}}$ 3300 (NH) and 1690 (CO) cm$^{-1}$, T[($\text{CD}_3$)$_2$SO] 2.10 [2H, d(J 8Hz), ArH], 2.58 [2H, d(J 8Hz), ArH], 7.56 (3H, s, CH$_3$), and 7.62 (3H, s, CH$_3$).

C$_{11}$H$_{12}$N$_4$O$_3$S$_2$ requires: C, 42.3; H, 3.9; N, 17.9; S, 20.2%; M 312.

Found: C, 42.4; H, 3.8; N, 17.4; S, 20.0%; M$^+$ 312.

(g) **Hydrolysis of 1,2,3-Triazole Amides and Hydrazides**

The amides (270a and c), (275a) and (277a and b) and the hydrazide (275d) (0.002 mol) were heated at 100° in 4M aqueous sodium hydroxide (5 ml) for 17 h. The solutions were acidified with dilute aqueous hydrochloric acid and the colourless products were collected, washed with water and purified by crystallisation.

(i) The amide (275a) and the hydrazide (275d) afforded 5-(toluene-p-sulphonylamino)-1H-1,2,3-triazole-4-carboxylic acid (275h)

(68 - 87%), as a colourless hydrate m.p. 123° (from water),

$v_{\text{max}}$ 3200 - 2400 br (OH) and 1690 (CO) cm$^{-1}$.

C$_{10}$H$_{10}$N$_4$O$_4$S.H$_2$O requires: C, 40.0; H, 4.0; N, 18.7%; M 282.

Found: C, 40.2; H, 4.0; N, 18.8%; M$^+$ 282.

(ii) The amide (270e) gave an acid (69%) m.p. 250° (slow decom.)
which was insoluble in boiling water or dimethylsulphoxide. The sodium salt of the acid was produced on treatment with saturated aqueous sodium hydrogen carbonate, but this also proved to be insoluble in boiling water or dimethylsulphoxide.

(iii) The amides (270a) and (277 a and b) gave after acidification of the mixtures colourless solids which left a residue on burning. These insoluble salts were not decomposed by boiling aqueous hydrochloric acid.

7.6. The Synthesis and Reactions of 1,2,3-Triazolo[1,5-b]-1,2,4-triazines

(A) From 2-Amino-5-anilino-4-phenyl-1,2,3-triazole (279a)

(a) Reactions of the Amine (279a) with 1,2-Dicarbonyl Compounds

The triazole (279a) (1.0g, 0.004 mol) was added to methanol (15 ml) containing concentrated sulphuric acid (0.5 ml). Water (5 ml) was added to the solution followed by a solution of the 1,2-dicarbonyl compound (0.004 mol) in methanol (10 ml). The mixtures were stirred at room temperature for 17 h (5 min. in the case of glyoxylic acid). Any solid product (A) was filtered off and the reaction mixtures were concentrated, diluted with water and extracted with chloroform to yield further products (B).

(i) Glyoxylic acid hydrate gave (B) 5-anilino-1-(methoxycarbonylmethyleneamino)-4-phenyl-1,2,3-triazole (283b) (1.04g, 81%) as yellow needles m.p. 158° (from ethanol-glacial acetic acid),
$\nu_{\text{max}}$ 3400 (NH), 1740 (CO) and 1600 (NH def) cm$^{-1}$, $T$(CDCl$_3$)

1.24 (1H, s, CH), 2.30 - 3.37 (1OH, m, ArH), and 6.02 (3H, s, CH$_3$).

C$_{17}$H$_{15}$N$_5$O$_2$ requires: C, 63.5; H, 4.7; N, 21.8%; M 321.

Found: C, 63.5; H, 4.7; N, 21.8%; M$^+ 321$.

(ii) Ethyl pyruvate gave (B) 5-anilino-1-(1'-ethoxycarbonylvinylideneamino)-4-phenyl-1,2,3-triazole (283c) as a yellow gum (1.24g) which was shown to be homogeneous by t.l.c., $\nu_{\text{max}}$ (thin film) 3350 (NH), 1740 (CO) and 1600 (NH def) cm$^{-1}$, $T$ (CDCl$_3$) 2.00 - 3.64 (1OH, m, ArH), 6.32 [2H, q(J 8Hz), CH$_2$], 6.79 (3H, s, CH$_3$), and 8.85 [3H, t(J 8Hz), CH$_3$]. The gum was used without further purification.

Benzoylformic acid gave (A) the insoluble, colourless 5-anilino-1-(1'-carboxylbenzylideneamino)-4-phenyl-1,2,3-triazole (283d) (0.62g, 41%) m.p. 192$^\circ$ (from glacial acetic acid), $\nu_{\text{max}}$ 3300 (NH), 2900 - 2300 br (OH), 1710 (CO) and 1600 (NH def) cm$^{-1}$.

C$_{22}$H$_{17}$N$_5$O$_2$ requires: C, 68.9; H, 4.5; N, 18.3%; M 383.

Found: C, 68.9; H, 4.7; N, 18.1%; M$^+ 383$.

Work up of the mother liquor gave a yellow gummy solid (b) (0.76g) whose spectral properties, $\nu_{\text{max}}$ 3400 - 3200 br (NH), 1740 and 1710 (CO) and 1600 (NH def) cm$^{-1}$, and t.l.c. indicated that it was a mixture of the starting amine (279a), the acid (283d) and the corresponding methyl ester.
Ethyl benzoylformate gave (A) the insoluble 5-anilino-1-(1'-ethoxycarbonylbenzylideneamino)-4-phenyl-1,2,3-triazole (283c) (0.95g, 61%) m.p. 134°, v_max 3400 (NH), 1730 (CO) and 1600 (NH def) cm⁻¹, T [(CD₃)₂SO] 1.30 - 3.42 (15H, m, ArH), 5.52 (3H, br, CH₂ and NH), and 8.66 [3H, t(J 8Hz), CH₃]. On attempted crystallisation from ethanol-glacial acetic acid the ester cyclised to the triazolotriazinone (284c). Work up of the mother liquor (B) gave the starting aminotriazole (279a) (36%) (identified by its i.r. spectrum).

