THE SYNTHESSES OF A-HOMO STEROID KETONES

by

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TO JOAN
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NOTE

1. The configuration of the hydrogen atoms at the ring junctions will always be $5\alpha$, $8\beta$, $9\alpha$, and $14\alpha$. All other configurations will be shown as follows:
   a) A solid line indicates a $\beta$-configuration
   b) A broken line indicates an $\alpha$-configuration.
   c) A wavy line indicates either unknown or unspecified configuration.

   The configuration at $C_{20}$ will be indicated as follows:

   ![Structure](image)

   - $20\alpha$ - hydroxy
   - $20\beta$ - hydroxy
   - Unknown or unspecified.

2. The nomenclature, adopted by Bladon and McMeeken $^{32}$, for exocyclic steroid epoxides has been followed. The exocyclic carbon at $C_3$ will be named the $3'$ position.

   ![Structure](image)

   e.g. $3\beta$ - methyl - $3\alpha, 3' \alpha$ - oxidocholestane
INTRODUCTION
Figure 1: Pinacolic Rearrangements

1. $R_1\cdot CO\cdot R_2 + CH_3\cdot OH \xrightarrow{H^+} R_1\cdot CO\cdot CH_2\cdot R_2$

2. $R_1\cdot CO\cdot R_2 \xrightarrow{HNO_2 (-N_2)} R_1\cdot CO\cdot R_3$

3. $R_1\cdot CO\cdot R_2 \xrightarrow{E_1} R_1\cdot CO\cdot R_3$

4. $R_1\cdot CO\cdot R_2 \xrightarrow{H^+} R_1\cdot CO\cdot R_3$

5. $R_1\cdot CO\cdot R_2 \xrightarrow{H^+} R_1\cdot CO\cdot R_3$

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INTRODUCTION

The effect of ring homologation on the biological activity of steroids presents points of considerable theoretical interest. Investigations in this field have, however, uncovered hormone analogues of practical use to medicine.

A-homostestosterone propionate\(^1\) has androgenic and myotrophic as well as pituitary inhibiting potency. The activity is of the same order of magnitude as testosterone propionate. A-homodihydrotestosterone\(^2\) is practically inactive, whilst A-homoprogesterone\(^2\) is one fifteenth as active as progesterone.

D-homotestosterone\(^3\) and other derivatives of the D-homoandrostan series possess insufficient androgenic activity to challenge the natural hormones, D-homodihydrotestosterone being practically inactive. D-homoestrone\(^4\) and D-homoestradiol are both only about one thirtieth as active as estrone in rats, and D-homocortisoneacetate\(^5\) has one third the activity of cortisone acetate.

The purpose of these investigations, however, was not to synthesise steroids with biological activity.

The present study was undertaken to correlate the mode of homologation of steroids in pinacolic rearrangements and to determine which of the adjacent bonds migrated when the substituents beta to the carbonium ion were modified.

The pinacolic rearrangement involves the migration of an alkyl or aryl group to an electron deficient carbon atom formed during the dehydration of the glycol (1) with the subsequent formation of the ketone (3). Closely analogous are the rearrangements of 2-amino alcohols (4) on treatment with nitrous/
nitrous acid, halohydrins (5) in ionising solvents and the treatment of substituted oxides (6) with acid. Mechanistically similar is the action of diazomethane on a ketone (7-9).

Attempts have been made, with a certain measure of success, to correlate type of migrating group with its migratory aptitude. As the migrating group moves with its electron pair it might be expected that the more nucleophilic group migrates. Thus, in the rearrangement of the glycol$^6$ (10), it is the para-methoxyphenyl that migrates in preference to phenyl. Steric factors, however, also play a part and it is found that ortho-methoxyphenyl$^7$ migrates more than a thousand times less readily than the corresponding p-substituted group.

In the case of alkyl substituents the relative migratory aptitudes of substituents might be expected to follow the order tertiary $>$ secondary $>$ primary, the stability sequence of alkyl carbonium ions resulting from delocalisation of charge by inductive and hyperconjugative effects.

Using isotopic techniques, Stiles and Mayer$^8$ have investigated the pinacolic rearrangements of a series of glycols and have found the expected order of migratory aptitudes. Similarly this order is found in a series of ketones undergoing the peracid rearrangement$^9$. In this case migration of alkyl groups occurs to an electron deficient oxygen atom.

In the case of the reaction of diazomethane on certain aliphatic ketones, however, the migratory aptitudes of alkyl groups were found to follow the reverse order$^{10}$ e.g. Methyl $>$ n-propyl $>$ t-buty1. These pinacolic rearrangements may be adapted to the synthesis of homosteroid ketones by migration of a carbon in the ring to an electron deficient/
**Figure 2: Homologation Reactions**

![Chemical Structures]

(12) $\xrightarrow{\text{HNO}_3} (13)$

(14) $\xrightarrow{\text{CH}_3\text{N}_3}$

(15) $\text{[O]}$

(16) $\text{[O]}$

(17) $\xrightarrow{\text{CH}_3\text{N}_3}$

(18)

(19, 20) a; R = H

(19, 20) b; R = CH$_3$

(21) $\xrightarrow{\text{[O]}}$

(22a)

(23)

(22b)
deficient carbon atom in an exocyclic side chain. A simple example is the rearrangement of the amino alcohol (12) with nitrous acid to yield the ketone (13).

A brief review of homologation reactions in all the steroid rings follows. Where relevant, the peracid reactions of steroid ketones will also be discussed since these reactions also involve the movement of an alkyl group to an electron deficient centre.

(a) A-ring

The homologation of the A-ring has been carried out using the nitrous acidamine reaction (12-13) and also diazomethane (14-13). By the former method, cholestan-3-one and dihydrotestosterone3 both yield as the major product, the A-homo-β-ketone (13). The reaction of diazomethane11 also gives this product. These reactions occur with almost exclusive C₂-C₃ bond migration in contrast to the Baeyer Villiger reaction12, during which either C₂-C₃ or C₃-C₄ bond migration occurs in the formation of the expanded lactones (15, 16).

Recently, the Lewis acid catalysed reactions of alpha-beta unsaturated steroid ketones with diazomethane have received considerable attention. The homologation of the A-ring by this method, with C₃-C₄ bond migration, has been reported in the case of a number of Δ⁴-3-keto steroids 1,2,13 (17-18). Similarly in the case of Δ¹-3-keto steroids14, the C₂-C₃ bond migration is observed during this reaction (19-20). Similar results have been reported using phenyldiazomethane2.

The/
Figure 3: Homologation Reactions

\[ (24) \xrightarrow{\text{HNO}_2} (25) + (26) \xrightarrow{\text{HNO}_2} (27) \]

\[ (28) \xrightarrow{\text{HNO}_2} (29a) \xrightarrow{\text{Acid}} (32) \]

\[ (33) \xrightarrow{\text{BASE}} (29a) \]

\[ (34) \xrightarrow{[\text{CO}_3]} (35) \]
The peracid reaction of $\Delta^4$-3-keto steroids also appears to follow the same pattern of C$_3$-C$_4$ bond migration. The conversion of cholest-4-en-3-one (17) to 4-oxacholesterol-3-one (21) may be interpreted as a repetitive oxygen insertion hydrolysis sequence$^{15}$.

(b) B-Ring

In an analogous manner to the formation of A-homocholesterol-4-one, B-homosteroids (23) have been prepared from the corresponding 6-keto and 7-keto steroid precursors$^{16}$ (22a,b).

(c) C-Ring

The interpolation of oxygen between C$_{12}$ and C$_{13}$ via the peracid reaction has been described$^{17}$.

(d) D-Ring

The homologation of the D-ring has been carried out using the nitrous acid/amine reaction$^{18}$. The epimeric hydroxy amines (24, 27) on treatment with nitrous acid give the same 6:1 ratio of D-homo-17a and 17-ketones (25, 26)$^{19}$. This result is a notable exception to the general trend in D-ring homologation of C$_{13}$-C$_{17}$ bond migration.

The epimeric amines (28, 30) rearrange stereoselectively to the respective epimeric-D-homo-17-ketones (29a,b)$^{20}$. Similarly, the pinacol rearrangement$^{21}$ of the ditertiary glycol (31) to the 17-ketone (32), and the controlled pinacolic rearrangement$^{22}$ of the monotosylated glycol (33), in the presence of base, to the D-homo-17-ketone (29a) occur with C$_{13}$-C$_{17}$ bond migration.

Conforming with the general pattern, oxygen insertion$^{23}$ with the predominant migration of the C$_{13}$-C$_{17}$ bond is also reported in the case of the peracid rearrangement of the 17 ketone (34-35).
EXPERIMENTAL RESULTS AND DISCUSSION
SECTION 1: RING ENLARGEMENT REACTIONS WITH DIAZOMETHANE

Ring enlargements of saturated steroid ketones with diazomethane have not been extensively studied. Nelson and Schutt\textsuperscript{11} have studied the ring enlargement of cholestan-3-one and reported the major product to be A-homocholestan-4-one.

Homologation of some aliphatic ketones\textsuperscript{10} have been studied in detail in order to find out the migratory aptitudes of certain aliphatic side chains. In order to minimise the formation of epoxides, boron trifluoride etherate was used as a catalyst. The Lewis acid also has the effect of increasing the rate of reaction by polarisation of the carbon-oxygen bond. Lewis acids, as indeed protonic acids, bring about the rapid decomposition of diazomethane and so the reaction of diazomethane with a ketone must proceed at an equal or faster rate than the rate of decomposition of diazomethane with boron trifluoride for satisfactory yields of products.

The ring enlargement of cholestan-3-one\textsuperscript{11} with diazomethane was carried out and the results obtained were very similar to those already described.

When 2\alpha-methylcholestan-3-one, 2,2\textsuperscript{\prime}-dimethylcholestan-3-one, 4\alpha-methylcholestan-3-one and 4,4\textsuperscript{\prime}-dimethylcholestan-3-one were treated with an ethereal solution of diazomethane and methanol, as a protonic solvent, to promote the reaction, no reaction was observed even after eighteen hours. Gas chromatography of the samples recovered after eighteen hours showed that reaction had not occurred even to a slight extent. A control reaction using cholestan-3-one proceeded to A-homocholestan-4-one in 75\% yield.
Cyclohexamones which have an alkyl alpha to the carbonyl have previously been observed to be unreactive to diazomethane under these conditions.\textsuperscript{24} It was therefore decided to investigate the reactions using boron trifluoride as an acid catalyst. Cholestan-3-one and diazomethane were allowed to react in the presence of boron trifluoride. The crude product was chromatographed on alumina. The ketonic fraction obtained had infra red absorption corresponding to a six membered ring ketone ($\nu_{\text{max}}$ 1708 cm$^{-1}$). Crystallization of the ketone gave a product, the melting point of which did not correspond to cholestan-3-one or A-homocholestan-4-one. Gas chromatography indicated that the ketonic fraction was in fact a mixture of cholestan-3-one and A-homocholestan-4-one.

Since separation of the parent and homologated ketones was not possible by alumina chromatography, boron trifluoride catalysed diazomethane homologation reactions are therefore unsuitable for the synthesis of A-homocholestanones. Also the unreactivity of methylated cholestan-3-ones, mentioned above, to diazomethane would favour the decomposition of diazomethane with boron trifluoride rather than reaction with the ketones.
**Figure 4: Generalised Tiffeneau Reaction**

(36 - 44a) : \( R_1, R_2, R_3, R_4 = H \)

(36 - 44b) : \( R_1, R_3, R_4 = H \); \( R_2 = CH_3 \)

(36 - 44c) : \( R_3, R_4 = H \); \( R_1, R_2 = CH_3 \)

(36 - 44d) : \( R_1, R_2, R_3 = H \); \( R_4 = CH_3 \)

(36 - 44e) : \( R_1, R_2 = H \); \( R_3, R_4 = CH_3 \)

*Note: The above chemical structures and reactions depict the generalised Tiffeneau reaction, with specific substituents denoted by the variables R1, R2, R3, and R4.*
SECTION 2: TIFFENEAU RING ENLARGEMENTS.

(a) General

Ring enlargements of the Tiffeneau type have been studied in most of the steroid rings. The generalised reaction sequence is shown on fig. 4. The parent ketone (36) is converted to its cyanohydrin (37) which is reduced to the amino alcohol (38). The nitrous acid amine reaction generates the carbonium ion (41) which rearranges to form the homologated ketones (42, 43).

There are two main methods for the synthesis of cyanohydrins of ketones. The exchange reaction of the ketone and acetone cyanohydrin, and the direct addition of hydrogen cyanide to the ketone, both result in the cyanohydrin (37).

Exchange reactions of ketones with acetone cyanohydrin have been accomplished with or without the presence of base as catalyst. 16-25

Reduction of the cyanohydrin may be accomplished either by catalytic hydrogenation 16,25, or by using lithium aluminium hydride 11,26,45 to obtain the amino alcohol (38).