The attempted reaction of glyoxylic acid hydrate with the aminotriazole (279a) in glacial acetic acid under reflux for 2h gave an orange gum which was shown by t.l.c. to be a multi-component mixture.

(b) Cyclisation of the Esters (283b, c and e) to the Triazolo-[1,5-b]triazinones (284a-c).

The esters (0.003 mol) in methanol (35 - 50 ml) were treated dropwise with stirring with piperidine (0.26g, 0.003 mol) and the mixtures were stirred at room temperature for 17 h. The solid products were filtered off, the mother liquors were concentrated to approximately 10 ml and further crops of solid product were collected. The filtrates were evaporated, treated with dilute aqueous hydrochloric acid and extracted with chloroform to give gums which yielded the aminotriazole (279a)
(0.2 - 0.3 g) m.p. 138° on trituration with ether. U.v. data are collected in Table 10.

(i) The ester (283b) gave 3,4-diphenyl-1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one (284a) (44%) m.p. 202° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 1690 (CO) and 1625 cm$^{-1}$, $\delta$ (CDCl$_3$) 2.06 (1H, s, CH), and 2.60 - 3.20 (1OH, m, ArH).

$\text{C}_{16}\text{H}_{11}\text{N}_{5}\text{O}$ requires: C, 66.4; H, 3.8; N, 24.2%; M 289.

Found: C, 66.1; H, 3.9; N, 24.2%; M$^+$ 289.

The ester (283b), heated under reflux in ethanol in the presence of piperidine for 1 h and the mixture worked up as described above, yielded the triazolotriazine (284a) 36% m.p. 200°, identical (i.r. spectrum) to a sample prepared before, together with a multicomponent gum. The ester (283b), heated under reflux in ethanolic sodium ethoxide or in aqueous ethanolic sodium carbonate or in xylene, dimethylformamide, or 2-ethoxyethanol, gave intractable oils or gums which were shown by t.l.c. to be multicomponent mixtures.

(ii) The ester (283c) gave 6-methyl-3,4-diphenyl-1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one (284b) (69%) m.p. 186° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 1690 (CO) and 1620 cm$^{-1}$, $\delta$ (CDCl$_3$) 2.64 - 3.20 (1OH, m, ArH), and 7.42 (3H, s, CH$_3$).

$\text{C}_{17}\text{H}_{13}\text{N}_{5}\text{O}$ requires: C, 67.3; H, 4.3; N, 23.1%; M 303.

Found: C, 67.6; H, 4.5; N, 23.2%; M$^+$ 303.
The ester (283c) afforded 3,4,6-triphenyl-1,2,3-triazolo-[1,5-b]-1,2,4-triazin-5(4H)-one (284c) 70% m.p. 195° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 1685 (CO) and 1610 cm$^{-1}$.

$C_{22}H_{15}N_5O$ requires: C, 72.3; H, 4.1; N, 19.2%; M 365.

Found: C, 72.0; H, 4.0; N, 19.3%; M$^{+}$ 365.

The Attempted Scission of the Triazolo[1,5-b]triazinone (284a) in Glacial Acetic Acid

The triazole (284a) (0.29g, 0.001 mol) was heated under reflux in glacial acetic acid (10 ml) for 2.5 h. The glacial acetic acid was evaporated under reduced pressure and the resultant gum was dissolved in chloroform. The chloroform solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated to afford the starting triazolotriazine (284a) (0.27g) (identified by its i.r. spectrum).

When the time of reflux of this experiment was increased to 17 h the product was a black intractable tar (0.29g).

B. (a) Condensation Reactions of the Diamine (279c) with 1,2-Dicarbonyl Compounds

The diamine (279c) (0.51g, 0.003 mol) in ethanol (10 ml) was treated with 1,2-dicarbonyl compounds (0.003 mol), followed by glacial acetic acid (0.5 ml) and the solutions were heated under reflux for 4 - 140 h. The mixtures were cooled and the crystalline products were collected and purified by crystallisation.
(A). The ethanol was evaporated from the filtrates and the residues were either crystallised or purified by dry column chromatography in ether over alumina (B). U.v. data are collected in Table 10.

(i) 3-Ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (290a) was obtained (72%) (B) from glyoxal, after heating under reflux for 5 h, as colourless needles, m.p. 123° (from ethanol), $\nu_{\text{max}}$ 1720 cm$^{-1}$, $T$ (CDCl$_3$) 1.05 [1H, d(J 1.75Hz), CH], 1.28 [1H, d (J 1.75Hz), CH], 5.46 [2H, q(J 7Hz), CH$_2$], and 8.54 [3H, t(J 7Hz), CH$_3$], followed by chromatography over alumina.

$\text{C}_7\text{H}_7\text{N}_5\text{O}_2$ requires: C, 43.5; H, 3.7; N, 36.3%; M 193.

Found: C, 43.5; H, 3.6; N, 36.4%; M$^+$ 193.

(ii) 5,6-Dimethyl-3-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (290b) was obtained (80%) (B) from biacetyl, after heating under reflux for 17 h, as colourless needles, m.p. 89° (from ethanol), $\nu_{\text{max}}$ 1710 (CO) cm$^{-1}$, $T$ (CDCl$_3$) 5.50 [2H, q(J 7Hz), CH$_2$], 7.20 (3H, s, CH$_3$), 7.29 (3H, s, CH$_3$), and 8.54 [3H, t(J 7Hz), CH$_3$], followed by chromatography.

$\text{C}_9\text{H}_{11}\text{N}_5\text{O}_2$ requires: C, 48.9; H, 5.0; N, 31.7%; M 221.

Found: C, 48.7; H, 5.1; N, 31.7%; M$^+$ 221.

(iii) 5,6-Diphenyl-3-ethoxycarbonyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (290c) was obtained (39%) (B) from benzil, after heating
under reflux for 56 h, as cream platelets, m.p. 149° (from ethanol), ν_{max} 1710 cm\(^{-1}\), \(T (CDCl_3) 2.34 - 2.86 (1\text{OH}, m, ArH)\), 5.50 [2\(H\), q(J 7Hz), CH\(_2\)], and 8.57 [3\(H\), t(H 7Hz), CH\(_3\)], followed by chromatography.

\(\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_2\) requires: C, 66.1; H, 4.4; N, 20.3%; M 345.

Found: C, 65.6; H, 4.4; N, 20.4%; M\(^+\) 345.

Benzil (50%) was also isolated from the dry column.

(iv) 3-Ethoxycarbonyl-5-methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (29Od) was isolated (87%) (A) from methylglyoxal dimethylacetal, after heating under reflux for 17 h, as colourless plates, m.p. 185° (from ethanol-glacial acetic acid), ν_{max} 1720 (CO) cm\(^{-1}\), \(T (CDCl_3) 1.30 (1\text{H}, s, CH), 5.46 [2\(H\), q(J 7Hz), CH\(_2\)], 7.21 (3\(H\), s, CH\(_3\)), and 8.53 [3\(H\), t(J 7Hz), CH\(_3\)].

\(\text{C}_{8}\text{H}_{9}\text{N}_5\text{O}_2\) requires: C, 46.4; H, 4.4; N, 33.8%; M 207.

Found: C, 46.2; H, 4.4; N, 33.8%; M\(^+\) 207.

(v) 3-Ethoxycarbonyl-5-phenyl-1,2,3-triazolo[1,5-b]-1,2,4-triazine (29Oe) was isolated (96%) from phenylglyoxal, after heating under reflux for 20 h, as colourless plates, m.p. 164° (from ethanol-glacial acetic acid), ν_{max} 1700 (CO) cm\(^{-1}\), \(T (CDCl_3) \) O.97 (1\(H\), s, CH), 1.64 - 1.80 (2\(H\), m, ArH), 2.31 - 2.43 (3\(H\), m, ArH), 5.42 [2\(H\), q(J 7Hz), CH\(_2\)], and 8.50 [3\(H\), t(J 7Hz), CH\(_3\)].

\(\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_2\) requires: C, 58.0; H, 4.1; N, 26.0%; M 269.

Found: C, 58.0; H, 4.1; N, 26.2%; M\(^+\) 269.
(vi) 5-Amino-1-carboxymethylideneamino-4-ethoxycarbonyl-1,2,3-triazole (289c) was isolated (91%) (B) from glyoxylic acid hydrate, after heating under reflux for 20 h, as a colourless solid, m.p. 189° (from ethanol), \( \nu_{\text{max}} \) 3300 and 3250 - 2250 br (NH and OH), 1700 sh and 1680 (CO), and 1620 (NHdef) cm\(^{-1}\).

\( \text{C}_7\text{H}_9\text{N}_5\text{O}_4 \) requires: C, 37.0; H, 4.0; N, 30.8%; M 227.

Found: C, 36.9; H, 4.1; N, 30.4%; \( \text{M}^+227 \).

(vii) 3-Ethoxycarbonyl-6-methyl-1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one (291b) was isolated (17%) (A) from ethyl pyruvate, after heating under reflux for 56 h, as colourless needles, m.p. 186° (from ethanol-glacial acetic acid), \( \nu_{\text{max}} \) 3200 (NH), 1720 and 1680 (CO) and 1640 (NHdef) cm\(^{-1}\), \( \delta (\text{CDCl}_3) 5.46 [\text{2H, q (J 7 Hz), CH}_2], 7.18 (\text{3H, s, CH}_3)\), and 8.53 [3H, t (J 7 Hz), \( \text{CH}_3 \)].

\( \text{C}_8\text{H}_9\text{N}_5\text{O}_3 \) requires: C, 43.0; H, 4.1; N, 31.4%; \( \text{M}^+223 \).

Found: C, 43.1; H, 4.2; N, 31.6%; \( \text{M}^+223 \).

Also isolated (B) was 5-Amino-4-ethoxycarbonyl-1-ethoxy-carbonylethyleneamino-1,2,3-triazole (289d) (80%) as a colourless solid, m.p. 38°, \( \nu_{\text{max}} \) 3300 - 2500 br (NH), 1710 sh and 1680 (CO), 1630 and 1590 (NHdef) cm\(^{-1}\), \( \delta (\text{CDCl}_3) 5.33 - 5.87 (\text{4H, m, CH}_2), 3.79 (\text{3H, s, CH}_3), 8.56 [3H, q (J 7 Hz), \text{CH}_3]\), and 8.67 [3H, q (J 7 Hz), \( \text{CH}_3 \)], which on attempted crystallisation from ethanol-light petroleum, precipitated as a gum.

A solution of the ester (289d) (0.27 g, 0.001 mol) in
ethanol (10 ml) was treated with piperidine (0.09 g, 0.001 mol), and stirred for 17 h at room temperature. The reaction mixture was evaporated under reduced pressure, dilute aqueous hydrochloric acid was added and the solution was extracted with chloroform to give the colourless ester (291b) (0.22 g, 98%) m.p. 182° (from ethanol-glacial acetic acid) which was identical (i.r. spectrum) to a sample obtained above.

(viii) 3-Ethoxycarbonyl-6-phenyl-1,2,3-triazolo[1,5-b]-1,2,4-triazin-5(4H)-one (291c) was obtained (28%) (A) from ethyl benzoylformate, after heating under reflux for 140 h, as cream needles, m.p. 187° (from ethanol-glacial acetic acid), ν max 3200 - 2500 br (NH), 1700 (CO) and 1640 (NH def) cm⁻¹, δ (CDCl₃) 1.69 - 1.92 (2H, m, ArH), 2.35 - 2.67 (3H, m, ArH), 5.55 [2H, q(J 7 Hz), CH₂], and 8.54 [3H, t(J 7 Hz), CH₃].

\[
\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_3 \quad \text{requires: C, 54.7; H, 3.9; N, 24.6%; M} + 285.
\]

\[\text{Found: C, 54.8, H, 4.0; N, 24.6%; M}^+ 285.\]

A yellow mobile gum (0.63 g), which was shown by t.l.c. to be a mixture of the starting diamine (279c) and ethyl benzoylformate, was also isolated (B).