The ring enlargement reactions of cholestan-3-one (36a) 11 have been extensively investigated and, for this reason, cholestan-3-one was chosen to find a satisfactory procedure for ring enlargement. Formation of the cyanohydrin (37a) was readily accomplished using acetone cyanohydrin in the presence of sodium hydroxide as a catalyst. Reduction of the cyanohydrin was attempted using lithium aluminium hydride and by catalytic hydrogenation with Adam's catalyst 16. Isolation of 3β-aminomethyl cholestan-3α-d (38a) was/
was not attempted and the crude products of both reductions were treated with nitrous acid. Separation of products on alumina showed that in both cases decomposition of the cyanohydrin back to the ketone had occurred before reduction. The products obtained using a lithium aluminium hydride reduction were cholestan-3\(\beta\)-ol nitrite ester (10\%), 3\(\beta\)-methyl-3\(\alpha\),3\(^{\prime}\)-oxidocholestane (4\(\alpha\)a)(5\%) cholestan-3\(\beta\)-ol(13.5\%), and A-homocholestan-4-one (4\(\alpha\)2a)(60\%).

Separation of the products obtained using catalytic hydrogenation gave rise to 3\(\beta\)-methyl-3\(\alpha\),3\(^{\prime}\)-oxidocholestane (4\(\alpha\)a)(4\%) and a chromatographically homogeneous ketonic fraction (90\%) with a sharp melting point but which was shown to consist of cholestan-3-one and A-homocholestan-4-one (1 : 1) by gas chromatography. Since decomposition of the cyanohydrin occurs to a lesser degree and products are more readily separated when using a lithium aluminium hydride reduction, this method is preferable.

Nelson and Schutt\(^{11}\) obtained pure 3\(\beta\)-aminomethylcholestan-3\(\alpha\)-ol (38a) isolated as its acetonide\(^{45}(40a)\) by the reaction of lithium aluminium hydride and 3\(\alpha\)-acetoxy-3\(\beta\)-cyanocholestan (39a). Their reaction sequence involved the acetylation of the cyanohydrin, but formation of the cyanohydrin acetates directly from ketones have however been reported\(^{27}\). The preparation of the cyanohydrin acetate of cholestan-3-one was attempted using potassium cyanide in the presence of acetic anhydride in ethanol\(^{27}\). Only the cyanohydrin however was formed and this was then acetylated with pyridine and acetic anhydride\(^{11}\). Reduction of the cyanohydrin acetate (39a) with lithium aluminium hydride gave rise to the \(\alpha\)-amino-alcohol (38a)/
which readily formed an acetonide (40a). Hydrolysis of the acetonide in acetic acid and treatment with nitrous acid gave rise to A-homocholestan-4-one (42a) (90%).

The best synthetic route to these amino-alcohols was, therefore, found to be the formation of the cyanohydrin acetate and its reduction with lithium aluminium hydride.

(b) Tiffeneau ring enlargements of methylated cholestan-3-ones

Preliminary experiments with 2,2'-dimethylcholestan-3-one indicated that complete formation of the cyanohydrin did not occur using exchange reactions, and for this reason, another method was adopted. Miramontes and his co-workers have reported that cyanohydrins are formed under basic conditions in good yield by the addition of acetic acid to a solution of potassium cyanide and the ketone in ethanol. This method was found to give a good yield of the cyanohydrin of 2,2'-dimethylcholestan-3-one.

2α-Methylcholestan-3-one (Fig. 4, 36b)

The cyanohydrin (37b) of 2α-methylcholestan-3-one was prepared by the addition of acetic acid to a solution of the ketone and potassium cyanide in ethanol. Acetylation followed by reduction with lithium aluminium hydride gave rise to the amino alcohol (38b) which was purified as its acetonide (40b). The acetonide was hydrolysed and the amino alcohol was treated with nitrous acid. Chromatography of the crude reaction product yielded a ketonic fraction (69%), 2α-methyl-3x3'-oxidocholestan (44b) (10%), and some unidentified steroid alcohol (10%).

The ketonic fraction was further fractionated on alumina and was found to consist of two ketones (A and B) approximately in the ratio, 

A/B = 2/3.

Ketone A/
Ketone A: 2α-methyl-A-homocholestan-3-one (43b)
Ketone B: 2α-methyl-A-homocholestan-4-one (42b)

The identification of these ketones will be discussed at the end of this section.

2,2'-Dimethylcholestan-3-one (Fig.4, (36c))

The cyanohydrin (37c) of 2,2'-dimethylcholestan-3-one was prepared by the addition of acetic acid to a solution of the ketone and potassium cyanide in ethanol. The cyanohydrin could not be acetylated using pyridine and acetic anhydride. Acetylation using perchloric acid and acetic anhydride was carried out but the acetate (39c) was obtained in very poor yield. The cyanohydrin itself was, therefore, reduced with lithium aluminium hydride. The amino alcohol (38c) formed could not be purified by the formation of the acetonide (40c). The crude product from the reduction was therefore treated with nitrous acid and the product chromatographed on alumina. The major products were 2,2'-dimethyl-3α-methyl-3κ,3'-oxidocholestane (0.5%), two ketones (28% and 10%) and 2,2'-dimethylcholestan-3β-ol (42%).

The ketone in 28% yield had a N.M.R. spectrum compatible with 2,2'-dimethyl-A-homocholestan-4-one (42c), having no signals of great amplitude less than 8.97T (cf. 2,2'-dimethylcholestan-3-one, 8.88T) and prominent signals at 7.15, 7.36, 7.51, 7.70T, associated with the protons alpha to the carbonyl function. A detailed discussion of this evidence will be found at the end of this section. This ketone was chromatographically homogeneous when examined by gas chromatography.

The ketone in 10% yield had a complicated N.M.R. spectrum and was found to be a mixture of two compounds from gas chromatographic evidence.
One component had a retention time identical to 2,2'-dimethyl-A-
homocholestan-4-one and the other, a retention time identical to 2,2'-
dimethylcholestan-3-one.

\[\text{4α-Methylcholestan-3-one (Fig. 4, 36d)}\]

The cyanohydrin (37d) of 4α-methylcholestan-3-one was prepared by
the addition of acetic acid to a solution of the ketone and potassium
cyanide in ethanol. Acetylation followed by reduction with lithium
aluminium hydride gave rise to the amino alcohol (38d) which was purified
as its acetonide (40d). The acetonide was hydrolysed and the amino
alcohol treated with nitrous acid. Chromatography of the crude reaction
product on alumina yielded a ketonic fraction (50%) 4α-methyl-3β-methyl-
3α,3'-oxidocholestan-4-one (44d)(11%) and 4α-methylcholestan-3β-ol (25%).

The ketonic fraction was refractionated on alumina and was found to
consist of two ketones (A and B) approximately in the ratio: A/B = 2.5/1.

Ketone A: 4αα-methyl-A-homocholestan-3-one (43d)

Ketone B: 4αα-methyl-A-homocholestan-4-one (42d)

The identification of these ketones will be discussed at the end of this
section.
**1,4'-Dimethylcholestan-3-one** (Fig. 1, (36e))

The cyanohydrin (37e) of 1,4'-dimethylcholestan-3-one was prepared by the addition of acetic acid to a solution of the ketone and potassium cyanide in ethanol. Acetylation followed by reduction with lithium aluminium hydride gave rise to the amino alcohol (38e). The acetonide (40e) of this amino alcohol could not be readily formed and the crude amino alcohol was, therefore, treated with nitrous acid. Chromatography of the crude reaction product on alumina yielded a ketone as the major product.

This ketone was chromatographically homogeneous, containing only one component from gas chromatographic evidence. The N.M.R. spectrum was very similar to 2,2'-dimethyl-A-homocholestan-4-one having no signals of great amplitude less than 8.98 T' and prominent bands in 7-8 T' region and was consistent with the expected spectrum of 4a,4a'-dimethyl-A-homocholestan-3-one (43e). This evidence will be discussed in detail at the end of this section.
Figure 5: Reactions of Exocyclic Epoxides

Reactions of Exocyclic Epoxides
(c) **Stereochemistry of Tiffeneau reactions**

(i) **Exocyclic steroid epoxides - byproducts of homologation reactions**

The oxides of the 3-methylenedionecholestanes have been isolated as minor products from the homologation reactions previously mentioned and their presence serves as an important clue to the stereochemistry of the rearrangements since at no time during their formation does the exocyclic methylene carbon become detached from the steroid skeleton. Percy and Chaykowsky have reported that the oxide (45) may be opened with sodamide to form the amino alcohol (46) necessary for ring enlargement.

A number of methods have been reported for the formation of these epoxides, all involving an ylide reaction.

The reaction of methylene triphenylphosphorane on androstan-17β-ol-3-one (14) yields 3-methylenandrostan-17β-ol (49). Treatment of exocyclic methylene compounds with peracid give rise to the oxides (50, 51). The two stereoisomeric oxides (50, 51) of 3-methylenandrostan-17β-ol have been synthesised by Cook, Corley and Wall from androstan-17β-ol-3-one (14) using dimethylsulphonium methylide and dimethylsulphoxoniuin methylide respectively. The reagents are stereospecific, each giving rise to different isomers. The configurations of the isomeric epoxides were determined by the reduction with lithium aluminium hydride and dehydration of the resulting alcohols (52, 54) to give compounds (49, 53). The isomeric epoxides derived from cholestan-3-one and 2,2′-dimethylcholestan-3-one have been recently synthesised using these methods.

The synthesis of isomeric 3-methylenedionecholestane oxides could, therefore, play an important part in the correlation of the stereochemistry of the Tiffeneau ring enlargements. At the same time the isomeric amino alcohols would/
would be made available and their rearrangement on treatment with nitrous acid could be studied.

(ii) *Synthesis and reactions of 3β-methyl-3α,3'-oxidocholestan-17(β)ol (50)*

The epoxide was synthesised by the reaction of dimethylsulphoxonium methyldide on cholestan-3-one (14). Reduction of this epoxide with lithium aluminium hydride gave rise to 3β-methylcholestan-3α-ol (52). Dehydration of this alcohol with phosphorylchloride gave rise to 3-methylcholest-2-ene (53).

The epoxide synthesised by this route had an identical I.R. spectrum to the epoxide isolated from the Tiffeneau ring enlargement, and the melting points of the epoxides obtained from the two routes were undepressed on admixture.

The epoxide, in tetrahydrofuran, was added to sodamide in liquid ammonia and the mixture stirred vigorously for eighteen hours. During this time no reaction had occurred and the epoxide was recovered unchanged. The experiment was repeated using lithamide, sodamide and potassamide in a variety of solvents but in no instance was the amino alcohol (38a, fig.4) isolated. The epoxide was recovered unchanged in all cases.

It would appear, therefore, that the steroid and sodamide are too different in their solubility properties for reaction to occur. To offset this inherent difficulty, it was felt that 3β-methyl-3α,3'-oxidoandrostan-17β-ol might have a more favourable solubility. This epoxide was synthesised from androstan-17β-ol-3-one using dimethylsulphoxonium methyldide33, but reaction of this epoxide with potassamide was equally unsuccessful and no amino alcohol was obtained.

Since/
Figure 6: Stereochemical Correlation

Tp ≡ Tetrahydropyranyl

Reaction Equations and Structures
Since the syntheses of the aminoalcohols were not possible, chemical correlation by a route involving a derivative common to the epoxide (50) and the cyanohydrin (37a) was proposed. Epoxides are reported to cleave with ethanolic potassium hydroxide to yield the diol, (56-57)36. Since cleavage of C₃-oxygen bond does not occur under nucleophilic attack35, this reaction should occur with no change in configuration at C₃.

Opening of the epoxide under acid conditions, however, results in the cleavage of C₃-oxygen bond and inversion of configuration or rearrangement may occur as is illustrated by the treatment of epoxides of this type with Lewis acids to give aldehydes30,34.

A synthetic route from the cyanohydrin (37a) to the diol (62a) was proposed. A cyanide may be readily hydrolysed to a carboxylic acid with sodium hydroxide in ethanol. Cyanohydrins, however, are unstable to base and revert to the parent ketones25. Therefore, to obtain the carboxylic acid (60), it is essential to protect the hydroxyl group so that it will be impossible for the cyanohydrin (37a) to decompose under the basic conditions of hydrolysis. A suitable derivative would be the tetrahydropyranyl ether (58), and this derivative of cyanohydrins has been synthesised25. Lithium aluminium hydride reduction of the carboxylic acid (59) and removal of the tetrahydropyranyl ether would also result in a diol (62a).

3β-methyl-3α,3'-oxidocholestane was refluxed with ethanolic potassium hydroxide. The I.R. spectrum of the purified product showed a prominent hydroxyl band and a strong band at 1125 cm⁻¹(ether). The N.M.R. spectrum was complicated, having a quartet with relative intensities 1:3:3:1 centred/
centred on 6.37 \( T \) with a coupling constant (\( J \)) of 7 cps, a singlet at 6.79 \( T \) and a triplet centred on 7.69 \( T \) with a coupling constant (\( J \)) of 8 cps. The ratio of the integrals of the quartet and singlet are equal. Acetylation did not take place under normal conditions, but on acetylation in the presence of perchloric acid it was apparent from N.M.R. evidence that acetylation had taken place at two centres. No reaction was observed with metaperiodate. The N.M.R. spectrum is too complicated to account for the formation of the diol (62a). Acetylation of the diol (62a) would be expected to occur readily on at least the primary hydroxyl and periodate oxidation of the diol (62a) would give rise to cholestan-3-one.