(ix) Heated under reflux in ethanol containing diethyl oxalate for 140 h, the starting amine (279c) was recovered (90%) and heated under reflux in diethyl oxalate for 3 h, it gave a brown gum which was shown by t.l.c. to be a multicomponent mixture.
Condensation Reactions of the Diamine (279c) with Carbonyl Compounds in the Presence of Concentrated Sulphuric Acid

A solution of the diamine (279c) (0.34g, 0.002 mol) in methanol (5 ml) was treated with concentrated sulphuric acid (1.0 ml) and water (2.5 ml) followed by a solution of the carbonyl compounds (0.002 mol) in methanol (5 ml). The solutions were left at room temperature for 17 h. Water (20 ml) was added and the solutions were extracted with chloroform to give the products.

(i) 5-Amino-1-benzylideneamino-4-ethoxycarbonyl-1,2,3-triazole (289a) was obtained (83%) from benzaldehyde, as colourless plates, m.p. 195° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 3450 and 3300 (NH), 1700 (CO) and 1620 (NH def) cm$^{-1}$, $\delta$(CDCl$_3$) O. 69 (1H, s, CH), 1.96 - 2.70 (5H, m, ArH), 4.50 (2H, br, NH), 5.56 [2H, q (J 7Hz), CH$_2$], and 8.58 [3H, t(J 7Hz), CH$_3$].

C$_{12}$H$_{13}$N$_5$O$_2$ requires: C, 55.6; H, 5.1; N, 27.0%; M 259.

Found: C, 55.3; H, 5.2; N, 27.3%; M$^+$ 259.

The benzylidene derivative (289a) (0.26g, 0.001 mol) was warmed with acetic anhydride (2.0 ml) for 1 min. and the solution was evaporated to a colourless solid which was collected using a little ether to give the acetyl derivative (289b) (0.19g, 63%), m.p. 189° (from ethyl acetate), $\nu_{\text{max}}$ 3200 (NH), and 1710 and 1680 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) O. 67 (1H, s, CH), 1.98 - 2.71 (5H, m, ArH), 5.56 [2H, q(J 7Hz), CH$_2$], 7.73 (3H, s, CH$_3$), and 8.57 [3H,
t(J 7Hz), CH$_3$],

C$_{14}$H$_{15}$N$_5$O$_3$ requires: C, 55.8; H, 5.0; N, 23.3%; M 301.

Found: C, 55.4; H, 5.2; N, 23.5%; M$^+$ 301.

(ii) The acid (289c), identical (m.p. and i.r. spectrum) to a sample obtained before, was isolated (93%) on reaction with glyoxylic acid hydrate. The acid (289c) was recovered unchanged on attempted cyclisation in ethanol in the presence of piperidine as described in (vii) above.

(iii) Biacetyl afforded the intermediate ketone (289e) as a yellow oil which was cyclised using piperidine [as in (vii) above] to the dimethyltriazolotriazine (290b) (84%), m.p. 86$^\circ$ (from ethanol), which was identical (i.r. spectrum) to a sample obtained before.

(c) Reactions of the Triazolo[4,5-b]triazine Derivatives (290a, and e).

(i) A solution of ester (290a) (1.54g, O.008 mol) in ethanol (40 ml) containing 2M aqueous sodium carbonate (20 ml) was heated under reflux for 0.5 h. The ethanol was evaporated under reduced pressure and the aqueous solution was extracted with chloroform to give a black tar (1.09g) which was shown by t.l.c. to be a multicomponent mixture. The aqueous layer was acidified and a black solid (0.22g) was collected and shown by its n.m.r. spectrum to be a multicomponent mixture.
(ii) A solution of the ester (290e) (0.27g, 0.001mol) in ethanol (10 ml) and 20% v/v aqueous sulphuric acid (5 ml) was heated under reflux for 6 h. On cooling the colourless starting ester crystallised from solution and was collected (0.17g) m.p. 160°. The ethanol was evaporated from the filtrate under reduced pressure and the aqueous solution was extracted with chloroform to give a further crop of starting ester (0.07g) m.p. 157°.

7.7. The Synthesis and Reactivity of 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives from the Hydrazinotriazole (257a)

(a) The diazonium salt (220) (1.05g, 0.005 mol) was added slowly to 80% v/v aqueous ethanol (50 ml) saturated at 0° with sulphur dioxide. The solution was resaturated at 0° with sulphur dioxide and was left at room temperature for 17 h. The dicarbonyl compounds were added to the solutions and the mixtures were heated under reflux for 2.0 h. The mixtures were cooled to 0° and the solids were collected and combined with further material obtained by concentrating the filtrates to approximately 20 ml, to give the products (A). The aqueous mother liquors were diluted with water and extracted with chloroform to yield red gums (B). U. v. data of the triazolo[5,1-c]triazines (285 a-e) and (285) are collected in Table 10.

(i) Biacetyl gave 6,7-dimethyl-3-phenyl-1,2,3-triazolo[5,1-c]-1, 2,4-triazine (285b) (59%) m.p. 192° (from ethanol-glacial acetic
acid), \( \Delta (\text{CDCl}_3) 1.63 - 2.65 \) (5H, m, ArH), 7.39 (3H, s, CH\(_3\)), and 7.43 (3H, s, CH\(_3\)).

\[
\text{C}_{12}H_{11}N_5 \text{ requires: C, 64.0; H, 4.9; N, 31.1%; M 225.}
\]

\[
\text{Found: C, 64.1; H, 5.0; N, 31.3%; M}^+325.
\]

The gum (B) on trituration with a little ether gave 4-phenyl-1H-1,2,3-triazole (67a) (0.27g, 37%) (identified by its i.r. and \( ^1H \) n.m.r. spectra).

1. **(ii)** Benzil gave on hot filtration of the reaction mixture 3,6,7-triphenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (285c) (18%) m.p. 241\(^\circ\) (from ethanol-glacial acetic acid).

\[
\text{C}_{22}H_{15}N_5 \text{ requires: C, 75.6; H, 4.3; N, 20.0%; M 349.}
\]

\[
\text{Found: C, 75.3; H, 4.3; N, 20.0%; M}^+349.
\]

Benzil (59%) crystallised from the cooled reaction mixture. The mother liquors on work up gave (B) an orange gum (0.39g) which was shown by t.l.c. to be a mixture of benzil and the deaminated triazole (67a).

2. **(iii)** Glyoxal yielded (A) 3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (285a) (39%) m.p. 190\(^\circ\) (from ethanol-glacial acetic acid), \( \Delta (\text{CDCl}_3) 1.48 [1H, d(J 1.75Hz), CH], 1.54 - 2.65 (6H, m, ArH and CH).

\[
\text{C}_{10}H_{7}N_5 \text{ requires: C, 60.9; H, 3.6; N, 35.5%; M 197.}
\]

\[
\text{Found: C, 60.5; H, 3.6; N, 35.5%; M}^+197.
\]

The yellow viscous gum (B) (0.51g) was shown by \( ^1H \) n.m.r. and
t. l. c. to be a multicomponent mixture the major component being
the deaminated triazole (67a).

(iv) Methylglyoxal dimethylacetal gave (A) 7-methyl-3-phenyl-1,2,
3-triazolo[5,1-c]-1,2,4-triazine (285d) (40%) m.p. 229° (from
ethanol-glacial acetic acid), $T(\text{CDCl}_3)$ 1.59 - 2.64 (6H, m, ArH and
CH), and 7.27 (3H, s, CH$_3$).

$C_{11}H_9N_5$ requires: C, 62.6; H, 4.3; N, 33.2%; M 211.

Found: C, 62.7; H, 4.3; N, 33.2%; M$^+$ 211.

The red gum (B) (0.60g) was heated under reflux in ethanol (30 ml)
and water (5 ml) containing anhydrous sodium acetate (0.4g) for
2 h. The solvent was evaporated and dilute aqueous hydrochloric
acid was added to the residue which was extracted with chloroform
to yield only the deaminated triazole (67a) (0.40g) (identified by its
$^1$H n.m.r. and i.r. spectra).

(v) Phenylglyoxal gave (A) 3,7-diphenyl-1,2,3-triazolo[5,1-c]-1,
2,4-triazine (285e) (14%) m.p. 218° (from ethanol-glacial acetic
acid), $T(\text{CDCl}_3)$ 1.16(1H, s, CH), and 1.48 - 2.70 (1OH, m, ArH).

$C_{16}H_{11}N_5$ requires: C, 70.3; H, 4.1; N, 25.6%; M 273.

Found: C, 69.9; H, 4.1; N, 25.4%; M$^+$ 273.

The gum (B) (1.45g) was heated under reflux with sodium acetate
as described in (iv) above. Further work up gave an orange gum
(1.09g) which on trituration with ether yielded the deaminated
triazole (67a) (0.42g) (identified by its $^1$H n.m.r. and i.r.)
spectra). The ethereal mother liquor yielded no more solid.

(vi) The chloroform extract (B), in the reaction of glyoxylic acid hydrate, was washed with saturated aqueous sodium hydrogen carbonate and gave a gum (0.55g) which was shown by t.l.c. to be a multicomponent mixture. The sodium hydrogen carbonate layer was acidified with dilute aqueous hydrochloric acid and extracted with chloroform to yield a gum (0.67g) which was shown by its $^1$H n.m.r. spectrum to be a multicomponent mixture.

(vii) Ethyl pyruvate gave (B) a red gum (1.06g) which was heated under reflux with sodium acetate as described in (iv) above. The chloroform extract yielded the deaminated triazole (67a) (0.41g) m.p. 146°. The basic aqueous layer was acidified with dilute aqueous hydrochloric acid to give the insoluble 6-methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one (286) (29%) m.p. 222° (from ethanol-acetic acid), $\nu_{\text{max}}$ 3250 - 2900 br (NH), 1680 (CO) and 1620 (NH$\text{def}$) cm$^{-1}$, T(CDCl$_3$) 1.52 - 2.70 (5H, m, ArH), and 7.41 (3H, s, CH$_3$).

C$_{17}$H$_9$N$_5$O requires: C, 58.1; H, 4.0; N, 30.8%; M 227.

Found: C, 57.5; H, 4.0; N, 30.9%; M$^+$ 227.

(viii) In the reaction of ethyl benzylformate a colourless solid was insoluble in the aqueous and chloroform layers and was filtered off (0.21g), m.p. 239° (from ethanol), $\nu_{\text{max}}$ 3300 - 2400 (NH) and 1690 (CO) cm$^{-1}$. 
Found: C, 61.4; H, 5.4; N, 22.3%; M$^+270$.

The chloroform layer gave an orange gum (1.60g) which was heated under reflux with sodium acetate as described above. Work up yielded a yellow solid (0.60g) which was shown ($^1$H n.m.r. and i.r. spectra) to be the deaminated triazole (67a).

(ix) Diethyl mesoxalate gave (B) a red gum (1.68g) which was then stirred at room temperature in ethanol (10 ml) containing piperidine (0.43g) for 17 h. The ethanol was evaporated under reduced pressure. Chloroform was added to the resultant red gum, and the solution was washed with dilute aqueous hydrochloric acid and evaporated to give a second red gum (1.59g) which was triturated with methanol to yield the insoluble 6-ethoxycarbonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-7(4H)-one (223a) (0.22g, 15%) m.p. 165° (from ethanol-glacial acetic acid) which was identical (i.r. spectrum and mixed m.p.) to the ester obtained before.

The methanol trituration liquors afforded a red gum which was shown by t.l.c. to be a multicomponent mixture.

A solution of ethyl 2-methylacetoacetate (0.36g, 0.0025 mol) in 2M aqueous potassium hydroxide (1.5 ml) was left for 24 h. at 0° and acidified to pH6 with concentrated hydrochloric acid. This solution was added dropwise with stirring at 0° to a solution of the diazonium salt (220) (0.53g, 0.0025 mol) in ethanol (12 ml) and 2M aqueous hydrochloric acid (12 ml). Solid sodium acetate
was added until the solution reached pH8, and the reaction mixture was stirred at room temperature for 17 h. The insoluble yellow solid was collected (0.35 g, 64%), m.p. 191° (from ethanol-glacial acetic acid) and was identical (mixed m.p. and i.r. spectrum) to the triazolotriazine (285b) obtained before.