The presence of the quartet and triplet in the N.M.R. spectrum is significant and indicates that instead of attack by the nucleophile hydroxide, attack by ethoxide had taken place with the formation of 3\( \beta \)-ethoxymethylcholestan-3\( \alpha \)-ol (63). A similar instance of this reaction has been observed in the case of the oxidoketone (68-69)\(^{37} \). The acetylation with perchloric acid presumably takes place with the disruption of the ether linkage, as has been observed with other steroid ethers\(^{38} \).

The opening of epoxides with perchloric acid to yield diols has been reported\(^{39} \). 3\( \beta \)-methyl-3\( \alpha \),3\( \beta \)-oxidocholestan was treated with a catalytic amount of perchloric acid. However, the product obtained could not be fractionated on alumina and C.L.C. indicated that the three components produced were present in approximately equal amounts. The I.R. spectrum of the crude product had a prominent carbonyl band (\( \nu_{\text{max}} \) 1725 cm\(^{-1} \)) and another band (\( \nu_{\text{max}} \) 2700 cm\(^{-1} \)) characteristic of an aldehyde (cf. ref. 30).

The/
The acetolysis of 3α-methyl-3κ,3'-'oxidocholestan gave rise to two fractions on chromatography. The spectrum of the first fraction (in 25% yield) had strong acetate bands and weak hydroxyl bands.

The N.M.R. spectrum had a prominent signal at 7.95 (acetate methyl), which when integrated against the C18 methyl signal appeared to correspond to 5-6 protons. It would seem therefore that acetylation has also taken place during acetolysis to give the diacetate (66), as has been observed previously.

The second fraction (50%) had an infra red spectrum which indicated that both acetate and hydroxyl groups were present. The N.M.R. spectrum had a prominent acetate methyl signal which when integrated against the C18 methyl signal appeared to correspond to three protons. When this fraction was treated with lithium aluminium hydride a product was obtained with an I.R. spectrum which had hydroxyl bands and no acetate bands. The N.M.R. spectrum also showed that the acetate had been removed, and that there was a sharp signal (1-2 protons) at 6.40 consistent with that of an exocyclic methylene group. Since acetolysis would be expected to bring about an inversion of configurations at C3, this product was tentatively ascribed the formula, 3κ-hydroxymethylcholestan-3β-ol (62b).

Thus the most convenient method of synthesis of the diols would be the acetolysis of the epoxides (50, 51) followed by removal of the acetate.

The synthesis of the tetrahydropyranyl ether (58) of cholestan-3-one cyanohydrin was attempted without success. Cholestan-3-one was the only product obtained.
The cyanohydrin acetate of cholestan-3-one was therefore refluxed with ethanolic hydrochloric acid. The product obtained was an oil which could not be fractionated on alumina. The I.R. spectrum of the crude oil indicated that the carboxylic acid (60) had not been formed.

Thus chemical correlation of the exocyclic epoxides with the corresponding cyanohydrins has not proved possible.

As was mentioned at the beginning of this section, these exocyclic epoxides do occur as minor products in the ring enlargement reactions previously described and their presence serves as a means of determining the stereochemistry of these reactions.

The epoxide obtained from the homologation reaction of cholestan-3-one has been shown to be 3α-methyl-3α,3′-oxidocholestane and hence it was derived from 3α-aminomethylcholestan-3α-ol (38α). The isomeric epoxides derived from 2,2′-dimethylcholestan-3-one have also been synthesised and the stereochemistry deduced by arguments based on spectra and nature of attacking reagent. Correlation of the epoxide obtained from the homologation reaction of 2,2′-dimethylcholestan-3-one has been made with 2,2′-dimethyl-3α-methyl-3α,3′-oxidocholestane (44c).

The epoxides obtained from the homologation reaction of 2α-methylcholestan-3-one, 4α-methylcholestan-3-one and 4α,4′-dimethylcholestan-3-one have not been identified.

With the exception of 2,2′-dimethylcholestan-3-one, these homologations are known to have resulted from one of the two configurations at C3 since in every instance a sharp melting cyanohydrin acetate was obtained.

Since the 2α- and 4α-methyl groups can be regarded as sterically neutral/
neutral, it would seem likely that the cyanohydrins of 2α-methylcholestan-3-one and 4α-methylcholestan-3-one are of the same configuration as that of cholestan-3-one.

The evidence mentioned above suggests that the cyanohydrins of 2,2'-dimethylcholestan-3-one and 4,4'-dimethylcholestan-3-one also have the 3β-cyano-3α-hydroxyl configuration.

It therefore appears that the homologation products of the Tiffeneau ring enlargements are all derived from a 3β-aminomethyl-3α-hydroxyl configuration.

(iii) The stereochemical fate of the migrating group in Tiffeneau reactions.

In the case of 2α-methyl and 4α-methylcholestanes an asymmetric centre is involved in the homologation reaction. It is, therefore, of importance to consider the stereochemical fate of the migrating group e.g. C₂ or C₃ during the reaction.

In the nitrous acid/amine rearrangements of the 20 amino-17-hydroxy (iso) allopregnanes (28,30) and the peracid rearrangement of the androstan-17-one (34) no change in configuration at C₁₃ is reported. Similarly, in the Hoffmann⁷³, Curtius and Lossen⁷⁴ reactions retention of configuration of the migrating group is reported.

Thus, it is probable, when an asymmetric centre is involved in the Tiffeneau reaction, that retention of configuration of the migrating group (C₃ or C₄) takes place.
(d) DISCUSSION OF RESULTS.

The independent synthesis of 2 and 4a-methylated A-homo steroid ketones has not proved possible. Bis-homologation of 2,3-secocholestan-2,3-dioic acid to A-bishomo-3,4-secocholestan-3,4-dioic acid and pyrolysis of its thorium salt to yield A-homocholestan-3-one has been described. This method was ruled out as impracticable in the case of the methylated ketones since they are less readily available than cholestan-3-one. The acid catalysed reactions of diazomethane and 2- and 4-methylated cholestenones seemed to be a suitable alternative method of syntheses. As described later, these reactions did not however proceed.

The structure of 2 and 4a-methylated A-homocholestanones has been elucidated solely on physical evidence.

It is unlikely during the nitrous acid/amine reaction that any ketonic material other than an A-homo ketone will be formed. However, small quantities of the parent ketone have been observed in the final reaction product. Since the parent ketones tend to co-crystallise with the corresponding A-homoketones, melting point and infra red absorption cannot be relied upon as evidence for the formation of an A-homoketone. The melting points of these mixtures may be over a reasonable range and the carbonyl absorption of an A-homoketone is indistinguishable in a mixture from that of the parent ketone.

Good evidence of the presence of an A-homo ketone is provided by Gas chromatography. The results are summarised on Table 1. In every case the corresponding A-homo ketone has a retention time with respect to cholestan/e/
cholestane considerably longer than the corresponding ketone. Furthermore, where two isomers are obtained, as is the case in the homologation reactions of 2α-methylcholestan-3-one and 4α-methylcholestan-3-one, each isomer has a different retention time. It has therefore been possible to demonstrate the homogeneity of the ketones formed. In certain cases it is also possible to distinguish quite clearly the movement upfield of C19 methyl signal in the N.M.R. spectrum 1,2.

The problem therefore is distinguishing between the two isomers (42,43).

A preliminary study of the N.M.R. spectra of 2 or 4-methylated cholestane-3-ones showed that it was often not possible to determine the exact position of the signals due to 2 or 4-methyl groups since in the case of 2α-methylcholestan-3-one and 4α-methylcholestan-3-one these signals are doublets, being split by the proton at C2 or C4 respectively, and tend to be masked by other resonances. However, when 2α-methylcholestan-3-one and 4α-methylcholestan-3-one are fully deuterated in positions alpha to the carbonyl42, a strong signal is observed at 9.00° (2-methyl protons) or 9.05° (4α-methyl protons).

Thus, if the monomethylated A-homoketones obtained from the Tiffeneau reactions were fully deuterated in positions alpha to the carbonyl42, only those which have a methyl group alpha to the carbonyl will have a noticeably different N.M.R. spectrum in the 8.8-9.4° region.

The protons alpha to the carbonyl generally appear as unresolved multiplets in the 7-8° region. However, in the case of 2,2'-dimethyl-A-homocholestan-4-one and 4a,4a'-dimethyl-A-homocholestan-3-one, vicinal coupling/
coupling cannot occur on the methylene group at \( C_3 \) and \( C_4 \) respectively. Since only geminal coupling can occur, these protons would be expected to give well resolved signals in the 7-8 \( \tau \) region conforming to a simple AB coupling pattern.

The observed N.M.R. spectra of the ketones and alpha deuterated ketones are summarised in the appendix. An account of their interpretation is given below.

2\( \alpha \)-Methyl-A-homocholestan-3-one (Ketone A) (43b)

When this ketone was fully deuterated, the resonances in the 7-8 \( \tau \) region and the resonances at 8.93 \( \tau \) and 9.05 \( \tau \) disappeared and a new resonance appeared at 8.99 \( \tau \), the uncoupled 2\( \alpha \)-methyl signal.

2\( \alpha \)-Methyl-A-homocholestan-4-one (Ketone B) (42b)

No change in the methyl resonances in the 8.89-9.4 \( \tau \) region was observed when this ketone was deuterated, but the resonances in the 7-8 \( \tau \) region disappeared.

2,2'-Dimethyl-A-homocholestan-4-one (42c)

The spectrum of this compound had a series of well defined resonances occurring at 7.14, 7.32, 7.52, 7.69 \( \tau \), which indicated an isolated methylene at \( C_3 \) exhibiting an AB splitting pattern (\( J_{AB} = 11 \) cps). These resonances disappeared, and the 8.8-9.4 \( \tau \) region was unaffected, after deuteration of this ketone.

4\( \alpha \)-Methyl-A-homocholestan-3-one (Ketone A) (43d)

No change in the methyl resonances in the 8.8-9.7 \( \tau \) region was observed.
observed after deuteriation of this ketone, but the resonances in the
7-8 υ region disappeared.

4a-Methyl-A-homocholestan-4-one (Ketone B) (42d)

After deuteriation, the resonances in the 7-8 υ region disappeared.

Two changes were observed in the 8.8-9.4 υ region. Firstly, the
signal at 8.97 υ disappeared and a shoulder (the uncoupled 4a-methyl
signal) appeared on the 9.10 υ signal and, secondly, the relative
intensities of the signals at 9.19 υ and 9.23 υ were changed. This
change could be due to the epimerisation of the methyl group at C4a
resulting in a change of conformation of ring A. A change in conformation
would also lead to a change in position of the signal due to the methyl
group at C19.

4a,4a'-Dimethyl-A-homocholestan-3-one (42e)

The spectrum of this compound had a series of well defined resonances
at 7.37, 7.48, 7.65 and 7.75 υ, which indicated an isolated methylene at
C4 exhibiting an AB splitting pattern (JAB = 6 CPS). These resonances
disappeared and the 8.8-9.4 υ region was unaffected after deuteriation.

Confirmatory evidence that the correct assignment of isomers had been
obtained by H.M.R. spectral deductions was provided by a comparison of the
molecular rotations, 1M/D and gas chromatographic retention times of these
ketones.

An/
<table>
<thead>
<tr>
<th>Ketone</th>
<th>$[\text{M}]_D$</th>
<th>Observed</th>
<th>$\Delta a$</th>
<th>$\Delta b$</th>
<th>$\Delta c$</th>
<th>$R_t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestan-3-one (36a)</td>
<td>174</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.95</td>
</tr>
<tr>
<td>A-homocholestan-3-one (43a)</td>
<td>-68.2</td>
<td>-242</td>
<td>-242</td>
<td>-</td>
<td>0</td>
<td>2.70</td>
</tr>
<tr>
<td>A-homocholestan-4-one (42a)</td>
<td>+112</td>
<td>-62</td>
<td>-62</td>
<td>0</td>
<td>2.80</td>
<td></td>
</tr>
<tr>
<td>2α-methylcholestan-3-one (36b)</td>
<td>+152</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.20</td>
</tr>
<tr>
<td>2α-methyl-A-homocholestan-3-one (43b)</td>
<td>-96</td>
<td>-248</td>
<td>-248</td>
<td>-</td>
<td>0</td>
<td>2.75</td>
</tr>
<tr>
<td>2α-methyl-A-homocholestan-4-one (42b)</td>
<td>+378</td>
<td>+226</td>
<td>-</td>
<td>-62</td>
<td>+288</td>
<td>2.90</td>
</tr>
<tr>
<td>2,2'-dimethylcholestan-3-one (36c)</td>
<td>+349</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.18</td>
</tr>
<tr>
<td>2,2'-dimethyl-A-homocholestan-4-one (42c)</td>
<td>+421</td>
<td>+42</td>
<td>-62</td>
<td>+104</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>4α-methylcholestan-3-one (36d)</td>
<td>+101</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.16</td>
</tr>
<tr>
<td>4αα-methyl-A-homocholestan-3-one (43d)</td>
<td>+253</td>
<td>+152</td>
<td>-</td>
<td>-62</td>
<td>+214</td>
<td>2.89</td>
</tr>
<tr>
<td>4αα-methyl-A-homocholestan-4-one (42d)</td>
<td>+8</td>
<td>-93</td>
<td>-</td>
<td>-93</td>
<td>0</td>
<td>3.12</td>
</tr>
<tr>
<td>4,4'-dimethylcholestan-3-one (36e)</td>
<td>+25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.46</td>
</tr>
<tr>
<td>4α,4α'-dimethyl-A-homocholestan-3-one (43e)</td>
<td>+43</td>
<td>+18</td>
<td>-242</td>
<td>-</td>
<td>+260</td>
<td>3.56</td>
</tr>
</tbody>
</table>
An empirical relationship was found between the molecular rotations of the isomers. The observed differences in molecular rotations, \( \Delta \), where \( \Delta = [M_\alpha]_D = [M_\beta]_D \) and \( [M_A]_D \) is the molecular rotation of the homologated ketone (42 or 43) and \( [M_B]_D \) is the molecular rotation of the ketone (36) from which it was derived, are summarised on table 1. This difference in rotation was attributed to the following molecular changes.

a) parent ketones (36) to A-homo-3-ketones (43)

b) parent ketones (36) to A-homo-4-ketones (42)

c) alpha methylated ketones to beta methylated ketones

such that

\[
\Delta a = [M]_D \text{ ketone (43a,b)} - [M]_D \text{ ketone (36a,b)} = -242^\circ, -248^\circ, \\
\Delta b = [M]_D \text{ ketone (42a,d)} - [M]_D \text{ ketone (36a,d)} = -62^\circ, -93^\circ \\
\Delta c = [M]_D \text{ ketone (42 or 43)} - [M]_D \text{ ketone (36)} - \Delta a \text{ or } b
\]

Good agreement is found for \( \Delta a \) and \( \Delta b \) values when \( \Delta c = 0 \). When \( \Delta c \neq 0 \), the values of \( \Delta a \) and \( \Delta b \) were interpolated and the calculated values of \( \Delta c \) were found always to be positive and to lie between +104° and +208°.