(b) **Scission of the Triazolo[5, 1-c]triazines (285 b, c, d and e) in Glacial Acetic Acid**

The triazolotriazines (285 b, c, d and e) (0.001 mol) were heated under reflux in glacial acetic acid (15 ml) for 40 h. The glacial acetic acid was evaporated under reduced pressure and chloroform was added. The chloroform solutions were washed with saturated aqueous sodium hydrogen carbonate and evaporated to give dark gums which were purified by dry column chromatography in ether over alumina.

(i) **6, 7-Dimethyl-3-phenyl-1, 2, 3-triazolo[5, 1-c]-1, 2, 4-triazine**

(285b) gave 3-(1-acetoxybenzyl)-5, 6-dimethyl-1, 2, 4-triazine (287a) (45%), $v_{\text{max}}$ (film) 1740 (OAc) cm$^{-1}$, $\delta$(CDCl$_3$) 2.35 - 2.73 (5H, m, ArH), 3.16 (1H, s, CH), 7.40 (3H, s, CH$_3$), 7.53 (3H, s, CH$_3$), and 7.81 (3H, s, OAc).

(ii) **3, 6, 7-Triphenyl-1, 2, 3-triazolo[5, 1-c]-1, 2, 4-triazine**

(285c) yielded 3-(1-acetoxybenzyl)-5, 6-diphenyl-1, 2, 4-triazine (287b) (79%) $v_{\text{max}}$ (film) 1740 (OAc) cm$^{-1}$, $\delta$(CDCl$_3$) 2.16 - 2.88 (15H, m, ArH), 2.93 (1H, s, CH), and 7.76 (3H, s, OAc).
(iii) 6-Methyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (285d) gave starting material (52%) m.p. 227° (identified by its i.r. and $^1$H n.m.r. spectra). The triazolotriazine (285d) (0.0005 mol) heated under reflux in glacial acetic acid (10 ml) containing concentrated hydrochloric acid (0.5 ml) for 17 h afforded on work up, as above, a black gum which was shown by t.l.c. to be a multicomponent mixture.

(iv) 3,6-Diphenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (285e) gave a yellow gum which was shown, by its $^1$H n.m.r. spectrum, to be a mixture of triazines, $\tau$(CDCl$_3$) O.20 (s, CH), O.48 (s, CH), 1.66 - 2.80 (m, ArH), 3.03 (s, CH), 5.53 (s, CH$_2$) and 7.73 (s, O.Ac), containing approximately 80% (287d), as estimated by the integrated ratio of the CH absorptions.

(c) The Attempted Catalytic Hydrogenation of the Acetoxybenzyltriazines (287 b and d)

The acetoxybenzyltriazines (287 b and d) (0.001 mol) were hydrogenated in ethanol over 10% palladium-charcoal. The catalyst was filtered off and the filtrates were evaporated to yield light coloured gums.

(i) The acetoxybenzyltriazine (287b) afforded the gummy dihydrotriazine (288) (0.29g) $\nu_{\text{max}}$ 3300 - 2700 br (NH) and 1740 (O.Ac) cm$^{-1}$, which was reconverted into the starting triazine (287b) by heating under reflux in acetone (100 ml) in the presence of
activated manganese dioxide (1.20g) for 0.5 h.

(ii) The acetoxybenzyltriazine (287d) was recovered (95%) on attempted hydrogenation as described in (i) above.

7.8. The Attempted Synthesis of Triazolotriazole Derivatives

(A) From the Anilinotriazole (279a)

(a) Reactions with Acylating Agents

(i) The anilinotriazole (279a) (0.5g, 0.002 mol) was heated under reflux in formic acid (15 ml) for 14 h. Evaporation of the mixture under reduced pressure gave a black gum which was dissolved in chloroform. The solution obtained was washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield a red oil (0.58g) which was shown by t.l.c. to be a multicomponent mixture.

(ii) The aminotriazole (279a) (0.25g, 0.001 mol) was heated under reflux in acetic anhydride (2 ml) for 1 h. The acetic anhydride was evaporated under reduced pressure to give a dark intractable gum (0.27g).

(iii) The aminotriazole (279a) (0.5g, 0.002 mol) was warmed at 100° in acetic anhydride (4 ml) for 5 min. The acetic anhydride was evaporated under reduced pressure and the product (282a) was collected using a little ether (0.4g, 60%), m.p. 178° (from ethyl acetate-light petroleum), νmax 3150 w (NH) and 1700 (N.Ac) cm⁻¹,
(iv) The diacetylaminotriazole (282a) (0.23g, 0.0015 mol) was warmed in 2M aqueous sodium hydroxide at 90° for 2 min. The solution was allowed to cool, acidified with dilute aqueous hydrochloric acid and the gummy solid was collected and crystallised from ethanol-light petroleum to give a colourless solid (282b) (0.09g) m.p. 167°, \( \nu_{\text{max}} \) 3350 and 3200 (NH), 1705 (CO) and 1600 (NHdef) cm\(^{-1}\), \( \tau \left( \text{CDCl}_3 \right) \) 1.79 - 3.52 (1OH, m, ArH), and 8.00 (3H, s, CH\(_3\)).

(b) **Reaction with Triethyl Orthoformate**

(i) The aminotriazole (279a) (0.50g, 0.002 mol) was heated under reflux in triethyl orthoformate (4 ml) for 2h. The solution was cooled, diluted with ether and the solid was collected and crystallised to give 5-anilino-1-ethoxymethyleneamino-4-phenyl-1,2,3-triazole (283f) (0.46g, 76%) m.p. 166° (from ethanol), \( \nu_{\text{max}} \) 3200 (NH) and 1610 (NHdef) cm\(^{-1}\), \( \tau \left( \text{CDCl}_3 \right) \) 1.18 (1H, s, CH), 2.12 - 3.43 (1OH, m, ArH), 4.21 (1H, s, br, NH), 5.75 [2H, q(J 8Hz), CH\(_2\)], and 8.70 [3H, t(J 8Hz), CH\(_3\)].