The retention times of parent and homologated ketones are also shown on table 1.

\[
R_T = \frac{\text{Retention time of ketone}}{\text{Retention time of cholestane}}
\]

The important feature is that the retention time of the A-homo-4-ketones (42) is always longer than that of the corresponding isomeric A-homo-3-ketones (43). This result was also found during alumina chromatography where the first ketones eluted were the A-homo-3-ketones (43).
**Figure 7: Mechanism of Nitrous Acid/Amine Reaction**

- **(70)**
  - Reaction with HNO₂
  - 
  - 
  - 
  - 
- **(71)**
  - 
- **(72)**
  - Reaction with HNO₂
  - 
  - 
- **(73)**
  - 
- **(28)**
  - Reaction with HNO₂
  - 
  - 
- **(29a)**
  - 
- **(29b)**
  - 
  - 
  - 
- **(30)**
  - 
- **(34)**
  - O₂
  - 
  - 
  - 
  - 
- **(35)**
  - 
  -
(e) Comparison of experimental results with previous work

The migration of alkyl groups to electron deficient centres has been studied. By examining a series of glycols, the tendencies of alkyl groups to migrate in pinacol rearrangements have been established to be: t-butyl/ethyl/methyl ≫ 4000:1. A similar situation occurs in the Bayer Villiger reactions of ketones. The migratory aptitude of alkyl groups was found to be: tertiary ≫ secondary ≫ primary. In the case of the reaction of diazomethane on certain aliphatic ketones, however, the migratory aptitude of alkyl groups was found to be the opposite e.g. Methyl ≫ n-propyl ≫ t-butyl.

In the case of cyclic ketones steric factors must also be taken into account and it appears that the configuration of the diazonium ion may be of importance. Cremlyn, Garmaise and Shopec have demonstrated that configuration of the 17-amino group of 17-amino-17a-hydroxy-17a-methyl-D-homoandrost-5-en-3α-ol is of importance in determining the products of deamination. Deamination of the 17α-amino steroid (72) gives rise to 17-isopregnene (73), whereas the 17β-amino steroid (70) on deamination gives rise to an epoxide or the methyl ketone (71).

Ramirez and Stafiej have studied the nitrous acid rearrangements of 3β, 17β-dihydroxy-20α-amino-17-isoallopregnane (30) and 3β, 17α-dihydroxy-20α-aminoallopregnane (28) which give rise to 3β-hydroxy-17αβ-methyl-D-homoandrost-17-one (29b) and 3β-hydroxy-17αβ-methyl-D-homoandrost-17-one (29a) respectively. The fact that only one isomer
Table 2: Products of Tiffeneau reactions

<table>
<thead>
<tr>
<th>Parent Ketone</th>
<th>3α-methyl-3α,3'-oxido (44a-e)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A-homo-3-keto (43a-e)</td>
</tr>
<tr>
<td>cholestan-3-one (36a)</td>
<td>10%(44a)</td>
<td>-</td>
</tr>
<tr>
<td>2α-methylcholestan-3-one (36b)</td>
<td>10%(44b)</td>
<td>45%(43b)</td>
</tr>
<tr>
<td>2,2'-dimethylcholestan-3-one (36c)</td>
<td>6%(44c)</td>
<td>-</td>
</tr>
<tr>
<td>4α-methylcholestan-3-one (36d)</td>
<td>20%(44d)</td>
<td>60%(43d)</td>
</tr>
<tr>
<td>4,4'-dimethylcholestan-3-one (36e)</td>
<td>5%(44e)</td>
<td>95%(43e)</td>
</tr>
</tbody>
</table>

The proportions of the products are calculated on the assumption that the amino alcohol (38) on treatment with nitrous acid gives rise solely to these three products.
is obtained from each amino alcohol instead of the thermodynamic mixture is strong evidence for a bridged type of transition state (70). The results are interpreted in terms of the steric strains of the transition state of deamination.

In contrast, Heuser and his co-workers⁴⁵ report that 17α-aminomethyl 17β-hydroxy steroids on deamination give rise to 17α-keto-D-homo steroids and 17β-aminomethyl-17α-hydroxy steroids give rise to 17-keto-D-homo steroids (Fig. 3). More recent work by Wendler, Taub and Slates¹⁹ (on compounds having an additional 11-keto substituent) cast doubt on these conclusions. Both isomeric 17-aminomethyl-17-hydroxy steroids on deamination give an identical ratio (6:1) of 17α-keto and 17-keto-D-homo steroids (Fig.3). This preponderant C₁₆₋C₁₇ bond migration is also in contrast to the essentially exclusive C₁₃₋C₁₇ bond migration of the peracid reaction²³ of the ketone (34-35).

Since all these reactions involve essentially the same step, e.g. movement of an alkyl group to an electron deficient centre, it would appear that, as far as alkyl substituents are concerned, more subtle effects are involved in the transition states than can be predicted on a simple theory based on anchimeric assistance of a particular substituent facilitating bond migration.

The results of the homologation reactions of the methylated cholestan-3-ones are summarised on Table 2.

No/
No clear pattern of behaviour is observed to account for the migration of either the \( C_2-C_3 \) bond or the \( C_3-C_4 \) bond during rearrangement and the substituents cannot be placed in a concise order of migratory aptitude as has been observed in the case of aliphatic ketones.

There is an important distinction between the 2 and 4-monomethylated and dimethylated-3-keto steroids which appears to be reflected in their products of homologation.

2,2'-dimethyl-3-keto steroids and 4,4'-dimethyl-3-keto steroids are known to have a strained conformation in the A ring. Homologation of these two ketones occurs exclusively towards the geminal methyl groups. Although this observation could be interpreted on the basis that the electron donating methyl groups are stabilising the transition state, another possible reason may be relief of steric strain during the formation of the transition state.

In the case of 2\( \alpha \)-methylcholestan-3-one and 4\( \alpha \)-methylcholestan-3-one, as far as the conformation of ring A is concerned, the methyl groups may be regarded as sterically neutral and the nature of the migrating group might be expected to influence the direction of homologation. On this basis, \( C_2-C_3 \) bond migration would occur in the deamination of 3\( \beta \)-aminomethyl-4\( \alpha \)-methyl cholestan-3\( \alpha \)-ol and \( C_3-C_4 \) bond migration would occur in the deamination of 3\( \beta \)-aminomethyl-4\( \alpha \)-methylcholestan-3\( \alpha \)-ol.

Taking into account the fact that the homologation of cholestan-3-one proceeds with exclusive \( C_2-C_3 \) bond migration, the homologation of 4 \( / \)
4α-methylcholestan-3-one could be regarded as following this pattern with the predominant migration of the C₃-C₄ bond.

In the deamination of 3β-aminomethyl-2α-methylcholestan-3α-ol, both C₂-C₃ and C₃-C₄ bond migration occur in equal amounts. Examination of the steric factors involved in a bridged type transition state does not reveal any obvious reason why this should be the case. It is of interest, however, that this result is analogous to the action of peracid on cholestan-3-one with the formation of the lactones¹² (15,16).
**Figure 8: Acid Catalysed Diazomethane Reactions**

- **(17)**
  - $\text{CH}_3\text{N}_2$ to $\text{BF}_3$
  - Reactant: $R = \text{CH}_3$
  - Product: $R = \text{CH}_3$

- **(19)**
  - $\text{CH}_3\text{N}_2$ to $\text{AlCl}_3$
  - Reactant: $R = \text{H}$
  - Product: $R = \text{H}$
- **(17)**
  - $\text{Ph} \cdot \text{CH}_3\text{N}_2$ to $\text{AlCl}_3$
  - Reactant: $R = \text{Ph}$
  - Product: $R = \text{Ph}$

- **(17)**
  - $\text{CH}_3\text{N}_2$ to $\text{BF}_3$
  - Reactant: No reaction

- **(75)**
  - $\text{AlCl}_3$ to $\text{BF}_3$
  - Reactant: No reaction

- **(18)**
  - $\text{AlCl}_3$ to $\text{BF}_3$
  - Reactant: No reaction
SECTION 3 THE ACID CATALYSED REACTION OF DIAZOMETHANE WITH SOME
ALPHA-BETA UNSATURATED KETONES.

Recently work has been carried out on the acid catalysed reaction of
diazomethane with $\Delta^1$ and $\Delta^4$-3-keto-steroids.

The acid catalysed reaction of diazomethane to effect linear
homologation is new $^{10,13}$. Previously it was known that treatment of
unsaturated ketones with diazomethane gave either pyrazoline derivatives $^{17}$
or no reaction at all.

These reactions are of particular interest since the A-homo steroids
obtained may be catalytically hydrogenated to give the corresponding
saturated ketones $^1$. An alternative synthetic route to the A-homo steroid
ketones obtained from the Tiffeneau ring enlargements is thus possible.

The ring enlargements $^2$ of testosterone acetate, progesterone and
cortisone acetate (17) have been carried out using diazomethane and
aluminium trichloride as catalyst. The corresponding A-homo-3-keto-steroids
(18) were obtained in 30% yield. The mechanism (75-18) is suggested.

In similar experiments, A-homo-3-keto steroids (18) have been
synthesised in 40%-45% yield using diazomethane with boron trifluoride as
catalyst $^1$.

The A ring homologations of androst-1-en-17$\beta$-ol-3-one$^{14}$ (19a) and
1-methylandrost-1-en-17$\beta$-ol-3-one (19b)$^{14}$ have been carried out using
diazomethane and aluminium trichloride as catalyst to give the corresponding
A-homo-4-keto steroids (20a, 20b) in 20% yield.

Similar/
Similar experiments have been carried out using phenyl diazomethane to yield phenyl substituted A-homo steroid ketones (73).

Two unsaturated ketones, cholest-1-en-3-one and 4-methylcholest-4-en-3-one, were selected for a preliminary study of the reaction.

The homologation of cholest-4-en-3-one to A-homocholest-4a-en-3-one using diazomethane and boron trifluoride as catalyst was readily reproduced.

The homologation of cholest-1-en-3-one (19a) and 4-methylcholest-4-en-3-one (74) using the same conditions, however, did not proceed as readily. The infra-red spectra of the crude products showed that carbonyl absorption due to non-conjugated ketones was markedly less than in the case of the homologation product of cholest-4-en-3-one.

Alumina chromatography of the crude homologation product of cholest-1-en-3-one gave rise to two crystalline fractions. The latter fraction was found to be unreacted cholest-1-en-3-one (19a). The first fraction was found to have an infra-red spectrum of a saturated steroid ketone. This ketone was found to be homogenous, showing only one component during gas chromatography. The N.M.R. spectrum indicated the partial structure - CH₂.CO.CH₂CH = CH- having a complicated series of signals in the 4.1 - 4.6 \( \tau \) region (vinyl protons), two unresolved multiplets centred on 6.25 \( \tau \) and 6.60 \( \tau \) (protons allylic to a double bond and alpha to a carbonyl) and a series of signals lying between 7.0 \( \tau \) and 7.75 \( \tau \), better resolved than the signals of the corresponding protons.
protons alpha to the carbonyl in N.M.R. spectrum of A-homocholest-4a-en-3-one. The remaining significant features of the N.M.R. spectrum included sharp signals at 9.09 (C$_{19}$-methyl) and 9.32 (C$_{18}$-methyl). This ketone gave a yellow colour with tetranitromethane and underwent partial isomerisation after reflux for $3/4$ hour with anhydrous oxalic acid in ethanol. Isomerisation in this case took place much more readily than in the case of A-homocholest-4a-en-3-one where no isomerisation took place with oxalic acid. These results are consistent with the structure A-homocholest-1-en-4-one (20a).