C\(_{17}H\(_{17}\)N\(_5\)O requires: C, 66.4; H, 5.6; N, 22.8%; M 307.

Found: C, 67.5; H, 5.3; N, 23.3%; M\(^+\) 307.
(ii) The Attempted Cyclisation of the Ethoxymethyleneaminotriazoles (283f)

The ethoxymethyleneaminotriazole (283f) (0.31g, 0.001 mol) was heated under reflux in ethanol (10 ml) containing 10% w/v aqueous potassium hydroxide (1.0 ml) for 0.5 h. The ethanol was evaporated under reduced pressure and the aqueous mother liquor was extracted with chloroform to give a colourless semi-solid (0.23g) which was shown by t.l.c. to contain at least three close running components.

(c) The Attempted Oxidative Cyclisation of 1, 2, 3-Triazole Hydrazones (283a) and (224)

(i) 5-Anilino-1-benzylideneamino-4-phenyl-1, 2, 3-triazole (283a)

The aminotriazole (279a) (2.0g, 0.008 mol) was added to methanol (30 ml) containing concentrated sulphuric acid (0.5 ml). The mixture was treated with water (10 ml) followed by benzaldehyde (0.86g, 0.008 mol). On scratching the product (283a) precipitated and was filtered off (2.55g, 73%) m.p. 169° (from ethanol), $v_{\text{max}}$ 3300 (NH) and 1600 (NHdef) cm$^{-1}$, T (CF$_3$CO$_2$H) O.62 (1H, s, CH), and 1.86 - 3.20 (15H, m, ArH).

C$_{21}$H$_{17}$N$_5$ requires: C, 74.3; H, 5.1; N, 20.6%; M 339.

Found: C, 74.1; H, 5.1; N, 20.5%; M$^+$ 339.

(ii) A solution of the hydrazone (283a) (1.02g, 0.003 mol) in acetone (60 ml) was heated on a boiling water bath with activated
manganese dioxide (6.0g) for 6h. The mixture was filtered hot and the residue was washed with warm acetone. The combined filtrate and washings were evaporated to give a brown gum (0.98g) which was triturated with ether to afford the starting hydrazone (283a) (20%) (identified by its i.r. spectrum). The oil recovered by evaporating the ether filtrate was chromatographed over alumina, but gave no characterisable product.

(iii) A solution of the hydrazone (283a) (0.34g, 0.001 mol) in methylene chloride (10 ml) was stirred with lead tetraacetate (0.5g) at 0° for 2h. The supernatant liquor was decanted from insoluble material, washed with water and evaporated to a dark gum (0.28g) which was shown by t.l.c. to be a multicomponent mixture.

(iv) A solution of the hydrazone (224c) (0.40g, 0.001 mol) in acetone (200 ml) was heated under reflux on a boiling water bath with activated manganese dioxide (2.0g) for 2h. The mixture was filtered hot and the residue was washed with hot acetone. The combined filtrate and washings were evaporated to give a red solid (0.30g) which was shown by t.l.c. to be a mixture of at least three components. Chromatography of the solid over silica failed to effect a separation. Chromatography over alumina led to multicomponent mixtures suggesting that the solid was reacting on the alumina column.
(B) **From the Diazonium Salt (220)**

The diazonium salt (220) (1.05g, 0.005 mol) was reduced in situ with sulphur dioxide in 80% v/v aqueous ethanol, (50 ml) as described in Section 7.7. Formic acid (0.46g, 0.01 mol) was added and the solution was heated under reflux for 2.0h. The ethanol was evaporated under reduced pressure and water (20 ml) was added. The solution was extracted with chloroform and the extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield a red gum. Trituration of the gum with ether afforded a colourless solid (0.10g) which was identical (m.p. and i.r. spectrum) to the compound obtained from the reaction with ethyl benzoylformate [see section 7.7. (viii)]. The residue from the ether mother liquors was the deaminated triazole (67a) (0.52g) m.p. 140°.

(C) **From the Diamine (279c)**

(a) **Reactions with Acylating Agents**

(i) The diamine (279c) (0.26g, 0.0015 m) was heated under reflux in formic acid (3 ml) for 3 h. Evaporation of the mixture under reduced pressure gave a yellow gum (0.29g) which was shown by t.l.c. and its $^1$H n.m.r. spectrum to be a mixture.

(ii) The diamine (279c) (0.26g, 0.0015 mol) was heated under reflux in acetic anhydride (2 ml) for 1h. The acetic anhydride was evaporated under reduced pressure to a yellow gum which was
shown by t.l.c. to be a multicomponent mixture.

(b) Reaction with Triethyl Orthoformate

(i) The diamine (279c) (0.51g, 0.003 mol) in triethyl orthoformate (4 ml) was heated under reflux for 2 h. The solution was allowed to cool and the crystalline solid was collected. Evaporation of the triethyl orthoformate under reduced pressure, followed by trituration with a little ether afforded a further crop of product. The combined crops were crystallised from ethanol to give 5-amino-4-ethoxycarbonyl-1-ethoxymethyleneamino-1,2,3-triazole (289f) as colourless plates, (0.47g, 78%) m.p. 154° (from ethanol),

\[ \text{v}_{\text{max}} = 3400, 3200 \text{ and } 3100 \text{ sh (NH)}, \ 1690 \text{ (CO) and } 1630 \text{ (NH def)} \]

\[ \text{cm}^{-1}, \text{T(CDC}_1\text{)}_3 = 1.11 \text{ (1H, s, CH)}, \ 4.80 \text{ (2H, br, NH)}, \ 5.59[2H, q(J 7Hz), \text{CH}_2], \ 5.64[2H, q(J 7Hz), \text{CH}_2], \text{ and } 8.58[6H, t(J 7Hz), \text{CH}_3]. \]

\[ \text{C}_8\text{H}_{13}\text{N}_5\text{O}_3 \text{ requires: C, 42.3; H, 5.8; N, 30.8%; M 227.} \]

\[ \text{Found: } \text{C, 42.3; H, 5.9; N, 31.1%; M}_2\text{227.} \]