It is of interest to compare some of the physical and chemical properties of A-homocholest-1-en-4-one and A-homocholest-4a-en-3-one. Firstly, an upfield shielding of C$_{19}$-methyl ($8.92 > 9.01$) in the case of A-homocholest-1-en-3-one, since there is no double bond at the ring junction, was observed. Secondly, the comparative ease of isomerisation of A-homocholest-1-en-4-one, accompanied by U.V. absorption ($\lambda_{\text{max}} = 227$ mp), contrasts with the favoured $\beta$ - $\gamma$ tautomer, A-homocholest-4a-en-3-one.

Catalytic hydrogenation of A-homocholest-1-en-4-one (20) did not proceed. This result is perhaps surprising, but insufficient material was available for an exhaustive study of this reaction and the results are based on only one attempt.

After/
After chromatography, oily fractions with IR absorption at 1700 cm\(^{-1}\) were also obtained. No further separation of components was obtained after repeated chromatography on alumina. Separation by gas chromatography showed that these oily fractions contained seven components. Since each of these components represented only a very small proportion of the crude product, no further attempt was made to identify them.

The I.R. spectrum of the crude product from the homologation reaction of 4-methylcholest-4-en-3-one (714) indicated that virtually no reaction had occurred at all. The separation of the ketones with I.R. absorption at \(\nu_{\text{max}}\) 1700 cm\(^{-1}\) could not be accomplished.

The effect of using aluminium trichloride as catalyst was then investigated. The homologation procedure of Muller and his co-workers\(^2\) was tried with cholest-1-en-3-one. Examination of the products by gas chromatography showed that the saturated ketone formed had a retention time inconsistent with A-homo-cholest-1-en-4-one. A control reaction was carried out in which the reaction of aluminium trichloride with cholest-1-en-3-one alone gave a similar product.

It is apparent from these results, and the results obtained by other workers, that these acid catalysed reactions of diazomethane proceed best in the case of \(\Delta^4\)-3-keto steroids. Any deviation from this system is accompanied by a marked decrease in yield of homologated product.
Figure 9: Proposed Route To A-Homocholesteneones
Attack of the ketones with diazomethane occurs almost certainly at C-3 and the reactivity of the ketones will be governed by the electron deficiency at this position. This 1-2 addition product contrasts with anticipated 1,4 addition products of \( \alpha, \beta \) unsaturated ketones. Another instance in which 1,2 addition occurs in preference to 1,4 addition is the action of Grignard reagent on cholest-4-en-3-one.

b) Another possible route to A-homocholestenones.

The dehydration of the C20 tertiary carbinol (76) and the solvolytic rearrangement of pregnane-3\( \beta \),20\( \beta \)-dihol-3-acetate-20-toluene-sulphonate (78) give rise to the D-homosteroids (77, 79). By the synthesis of a suitable molecule similar rearrangements might be applicable in the syntheses of A-homocholestenones.

It was therefore proposed to study nitrous acid deamination reactions of 5\( \alpha \)-aminomethylcholestan-3-one (81) and 1\( \alpha \)-aminomethylcholestan-3-one (80) in an attempt to synthesise A-homocholestan-4a-en-3-one (18) and A-homocholest-1-en-3-one (20a) respectively.

The synthesis of 5\( \alpha \)-cyanocholestan-3-one (82) was carried out as described by Nagata and his co-workers. Catalytic reduction resulted in preferential hydrogenation of the carbonyl group and no reduction of the nitrile group to give the alcohol (83).

The carbonyl group was therefore protected as its ethylene ketal (84) and reduction then carried out with lithium aluminium hydride.
A product was obtained with no band at 2250 cm$^{-1}$ in the infra red. Attempts to destroy the ketal with ethanolic hydrochloric acid resulted in a product with bands at 1680 cm$^{-1}$ and 1745 cm$^{-1}$. These results suggest that reduction of the cyanide had not been accomplished and that the actual products were the lactamol (86) and lactonol (85) resulting from hydrolysis of the nitrite group.

Finally the reduction of 5$\beta$-cyanocholestan-3-one was attempted using lithium aluminium hydride. The resulting product was treated with chromic acid in an attempt to preferentially oxidise the hydroxyl group back to the carbonyl group. Similar products (85, 86) to those found above were obtained.

Since the nitrile was so resistant to reduction the synthesis of 1$\alpha$-aminomethylcholestan-3-one was not attempted. Recently, however, the synthesis of 1$\alpha$-aminomethylcholestan-3$\beta$-ol from 1$\alpha$-cyanocholestan-3-one$^{53}$ has been reported. Here, too, reduction of the carbonyl group takes place in preference to the nitrile group. It would, therefore, appear that the C$_5$ position is too sterically hindered for reduction of the nitrile group to take place.
Figure 10: Rearrangements of Exocyclic Ethyl and Isopropyl Side Chains
SECTION 4. REARRANGEMENTS OF EXOCYCLIC ETHYL AND ISOPROPYL SIDE CHAINS TO GIVE METHYLATED HOMO STEROID KETONES.

The rearrangements\textsuperscript{22} of $3\beta, 17\beta$-dihydroxy-20$\beta$-amino-17-isoallopregnane and $3\beta, 17\alpha$-dihydroxy-20$\alpha$-aminoallopregnane to give the $3\beta$-hydroxy-17$\alpha$-methyl-D-homoandrostan-17-ones have already been mentioned in Section 2 c. Similar reactions\textsuperscript{49, 50} have also been discussed in section 3b. Williams and his co-workers\textsuperscript{22} have investigated the controlled pinacol rearrangement of the pregnane-17,20-glycol-20-tosylate (33) in the presence of base to the 17-ketone (29). The pinacol rearrangement of the ditertiary glycol (31) to the 17-ketone (32) has also been recorded\textsuperscript{21}.

These rearrangements proceed in the expected manner with the migration of $C_{13}-C_{17}$ bond, in contrast to the rearrangements of 17-hydroxy-17-aminomethyl steroids where migration of $C_{16}-C_{17}$ bond occurs.

A study of similar rearrangements in the A-ring would therefore be of great interest. A-homo ketones where the methyl group is known to be in the position alpha to the carbonyl would be of use as N.M.R. standards to substantiate evidence obtained in section 2c. The direction of homologation, whether with migration of $C_{2}-C_{3}$ bond or $C_{3}-C_{4}$ would also be of interest.

It was therefore proposed that the rearrangements of the aminoalcohol (94) and the ditertiary glycol (95) be studied.
3β-Acetylcholestan-3α-ol acetate (92) was synthesised by a method similar to the synthesis of pregnanes from androstanes. 3α-Ethynylcholestan-3α-ol (87) was synthesised by saturating a solution of cholestan-3-one (14) and base with acetylene. The product was purified as its acetate (88) since crystallisation did not adequately purify the compound. Treatment with N-bromoacetamide and removal of bromine with zinc in acetic acid gave 3β-acetylcholestan-3α-ol acetate (92).

The configuration at C3 is most likely to be 3α-acetoxy-3β-acetyl since formation of the ethynyl compound follows the same course as that of the cyanohydrin. When acetylation of 3β-ethynylcholestan-3α-ol was attempted with acetic acid in the presence of p-toluenesulphonic acid, a product was obtained which had spectral properties compatible with 3α-acetylcholestan-2-ene (90). This reaction could be envisaged as following the hydration, dehydration sequence (87-90). On the assumption that the trans-parallel coplanarity condition is applicable, this evidence also favours an axial hydroxyl group.

Attempts to synthesise the oxime of 3β-acetylcholestan-3α-ol (93) with hydroxylamine hydrochloride in the presence of base resulted in a product with no infra red carbonyl absorption. The absorption pattern above 3000 cm\(^{-1}\) was consistent with that of an oxime. Although the product crystallised spontaneously, it could not be further purified by chromatography or crystallisation.
Catalytic hydrogenation of the crude oxime with Adam's catalyst was attempted but no reduction was observed. Reduction with lithium aluminium hydride gave rise to an oil with a broad absorption band (2500 cm\(^{-1}\)-3500 cm\(^{-1}\)) from which no crystalline product could be obtained. Treatment of the oil with nitrous acid produced no obvious change in spectra.

Attempts to synthesise the ditertiary glycol (95) were equally unsuccessful. The reaction of methyl magnesium iodide and methyl lithium with \( \beta \)-acetylcholestan-3-ol acetate in a method similar to Uskokovic, Gut and Dorfman\(^{21}\) resulted in a series of products. None of these products resembled the glycol. No formation of \( \alpha \)-homo ketones was observed when the crude products were treated with acid.

The most probable reason for the failure of these reactions is due to the acetate at C\(_3\). Since this acetate is axial, tertiary and alpha to a carbonyl, it is quite conceivable that it might behave abnormally under the basic conditions of oxime formation and Grignard reaction.

Attempts to remove the acetate before oxime and glycol formation, however, proved unsatisfactory. Further experiments on these systems were not proceeded with.
EXPERIMENTAL

Melting points were determined on a Kofler block and are corrected. Rotations were measured for chloroform solutions at room temperature on an E.T.L. - N.P.L. Automatic Polarimeter Type 143A. Infra-red spectra, unless otherwise specified, were recorded for carbon disulphide solution on a Unicam S.P.200 spectrophotometer. Ultraviolet absorption spectra were recorded for ethanol solutions on a Perkin-Elmer 137 U.V. spectrophotometer. N.M.R. spectra were recorded for deuterochloroform solutions using tetramethylsilane as an internal standard, on a Perkin-Elmer R10 (60Mc/s)N.M.R. spectrometer. For G.L.C. analysis a column (6 ft. x $\frac{1}{8}$ in.) of S.E.30/Epon on A.W.-D.M.C.S. Chrom G (80-100 mesh) or S.E.30 on A.W.-D.M.C.S. Chrom P (80-100 mesh) at temperatures of 240-260°C, with an inlet heater at ca.270°C and inlet pressures of nitrogen of 20-35lb./sq.in., was used in conjunction with a flame ionisation detector. Retention times (where applicable) are quoted relative to cholestane or cholest-1-en-3-one as internal standards. Unless otherwise specified:

(a) Chromatography was carried out on a deactivated alumina prepared by treating Peter Spence Type "H" alumina with 5% (by volume) of 10% acetic acid. A weight of alumina, fifty times that of the material for chromatography, was used and the column was eluted with mixtures of light petrol (b.p. 60-80°C) and benzene.

(b) Solutions were dried with magnesium sulphate.
Starting Materials

Cholestan-3β-ol^57

Cholesterol was reduced by catalytic hydrogenation over 10% Pd/C using perchloric acid as catalyst.

Yield: 20.2g. from 30.0g. cholesterol = 67%

m.p. 140-141°C (lit. 142°C), [α]^D +25° (c, 0.42) lit: +24°

Cholestan-3-one^57

Cholestan-3β-ol was oxidised using 8N chromic acid (Jones' reagent^58) in the presence of acetone.

Yield: 9.1g. from 10.0g. cholestan-3β-ol = 91%

m.p. 128-129°C (lit. 129°C) [α]D +45° (c, 0.46) lit: +43.5°

Cholest-4-en-3-one^59

Cholest-4-en-3-one was prepared from cholesterol using the procedure described in "Organic Syntheses".

Yield: 80g. from 150g. cholesterol = 54%

m.p. 80-82°C (lit. 82°C)

λ max (ε) = 244 mµ (16,300),

[α]D + 89° (c, 0.34) lit: + 89°.

2α-Methylcholestan-3-one^60 (2-hydroxymethylenecholestan-3-one)

2-hydroxymethylenecholestan-3-one was prepared from cholestan-3-one by condensation with ethyl formate. 2α-methylcholestan-3-one was obtained by the hydrogenolysis of 2-hydroxymethylenecholestan-3-one with 10% Pd/C.

2-hydroxymethylenecholestan-3-one

Yield:
Yield: 4.8g. from 5.0g. cholestan-3-one = 94%  
m.p. 164-166°C.

2α-methylcholestan-3-one
Yield: 2.8g. from 4.0g. 2 hydroxymethylenecholestan-3-one  
m.p. 119.5-120°C lit. 121°C, [α]_D + 38.5 (c, 0.35)  
lit. + 32°.

2,2'-Dimethylcholestan-3-one61,62.

Cholestan-3-one was methylated using methyl iodide in the presence of potassium t-butoxide. Separation of the methylated ketones was accomplished by alumina chromatography.

Yield: 8.5g. from 12g. cholestan-3-one = 70%  
m.p. 99.5-101°C (lit. 99.5-101°C) + 84.5° (c, 0.40)

4-Methylcholest-4-en-3-one and 4,4'-dimethylcholest-5-en-3-one63

Cholest-4-en-3-one was methylated with methyl chloride in the presence of potassium t-butoxide. Separation of the methylated ketones by alumina chromatography gave 4-methylcholest-4-en-3-one (31%), 4,4'-dimethylcholest-5-en-3-one (28%) and unreacted cholest-4-en-3-one (30%)

Yield: 3.1g. 4-methylcholest-4-en-3-one 61,64 from 10g. cholest- 

m.p. 102.5-103.5°C lit. 103°C, [α]_D + 97° (c, 0.32)  
lit. + 110°.

2.8g. 4,4'-dimethylcholest-5-en-3-one from 10g. cholest- 

m.p. 165-170°C (lit 176-177°C) [α]_D + 3° (c, 0.35) lit. + 1°.
**4,4'-Dimethylcholest-5-en-3-one**

Cholest-4-en-3-one was methylated with methyl iodide in the presence of potassium t-butoxide. The product was purified by crystallisation from methanol/chloroform.

Yield: 5.3g. from 12.0g. cholest-4-en-3-one = 50%  
m.p. 175-177°C (lit. 177°C) \( [\alpha]_D +3^\circ \) (c, 0.35°) lit. +1°.

**4-Methylcholestan-3-one**

4-methylcholest-4-en-3-one was reduced with lithium in liquid ammonia. The product was purified by chromatography on alumina.

Yield: 0.5g. from 1.0g. 4-methylcholest-4-en-3-one = 50%,  
m.p. 121-123°C lit. \( [\alpha]_D +28^\circ \) (c,0.30) lit. + 26°

**4,4'-Dimethylcholestan-3-one**

4,4'-dimethylcholest-5-en-3-one was reduced catalytically in glacial acetic acid at 60°C using Adam's catalyst. The 4,4'-dimethylcholestan-3β-ol obtained was oxidised with 8N chromic acid in the presence of acetone.

Yield:  
a) 2.8g. 4,4'-dimethylcholestan-3β-ol from 4.0g. 4,4'-dimethylcholest-5-en-3-one = 70%, m.p. 149-154°C,  
lit. 157-158°C \( [\alpha]_D +10^\circ \) (c,0.40) lit. + 11°.

b) 2.3g. 4,4'-dimethylcholestan-3-one from 2.5g.  
4,4'-dimethylcholestan-3β-ol = 92%, m.p. 102.5-104°C: \( [\alpha]_D + 6^\circ \) (c,0.30) lit. + 8°.

**Cholest-1-en-3-one (2α-bromocholestan-3-one)**
Cholest-1-en-3-one (2α-bromochol estan-3-one)

2α-bromochol estan-3-one was prepared by bromination of cholest-1-en-3-one. Dehydrobromination of the bromoketone took place with lithium carbonate in dimethylformamide. The product obtained contained a small proportion of ketone ($\nu_{\text{max}}$ 1710 cm$^{-1}$) which could not be completely separated by alumina chromatography. The crude cholest-1-en-3-one (1.05 g.) and lithium aluminium hydride (0.50 g.) in anhydrous ether (20 ml.) were refluxed for one hour. The lithium aluminium hydride was destroyed and the ether solution washed with dilute acid and dried. Removal of solvent gave crude cholest-1-en-3-ol (1.0 g.) $\nu_{\text{max}} = 3600$ cm$^{-1}$ (hydroxyl). This material, manganese dioxide (7.0 g.) and chloroform (100 ml.) were shaken together for 5 hours. The manganese dioxide was filtered off and the solvent removed in vacuo from the filtrate giving a crystalline product. The product was recrystallised from ethanol to give cholest-1-en-3-one (0.90 g.)

m.p. 99.5-100°C lit. $[\alpha]_D + 63^\circ$ (c, 0.32) lit. + 57°

Yields: a) 6.2 g 2α-bromochol estan-3-one from 10 g. cholest-1-en-3-one = 50%

m.p. 165-168.5°C lit. 166-168.5°C

b) 3.0 g. crude cholest-1-en-3-one from 5.6 g. 2α-bromochol estan-3-one = 75% m.p. 95-99°C.
4α-methylcholestan-3β-ol: 64b

4α-methylcholestan-3-one was reduced using lithium aluminium hydride.
Yield: 0.25g. 4α-methylcholestan-3β-ol from 0.50g 4α-methylcholestan-3-one = 50%
m.p. 160-163°C lit. 160-163°C $[α]_D^2$ + 25° (c, 0.33) lit. + 27°.

Deuteromethanol 71

Deuteromethanol was synthesised from dimethyl carbonate and deuterium oxide in the presence of dimethyl sulphate.
Yield: 12.0g. 96% deuteromethanol from 10g deuterium oxide (purity estimated from the ratio of isotopic spinning side bands and hydroxyl signal in the N.M.R.)

Tri-D-2α-methylcholestan-3-one and Tri-D-4α-methylcholestan-3-one 42

The ketones (35mg.) were each dissolved in a solution of sodium (40mg.) in deuteromethanol (1.5ml.). The solutions were poured into deuterium oxide (1ml.) and the ethereal solutions dried and the solvent removed in vacuo. The N.M.R. spectra of the alpha deuterated ketones are recorded in the appendix.

A-homocholestan-3-one 11

The bis-homologation of 2,3-secocholestan-2,3-dioic acid was carried out. Pyrolysis of the thorium salt of A-bishomo-3,4-secocholestan-3,4-dioic acid, obtained, gave rise to A-homocholestan-3-one.
Yield 0.4g. A-homocholestan-3-one from 15g. cholestan-3-one = 2.5%
m.p. 72-75°C lit. 81-83°C $[α]_D^2$ -18° (c, 0.31).

Androstan-17β-ol-3-one 72 (Dihydrotestosterone)
Androstan-17β-ol-3-one\textsuperscript{72} (dihydrotestosterone)

Testosterone was catalytically reduced at room temperature using Pd/C catalyst. The semicarbazone (m.p. 253-254°C) of dihydrotestosterone was prepared from the crude product and hydrolysis of the semicarbazone gave androstan-17β-ol-3-one

Yield: 0.5g. dihydrotestosterone from 5g. testosterone = 10%

m.p. 176-181°C \textsuperscript{176} \textsuperscript{\textdegree} C \textsubscript{D} + 28° (c, 0.38) lit. + 30°

Cholestan-3β-ol nitrite ester

Cholestan-3β-ol (2.0g.) was dissolved in acetic acid (80ml.) and cooled to -10°C. A solution of sodium nitrite (7.0g) in water (40ml) was added over 3 hours so that the temperature did not exceed 0°C. The solution was poured into water and the steroid extracted into ether. The ether layer was washed with sodium carbonate solution and dried. On removal of solvents the white crystalline product was recrystallised from acetone to give white prisms m.p. 105-106°C \textsuperscript{105} \textsuperscript{\textdegree} C \textsubscript{max} 780, 805, 16140cm\textsuperscript{-1}, \textsuperscript{140} \textsubscript{max} 238m\textmu, (1.8g., 90%).

A small sample was recrystallised from ethanol to give cholestan-3β-ol m.p. 140-142°C \textsuperscript{140} \textsubscript{max} 3600, 1040 cm\textsuperscript{-1}.

Diazomethane solutions

a) Ethereal solutions\textsuperscript{75} of diazomethane were prepared from p-toluene sulphonyl methyl nitrosamide.

b) /
b) **Methylene chloride solutions** were prepared from nitrosomethylurea\(^{76}\).

The solutions were dried over potassium hydroxide pellets\(^{76}\) and in the case of ethereal solutions, sodium wire\(^{76}\).

Standardisation\(^{76}\) of the solutions was accomplished by the reaction of diazomethane with benzoic acid and back titration of the excess acid. **Trimethylsulphoxonium iodide**\(^{30}\)

Dimethylsulphoxide (32g.) and methyl iodide (60 ml.) were refluxed for three days during which time the solution darkened and a white precipitate was formed. The precipitate was filtered off and washed well with chloroform and dried. Crystallisation from water gave colourless large needles of trimethylsulphoxonium iodide, 50g., m.p. 237\(^{\circ}\)C.
SECTION 1: RING ENLARGEMENT REACTIONS WITH DIAZOMETHANE

A-homocholestan-4-one

The reaction of diazomethane and cholestan-3-one was carried out as indicated by Nelson and Schutt.\(^1\)

Cholestan-3-one (6.4 g.) in absolute ether (250 ml.) and potassium hydroxide (14 g.) in methyl alcohol (400 ml) were mixed and cooled to 0°C. Nitrosomethyl urea (8.5 g.) was added over 20 min. The solution was stirred for five hours at 0°C. Dilute hydrochloric acid (150 ml., 2N.) was then added and the insoluble precipitate formed filtered and washed well with ether. The filtrate was concentrated under reduced pressure. The aqueous suspension was extracted with ether, and the ether layer was washed with water and dried. Removal of solvent gave a white crystalline solid (5.8 g) which was chromatographed on alumina. The principal product was A-homocholestan-4-one (5.8 g.). Crystallisation from methanol/chloroform gave white needles, 5.3 g. (83%) m.p. 85-87°C \([\alpha]_D^0 + 28^\circ (c, 0.46)\).

The action of diazomethane on 2 and 4 methylated 3-oxosteroids

A solution of diazomethane (0.35 M.) in ether was prepared from p-toluene sulphonylmethyl nitrosamide.\(^7\)

To 2\(\alpha\)-methylcholestan-3-one (30 mg) was added methanol (5 ml) and ethereal diazomethane (5 ml.) and the solution set aside at 0°C for 18 hours. The solvent was removed and a crystalline product was obtained which had an identical l.R. spectrum to the starting material.

The/
The experiment was carried out with cholestan-3-one, 4α-methylcholestan-3-one, 2,2'-dimethylcholestan-3-one and 4,4'-dimethylcholestan-3-one using an identical procedure. No reaction was observed except in the case of cholestan-3-one. In this case the l.r. spectrum of the product was similar to A-homocholestan-4-one.

Small samples were examined by G.L.C. on an SE 30 column at 260°C. The methylated ketones and their homologated products obtained from the Tiffeneau ring enlargements were used as standards. The retention times with respect to cholestane are summarised below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative Retention Time (R_t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestan-3-one</td>
<td>1.95</td>
</tr>
<tr>
<td>A-homocholestan-3-one</td>
<td>2.70</td>
</tr>
<tr>
<td>A-homocholestan-4-one</td>
<td>2.80</td>
</tr>
<tr>
<td>Action of diazomethane on cholestan-3-one</td>
<td>1.94, 2.78</td>
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<tr>
<td>2α-methylcholestan-3-one</td>
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<tr>
<td>2α-methyl-A-homocholestan-3-one</td>
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<tr>
<td>2α-methyl-A-homocholestan-4-one</td>
<td>2.90</td>
</tr>
<tr>
<td>Action of diazomethane on 2α-methylcholestan-3-one</td>
<td>2.19</td>
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<tr>
<td>2,2'-dimethylcholestan-3-one</td>
<td>2.18</td>
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<tr>
<td>2,2'-dimethyl-A-homocholestan-4-one</td>
<td>3.00</td>
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<td>Compound</td>
<td>Relative Retention Time (R&lt;sub&gt;t&lt;/sub&gt;)</td>
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<tr>
<td>----------</td>
<td>--------------------------------------</td>
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<tr>
<td>Action of diazomethane on 2&lt;sub&gt;1&lt;/sub&gt;,2&lt;sub&gt;1&lt;/sub&gt;-dimethylcholestan-3-one</td>
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</tr>
<tr>
<td>4&lt;sub&gt;a&lt;/sub&gt; methyl-A-homocholestan-4-one</td>
<td>3.12</td>
</tr>
<tr>
<td>Action of diazomethane on 4'-methylcholestan-3-one</td>
<td>2.15</td>
</tr>
<tr>
<td>4&lt;sub&gt;,4&lt;/sub&gt;'-dimethylcholestan-3-one</td>
<td>2.46</td>
</tr>
<tr>
<td>4&lt;sub&gt;a&lt;/sub&gt;,4&lt;sub&gt;a&lt;/sub&gt;'-dimethyl-A-homocholestan-3-one</td>
<td>3.56</td>
</tr>
<tr>
<td>Action of diazomethane on 4',4'-dimethylcholestan-3-one</td>
<td>2.44</td>
</tr>
</tbody>
</table>

The crude products were recrystallised and identified, except in the case of A-homocholestan-4-one, as unreacted starting material by mixed melting point. No depression of melting point was observed on admixture with the appropriate starting material.

Action of diazomethane on cholestan-3-one using BF<sub>3</sub> catalyst.

An solution of diazomethane(0.2M)in methylene chloride (200 ml) at 0°C was added over 30 minutes to a solution of cholestan-3-one (3.3g) containing 0.3 ml. BF<sub>3</sub> catalyst solution.* Vigorous nitrogen occurred on/

* A solution of 1 ml of freshly distilled boron trifluoride etherate in 25 ml anhydrous 3:1 ether:methylene chloride solution.
on addition of diazomethane and white fluculent polymethylene was precipitated. The solution at 0°C was stirred for a further hour and then filtered. The filtrate was washed with sodium carbonate solution and dried. The material obtained on removal of the solvents in vacuo was an amber oil (3.3 g) Chromatography of this oil on alumina gave a crystalline ketonic fraction (2.95g., 87%) which was recrystallised from methanol/chloroform. m.p. 99-104°C, [α]D + 39.5°, νmax 1708 cm⁻¹ carbonyl. Examination of this ketone by G.L.C. on an S.E. 30 column at 260°C showed that it contained two components in the ratio 2:1 with retention times with respect to cholestane identical to cholestan-3-one and A-homocholestan-4-one respectively. The specific rotation confirms the product ratio obtained by G.L.C.