(ii) The ester (289f) (0.23g, 0.001 mol) was heated under reflux in acetic anhydride (2 ml) containing 85% phosphoric acid (0.01g) for 1 h. The mixture was evaporated under reduced pressure to yield a black gum (0.23g) which was shown by t.l.c. to be a multicomponent mixture.
### Table 10

**U.v. Spectra of 1,2,3-Triazololo-1,2,4-triazines**

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{\text{max}} ) (nm)</th>
<th>( \log \epsilon )</th>
</tr>
</thead>
<tbody>
<tr>
<td>284a</td>
<td>220sh, 243, 340</td>
<td>4.18, 4.42, 3.21</td>
</tr>
<tr>
<td>284b</td>
<td>221 sh, 242, 303</td>
<td>4.23, 4.32, 4.20</td>
</tr>
<tr>
<td>284c</td>
<td>221 sh, 242</td>
<td>4.14, 4.35</td>
</tr>
<tr>
<td>290a</td>
<td>227, 330</td>
<td>4.31, 3.36</td>
</tr>
<tr>
<td>290b</td>
<td>228, 317</td>
<td>4.31, 3.41</td>
</tr>
<tr>
<td>290c</td>
<td>229, 171, 354</td>
<td>4.39, 4.28, 3.82</td>
</tr>
<tr>
<td>290d</td>
<td>227, 281, 321</td>
<td>4.44, 3.18, 3.08</td>
</tr>
<tr>
<td>290e</td>
<td>230, 268, 356 sh</td>
<td>4.06, 4.31, 3.71</td>
</tr>
<tr>
<td>291b</td>
<td>216sh, 233, 297</td>
<td>4.00, 4.35, 3.17</td>
</tr>
<tr>
<td>291c</td>
<td>210inf, 235, 296</td>
<td>4.17, 4.39, 4.13</td>
</tr>
<tr>
<td>285a</td>
<td>215, 245, 392</td>
<td>3.85, 4.38, 3.41</td>
</tr>
<tr>
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<td>215, 247, 375</td>
<td>3.95, 4.43, 3.42</td>
</tr>
<tr>
<td>285c</td>
<td>223, 253, 295, 410</td>
<td>4.35, 4.47, 4.37, 3.65</td>
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<tr>
<td>285d</td>
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<td>3.89, 4.40, 3.39</td>
</tr>
<tr>
<td>285e</td>
<td>211, 251, 288, 416</td>
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<tr>
<td>286a</td>
<td>228sh, 253, 358</td>
<td>3.97, 4.39, 3.08</td>
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</tbody>
</table>
BIBLIOGRAPHY

2. A. Werner and E. Stiasny, Ber., 1899, 32, 3256.
4. A. Ladenburg, Ber., 1876, 9, 219.


71. J.C. Mason and G. Tennant, unpublished results.
74. G. Tennant, unpublished results.


92. P. Griess, Ber., 1882, 15, 1878.


97. R. Metze, Ber., 1955, 88, 772.
106. S. Gabriel and G. Eschenbach, Ber., 1897, 30, 1126.
116. O. Dimroth, Annalen, 1904, 335, 102.


THE V-TRIAZOLO[5,1-C]-AS-TRIAZINE RING SYSTEM AND A SYNTHETIC ROUTE TO NOVEL AS-TRIAZINE DERIVATIVES

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In contrast to their benzenoid counterparts, the reactions of five-
membered heterocyclic diazonium salts\(^1\) have been comparatively little studied. In particular, the potential bifunctional reactivity of the derived diazonium betaines (2) might provide the basis for a general route [(1) + (2) → (3)] to fused as-triazines exemplified by the conversion of 1H-pyrazole diazonium salts into pyrazolo[5,1-c]-as-triazines.\(^2\)

The application of the annellation process [(1) + (2) → (3)] to the synthesis of the hitherto unknown \(\nu\)-triazolo [5,1-c]-as-triazine ring system is now described.\(^\dagger\) Acid-catalysed triazole scission\(^3\) of this ring system provides a valuable method for the synthesis of as-triazine derivatives\(^\dagger\) of a type which are otherwise obtainable only with difficulty and which are of potential value as synthetic intermediates (e.g. in azapteridine synthesis\(^4\)).

Acetylacetone coupled with the diazonium salt (4) in aqueous ethanol at room temperature in the presence of sodium acetate to give 6-acetyl-7-methyl-3-phenyl-\(\nu\)-triazolo[5,1-c]-as-triazine (5a) (90%), m.p. 210\(^\circ\), whose structure follows from its reaction with phenylhydrazine to give the azo-compound (8) thereby excluding the alternative structure (7), the product of a subsequent Dimroth rearrangement\(^3\) of (5a). The triazolotriazines (5b and c) were similarly obtained (80-90%) from the salt (4) and benzoylacetone or ethyl acetoacetate. Coupling of the salt (4) with diethyl malonate, ethyl
cyanacetate, or cyanacetamide gave mixtures of triazolotriazines (6a) and (5d and e) and the derived hydrazones (9a-c), whereas hydrazones (9d-f) were the sole products (60-90%) of the coupling reactions of benzoylacetonitrile, ethyl benzoylacetal, or dibenzoylmethane. Heated in aqueous ethanolic sodium acetate, the hydrazones (9a-e) afforded the corresponding triazolotriazines (6a) and (5d-g) (> 90%). In the cyclisation of the hydrazone (9f) both possible products (5h) and (6b) were obtained. Heating the amino-amide (5e) under reflux (17h) in glacial acetic acid gave 3-(g-acetoxybenzyl)-5-aminoas-triazine-6-carboxamide (10d) (67%), m.p. 105°. The as-triazines (10a-c) were obtained similarly.

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C. Temple, C. L. Kussner, and J. A. Montgomery, ibid., 1971, 36, 2974.