Let \( \chi \) = percentage of \( \text{A-homocholestan-4-one} \)

\[
(100 - \chi) + 28 \chi = 40 \times 100
\]

Hence \( \chi = 30\% \)
SECTION 2: TIFFENEAU RING ENLARGEMENTS

3\(\beta\)-Cyanocholstan-3\(\alpha\)-ol (37a)

Cholstan-3-one (6.4g) was dissolved in distilled acetone cyanohydrin (30 ml) and chloroform (10ml) and 10% aqueous sodium hydroxide (0.5 ml) was added. The solution was allowed to stand for 1 hour and then poured into water. The steroid was extracted into ether and the ether solution washed well with water and dried. The solvent was removed in vacuo to give a brown crystalline oil (6.8g)

\[
\begin{align*}
\lambda_{\text{max}} \text{ (hydroxyl)} & 3420, 3570 \\
\lambda_{\text{max}} \text{ (cyano) } & 2220 \text{ cm}^{-1}
\end{align*}
\]

Acetylation:

3\(\beta\)-Cyanocholstan-3\(\alpha\)-ol was dissolved in a 1:1 solution of pyridine and acetic anhydride and allowed to stand overnight. The solution was then poured into water and the steroid extracted into ether. The ethereal solution was washed well with dilute hydrochloric acid and dilute sodium carbonate solution and dried. Removal of solvent and recrystallisation from methanol gave 3\(\alpha\)-acetoxy-3\(\beta\)-cyanocholestan M.P. 125.5 - 129°C (lit 123 - 126°C)

\[
\begin{align*}
\left[\alpha\right]_D + 20^\circ (c,0.29) & 1030, 1220, 1750 \text{ (Acetate) 2220 cm}^{-1} \text{ (cyano)}
\end{align*}
\]

3\(\beta\)-Aminomethylcholestan-3\(\alpha\)-ol (A)

The crude cyanohydrin (3.4g.) and lithium aluminium hydride (1.5g.) in anhydrous ether (200 ml.) were refluxed for one hour. The excess lithium aluminium hydride was destroyed and the ether layer washed with 10% sodium hydroxide solution and dried. The solvent was removed to give a light brown oil \[
\lambda_{\text{max}} 3600 \text{ (hydroxyl) 3250 cm}^{-1} \text{ (amino)}.
\]

A-homocholestan-4-one (A)

The light brown oil (see above) was dissolved in acetic acid (60 ml.) and water (5 ml.) /
(5 ml.) and cooled to -10⁰C. A solution of sodium nitrite (7g.) in water (40 ml.) was slowly added so that the temperature did not exceed 0⁰C. The solution was allowed to stand at 0⁰C for three hours. During this time a white foam developed which was broken up with ether. The solution was then poured into water and extracted with ether. The ether layer was washed with sodium carbonate solution and dried. Removal of solvents gave a brown oil (1.9g.) \( \nu_{\text{max}} \) 1700 cm\(^{-1} \) which was chromatographed on alumina to give the following crystalline fractions in the order indicated.

- **Cholestan-3β-ol nitrite ester, (0.20g.), \( \nu_{\text{max}} \) 780, 805, 1640 cm\(^{-1} \), \( \lambda_{\text{max}} \) 438 m\( \mu \text{A} \), which was recrystallised from ethanol to give cholestan-3β-ol m.p. 137-143⁰C; 3β-methyl-3α, 3'-oxidocholestanate, (0.13g., 7%) m.p. 129-133⁰C \( \nu_{\text{max}} \) = 920 cm\(^{-1} \), melting point undepressed on admixture with an authentic sample.

- **A-homocholestan-4-one, (1.16g., 60%)** which was recrystallised from methanol/chloroform to give white needles (0.75g.) m.p. 88-90⁰C \( \nu_{\text{max}} \) 1700 cm\(^{-1} \). The melting point was undepressed on admixture with an authentic sample of A-homocholestan-4-one.

- **Cholestan-3β-ol; \( \nu_{\text{max}} \) 3600, 1040 cm\(^{-1} \) (hydroxyl) which was recrystallised from ethanol to give white crystals (m.p. 139-141⁰C). The melting point was undepressed on admixture with an authentic sample of cholestan-3β-ol.

**3β-Aminomethylcholestan-3α-ol**
3-aminomethylcholestan-3\(\alpha\)-ol B

The crude cyanohydrin (3.0 g) in glacial acetic acid at 40\(^\circ\)C was added to prehydrogenated Adam's catalyst. The theoretical amount of hydrogen had been taken up after 3 hours. The catalyst was filtered off and the solution of 3\(\beta\)-aminomethylcholestan-3\(\alpha\)-ol was used in the next experiment.

A-homocholestan-4-one B

The above solution was treated with sodium nitrite solution as described previously. A pale yellow semicrystalline oil (2.5 g), \(\nu_{max} 1706\ \text{cm}^{-1}\), was obtained. Chromatography on alumina gave a ketonic crystalline fraction (2.2 g) which was recrystallised from methanol/chloroform to give prisms m.p. 90-96\(^\circ\)C. Examination of this ketonic fraction by G.L.C. showed that it contained cholestan-3-one and A-homocholestan-4-one.

3\(\alpha\)-acetoxycrotyl-3\(\alpha\)-cyanocholestane (39a)

Cholestan-3-one (1.0 g) and potassium cyanide (0.25 g) were dissolved in ethanol (7 ml.) benzene (4 ml.) and water (0.05 ml.) and the solution was cooled to 0\(^\circ\)C. Acetic anhydride (0.25 ml) was added and the solution was stirred at 0\(^\circ\)C for 2\(\frac{1}{2}\) hours. The solution was poured into water and the steroid extracted into ether. The ether layer was washed with water and dried. A colourless glass (1.0 g), \(\nu_{max} 3420, 3570\) (hydroxyl) 2220 cm\(^{-1}\) (cyano) was obtained on removal of solvents.
solvents. The cyanohydrin was acetylated as described previously and after purification by alumina chromatography was recrystallised from methanol to give white needles, m.p. 110-125°C, ν_max 1750, 1225, 1030 (acetate) 2200 cm⁻¹ (cyano); 0.58g (58%) of 3α-acetoxy-3β-cyanocholestane.

3β-Aminomethylcholestane-3α-ol C

3α-acetoxy-3β-cyanocholestane (2.5g.) and lithium aluminium hydride (2.0g.) in anhydrous ether (150 ml.) were refluxed for 1 hour. The excess lithium aluminium hydride was destroyed and the ether layer washed with 10% sodium hydroxide solution and water and dried. A glass, ν_max 3600 (hydroxyl), 3200 cm⁻¹ (amino), was obtained on removal of solvent. The glass was dissolved in acetone and the acetone slowly distilled off until only 5 ml remained. The acetonide (0.98g) crystallised out on cooling. The acetonide had the following physical properties: m.p. 143-6°C (lit. 145-6°C) [α]_D +27° (C, 0.32), ν_max 810, 830 cm⁻¹. The N.M.R. spectrum had signals at 6.99 τ. (singlet, 2 protons alpha to imino) and 8.65 τ. (geminal methyl groups of acetonide).

A-homocholestan-4-one C

The acetonide (1.59 g) was dissolved in glacial acetic acid (30 ml) and ether (10 ml) and cooled to -10°C. A solution of sodium nitrite (4.0g) in water (20 ml) was added over 2½ hours so that the temperature did not exceed -5°C during this time. The solution was poured into water and the steroids extracted into ether. The ether layer was washed with sodium carbonate solution and dried. A pale brown oil (1.4g) was obtained when/
the solvent was removed. The oil was chromatographed to yield A-homocholestan-4-one (0.979, 95% of material off column) which was recrystallised from ethanol to give white needles (0.764g) m.p. 84-87°C $[\alpha]_D + 28^\circ$ (c, 0.46), $\nu_{\text{max}}$ 1700 cm.$^{-1}$, N.M.R. spectrum. See appendix.

3α-Acetoxy-3β-cyano-2α-methylcholestane (39b)

2α-methylcholestan-3-one (4.0g) and potassium cyanide were dissolved in ethanol and cooled to 10°C. Glacial acetic acid (20 ml) was added to the solution at 10°C over 3 hours. The solution was poured into water and the aqueous suspension extracted with ether. The ether layer was washed with sodium carbonate solution and dried. The white crystalline cyanohydrin (4.0g; $\nu_{\text{max}}$ 3500, 3610 (hydroxyl) 2240 cm.$^{-1}$ (cyano) was obtained, when the solvent was removed. The crude cyanohydrin (4.0g) was dissolved in a solution of pyridine (5 ml) and acetic anhydride (5 ml) was allowed to stand overnight. The solution was poured into water and the aqueous suspension extracted into ether. The ether layer was washed with dilute hydrochloric acid and dilute sodium carbonate solution and dried. A semicrystalline oil (4.0g) was obtained when the solvents were removed. After recrystallisation from ethanol, colourless plates of 3α-acetoxy-3β-cyano-2α-methylcholestane (2.6g; 65%) were obtained.
[α] D + 9° (C, 0.32) υ max 2250 (cyano) 1025, 1220, 1755 cm. -1 (acetate)

(Found C = 79.4%, H = 10.6%, N = 2.87%, C 31H 51NO 2 requires C = 79.3%,
H = 10.9%, N = 3.0%) N.M.R. signal at 7.90 τ (acetate protons)

3α-aminomethyl-2α-methylcholestan-3α-ol (38b)

3α-acetoxy-3β-cyano-2α-methylcholestan (2.6 g) and lithium aluminium hydride (2.6 g) in anhydrous ether (100 ml.) were refluxed for 2½ hours. The excess lithium aluminium hydride was destroyed and the ether layer washed with 10% sodium hydroxide solution and water and dried. A glass (ν max 3630, 3400 cm. -1) was obtained when the solvent was removed. The glass was dissolved in acetone and the acetone slowly distilled off until 5 ml. remained. The acetonide (1.75 g.) crystallised out as white rosettes on cooling. The acetonide had the following physical properties:

m.p. = 119-125°C; [α] D + 25° (c, 0.302), υ max 825 cm. -1. N.M.R. signals at 6.70; 6.90; 7.09; 7.29 τ (J gem = 12 c.p.s., 2 protons) and 8.59; 8.63 τ (geminal methyl groups); C 32H 57NO requires C = 81.5%,
H = 12.2%, N = 3.0% ; Found C = 81.4%, H = 12.3%, N = 3.0%. The acetonide (1.2 g) in ethanol (18 ml.) and concentrated hydrochloric acid (2 ml.) was refluxed for 30 mins. The solution was poured into sodium carbonate solution and the suspension extracted into chloroform. The chloroform layer was washed well with water and dried. White crystals of 3α-aminomethyl-2α-methylcholestan-3α-ol (υ max 3250 cm. -1) were obtained when the solvent was removed.

The action of nitrous acid on 3α-aminomethyl-2α-methylcholestan-3α-ol (Fig. 4)

3α-aminomethyl-2α-methylcholestan-3α-ol (1.2 g) was dissolved in glacial acetic acid (20 ml.) chloroform (2 ml.) and cooled to -10°C.
A solution of sodium nitrite (3.0g) in water (12 ml.) was added to the reaction mixture over 3 hours, so that the temperature did not exceed -5°C. The solution was then poured into water and the aqueous suspension extracted with ether. The ether layer was washed with sodium carbonate solution and dried. A pale brown oil ($\lambda_{\text{max}} = 1700\text{ cm}^{-1}$) was obtained when the solvent was removed. The oil was chromatographed on alumina and fractions were obtained in the order indicated:

$\alpha\beta$-methyl-$\beta\beta$-methyl-$3\beta$-$3'\text{-oxidocholestane}$ (0.159g; 7%) m.p. 68-70°C

$\lambda_{\text{max}} = 835 \text{ cm}^{-1}$ and $936 \text{ cm}^{-1}$, N.M.R.: signals at 7.20; 7.28; 7.59; 7.67 $\tau$. ($J_{\text{gem}} = 5 \text{ c.p.s.}$ - 2 protons of 3-methylene) 9.28; 9.38 $\tau$.

($J_{\text{AB}} = 6 \text{ c.p.s.}$ 3 protons of 2-methyl)

Ketonic fraction: (0.603g; 63%) $\lambda_{\text{max}} = 1700 \text{ cm}^{-1}$

The ketonic fraction was further fractionated on alumina and was finally separated into two components.

a) $\alpha\alpha$-methyl-$\alpha$-homocholestan-3-one: crystallised from ethanol as plates m.p. 71-75°C, [$\alpha$]$_D^0 = -23^0$ (c, 0.28), (Found C = 83.9%, H = 12.3%,

C$_{29}$H$_{50}$ 0 requires C = 84.0% H = 12.2%), $\lambda_{\text{max}} = 1705 \text{ cm}^{-1}$, 0.07g. (6%),

N.M.R. spectrum: Appendix

This ketone (25 mg.) was dissolved in a solution of sodium (25 mg.) in deuteromethanol (1 ml.) The solution was refluxed for one hour and then poured into deuterium oxide (1 ml.). The resultant suspension was extracted into ether and dried. A crystalline product (25 mg.) was obtained when the solvent was removed in vacuo. A change was observed in the N.M.R. spectrum: (Appendix).

b)
b) 2α-methyl-Α-homocholestan-4-one crystallised from ethanol as needles
m.p. 72.5 - 75°C, [α]D + 91°, (c, 0.34), (Found C = 84.1%, H = 12.1%,
C29H50O REQUIRES C = 84.0% H = 12.2%) \[\lambda_{\text{max}} 1705 \text{ cm}^{-1}\], 0.250 g. (21%),
N.M.R. spectrum, (Appendix) This ketone (25 mg.) was dissolved in a
solution of sodium (25 mg.) in deuteromethanol (1 ml.). The solution
was refluxed for 1 hour and then poured into deuterom oxide (1 ml.).
The resultant suspension was extracted into ether and dried. A
crystalline product (25 mg.) was obtained when the solvent was removed
in vacuo. A change was observed in the N.M.R. spectrum (Appendix).

A depression of melting point was observed when the two ketones were
mixed (m.p. 57-75°C) and the actual proportions of the two ketones, since
losses resulted from repeated alumina chromatography, were estimated as
equal.

3β-Cyano-2,2'-dimethylcholestan-3α-ol (37c)

2,2'-dimethylcholestan-3-one (2.0g) and potassium cyanide (15g.)
were dissolved in ethanol (120 ml.) and the solution cooled to 10°C.
Glacial acetic acid (15 ml.) was added to the stirred solution at 10°C
over 3 hours. The solution was poured into water and the resultant
suspension extracted into ether. The white crystalline solid of the
cyanohydrin (1.8g.) \[\lambda_{\text{max}} 2270 \text{ cm}^{-1}\text{(cyano) 3480, 3600 cm}^{-1}\text{(hydroxyl) was}
obtained when the solvent was removed in vacuo.

Acetylation:
Acetylation: (a) The cyanohydrin (0.25 g.) was dissolved in pyridine (3 ml.) and acetic anhydride (3 ml.) and the solution left for 3 days. The solution was then poured into water and the resultant suspension extracted into ether. The ether layer was washed well with dilute hydrochloric acid and dilute sodium carbonate solution and dried. 2,2'-dimethylcholestan-3-one m.p. 100-101°C (from acetone), $\nu_{\text{max}}$ 1700 cm$^{-1}$, was obtained when the solvents were removed in vacuo.

(b) A solution of ethyl acetate (3.6 ml.) in acetic anhydride (0.7 ml.) and perchloric acid (0.06 ml.) was prepared and left for 30 minutes. A further 1.2 ml. of acetic anhydride was added and the solution cooled to 5°C. The cyanohydrin (0.25 g.) was dissolved in this solution and a deep yellow colour developed. After 15 minutes the mixture was poured into water and the resultant suspension extracted into ether. The ether layer was washed with dilute sodium carbonate solution and dried. An oil was obtained when the solvents were removed in vacuo. Chromatography of the oil on alumina and crystallisation from ethanol gave white prisms of 3x-acetoxy-3y-cyano-2,2'-dimethylcholestan, m.p. 200-203.5°C, $[\alpha]_D + 44^o$ (c, 0.52), $\nu_{\text{max}}$ 1755; 1230; 1025 cm$^{-1}$ (acetate) 2270 cm$^{-1}$ (cyano), (Found C = 79.3%; H = 11.1%; N = 3.1%; $\text{C}_{32}\text{H}_{33}\text{NO}_2$ requires C = 79.4%, H = 11.0%, N = 2.9%), 0.055g. (20%).
3β-Aminomethyl -2,2'-dimethylcholestan-3α-ol (38c)

3β-cyano-2,2'-dimethylcholestan-3α-ol (2.0 g.) and lithium aluminium hydride (2.0 g.) in anhydrous ether (100 ml.) were refluxed for 3 hours. The excess lithium aluminium hydride was destroyed and the ether solution washed with 10% aqueous sodium hydroxide solution and water and dried. A white crystalline product ($\lambda_{\text{max}}$ 3400, 3600 cm$^{-1}$) was obtained when the solvent was removed in vacuo. This material was not soluble in acetone and the acetonides could not be prepared even by dehydration with anhydrous copper sulphate. The crude amino alcohol was used in the next experiment.

The action of nitrous acid on 3β-aminomethyl-2,2'-dimethylcholestan-3α-ol. (fig.4)

The crude amino alcohol (2.3 g) was dissolved in glacial acetic acid (25 ml.) and ether (10 ml.) and cooled to -10°C. A solution of sodium nitrite (4.0 g.) in water (20 ml.) was added over a period of 3 hours, so that the temperature did not exceed -5°C. The solution was then poured into water and the aqueous suspension extracted with ether. The ether layer was washed with dilute sodium carbonate solution and dilute hydrochloric acid and dried. An oil ($\lambda_{\text{max}}$ 1695 cm$^{-1}$) was obtained when the solvent was removed in vacuo. The oil was chromatographed on alumina and crystalline fractions were obtained in the order indicated. 2,2'
2,2'-dimethyl-3\beta-methyl-3\alpha,3'-oxidocholestane: m.p. 89-93°C
(from ethan) (lit\textsuperscript{34} 90-93°C), \( \nu \text{max} 780,931 \text{cm}^{-1} \). N.M.R. spectrum:
signals at 7.20, 7.29, 7.51, 7.60 \( \tau \). (\( J_{AB} = 6 \text{ c.p.s.} \), two doublets of
3\text{-}methylene protons)
Ketonic fraction: recrystallised from ethanol to give white prisms
0.180g (10%)
m.p. 78-85°C, \( \nu \text{max} 1700 \text{ cm}^{-1} \). G.L.C. on S.E. 30 at 260°C
showed that this fraction consisted of two compounds of
retention times with respect to cholestane of 2.20 (78%)
and 2.95 (22%). (cf. retention times of 2,2\text{'}-dimethylcholestan-
3-one: 2.19, and 2,2\text{'}-dimethyl-A-homocholestan-4-one: 3.00)
2,2'-dimethyl-A-homocholestan-4-one: recrystalli sed from ethanol to
give white needles, 0.42g (28%), m.p. 88-90°C \([\alpha]_D +98^\circ \) (c, 0.49)
(Found C = 83.6% H = 12.0%; \( C_{30}H_{52}O \) requires C = 84.0%
H = 12.2%) \( \nu \text{max} 1695 \text{ cm}^{-1} \)
N.M.R. spectrum doublets centred on 7.23, 7.60 \( \tau \). (\( J_{AB} = 12 \text{ c.p.s.} \);
2 protons at C - 3). This ketone (35 mg.) was dissolved in a
solution of sodium (30 mg.) in deuteronmethanol (1.5 ml.) and the
solution refluxed for 1 hour. On cooling, crystals of tetra\text{D} 2,2'-dimethyl-A-homocholestan-4-one, m.p. 80-83°C, \( \nu \text{max} 1695 \text{cm}^{-1}\)
N.M.R. spectrum: no signals in 7-8 \( \tau \) region. G.L.C. of 2,2\text{'}-
dimethyl-A-homocholestan-4-one showed that only one component (retention
time with respect to cholestane, 3.00) was present.
2,2'-dimethylcholestan-3β-ol: recrystallised from acetone to give a white powder 0.78g (42%), m.p. 140-145°C, \( [\alpha]_D + 27^\circ \) (c = 0.38).

3α-Acetoxy-3β-cyano-4α-methylcholestan (39d)

4α-methylcholestan-3-one (0.47g.) and potassium cyanide (2.5g.) were dissolved in ethanol (20 ml.) and the solution cooled to 0°C. Glacial acetic acid (2 ml.) was added to the stirred solution at 0°C over 3 hours. The solution was poured into water and the resultant suspension extracted into ether. The ether layer was washed with water and dried. The white crystalline cyanohydrin \( \text{max} \ 3450, 3600 \text{ cm}^{-1} \) (hydroxyl) and 2250 \text{ cm}^{-1} (cyano) was obtained when the solvent was removed. The crude cyanohydrin (0.47g.) was dissolved in a solution of pyridine (6 ml.) and acetic anhydride (6 ml.) and left for 24 hours. The solution was poured into water and the suspension extracted into ether. The ether layer was washed with dilute sodium carbonate solution and dilute hydrochloric acid and dried. Removal of solvent and crystallisation from acetone gave white needles of 3α-acetoxy-3β-cyano-4α-methylcholestan, 0.28g (60%), m.p. 160-162°C, \( [\alpha]_D + 11^\circ \) (c, 0.20)

(Found C = 79.4% H = 10.8% N = 2.9% Calculated for \( \text{C}_{31} \text{H}_{51} \text{NO}_2 \):

\[ \text{C} = 79.3\% \quad \text{H} = 10.9\% \quad \text{N} = 3.0\% \] \( \text{max} \ 1760, 1230, 1030 \text{ cm}^{-1} \) (acetate).

3β-Aminomethyl-4α-methylcholestan-3α-ol (38d) /
3β-Aminomethyl-4α-methylcholestan-3α-ol (38d)

3β-acetoxy-3β-cyano-4α-methylcholestan (0.80g.) and lithium aluminium hydride (0.80g) in anhydrous ether (100 ml.) were refluxed for 3 hours. The excess lithium aluminium hydride was destroyed and the organic solvents removed in vacuo. 10% Sodium hydroxide solution (50 ml.) was added and the white precipitate filtered and dried over phosphorous pentoxide. The precipitate was continuously extracted with acetone in a Soxlet extractor for 24 hours. The organic solvents were removed in vacuo and the oil obtained was crystallised from acetone to give the acetonide of 3β-aminomethyl-4α-methylcholestan-3β-ol. 0.57g. (70%), m.p. 127-133°C, [α]D + 18° (c, 0.30) (Found C = 81.6%, H = 12.15%, N = 3.3%; C32H57NO requires C = 81.5%, H = 12.2%, N = 3.0%) max 830 cm⁻¹. N.M.R. spectrum: Unresolved signals at 6.98, 7.07 (β-methylene protons) and signal at 8.61 (geminal methyl protons). The acetonide (0.64g.) in ethanol (9 ml.) and concentrated hydrochloric acid (1 ml.) was refluxed for 30 minutes. The mixture was poured into sodium carbonate solution and the oily suspension extracted into ether. The ether layer was washed with water and dried. White crystalline 3β-aminomethyl-4α-methylcholestan-3α-ol (0.64g), max 3450, 3600 cm⁻¹, was obtained when the solvent was removed in vacuo.
The action of nitrous acid on \(\text{3}^{\beta}-\text{aminomethyl}-4\alpha-\text{methylcholestan-3\beta-ol}\) (Fig. 4)

The amino alcohol (0.64g.) was dissolved in glacial acetic acid (10 ml.) and chloroform (2 ml.) and the solution cooled to \(-10^0\text{C}\). A solution of sodium nitrite (2g.) in water (8 ml.) was added over 3 hours so that the temperature of the reaction did not exceed \(-5^0\text{C}\). The solution was poured into water and the oily suspension extracted into ether. The ether layer was washed with sodium carbonate solution and dried. An oil, \(\nu_{\text{max}}^{\text{cm}^{-1}} 1705\) was obtained when the solvent was removed. The oil was chromatographed on alumina and crystalline fractions were obtained in the following order:

3\(\beta\)-methyl-3\(\beta\),3\(\prime\)-oxido-4\(\alpha\)-methylcholestan: recrystallised from acetone to give a white powder, 0.02g (3%) m.p. 92-97\(^0\text{C}\), \(\nu_{\text{max}}^{\text{cm}^{-1}} 710, 835, 890, 908\) N.M.R. spectrum: two doublets centred on 7.65, 7.30 \(\gamma\). \((J_{\text{AB}} = 6\text{ c.p.s. } 3\beta\)-methylene protons) and 9.33, 9.43 \(\gamma\). \((J_{\text{AB}} = 6\text{ c.p.s. } 4\alpha\)-methyl protons – doublet)

Ketonic fraction: 0.255g (40%) was refractionated on alumina to give two products

a) 4\(\alpha\)-methyl-A-homocholestan-3-one: recrystallised from ethanol to give white prisms 0.08g, m.p. 82-86\(^0\text{C}\),\([\alpha]_D^\text{c} + 2^0\) (c, 0.38)

(Found \(\theta = 84.6\%, \ H = 12.0\%, \ C_{29}H_{50}O\) requires \(\text{C} = 84.0\%, \ H = 12.1\%\)), \(\nu_{\text{max}}^{\text{cm}^{-1}} 1705\). N.M.R. spectrum; see appendix, G.L.C. indicated one component with a retention time with respect to cholestane (2.89).

This/
This ketone (25 mg.) was added to a solution of sodium (25 mg.) in deuteromethanol (1 ml.) and the mixture refluxed for 1 hour. The solution was poured into deuterium oxide (1 ml.) and the oily suspension extracted into ether and the ethereal solution dried. A semicrystalline product (25 mg.) was obtained on removal of solvent. The N.M.R. spectrum of the deuterated ketone is reported in the appendix.

b) 3α-methyl-5α-homocholestan-4-one: recrystallised from ethanol to give prisms, 35 mg., m.p. 91-95°C, $[\alpha]_D + 61^\circ$ (c, 0.32), (Found C = 83.3%, H = 11.5%, $C_{29}H_{50}O$ requires C = 84.0%, H = 12.2%), $\lambda_{\text{max}}$ 1705cm$^{-1}$, N.M.R. spectrum - see appendix, G.L.C. indicated one component with a retention time with respect to cholestane (3.12). This ketone (18 mg.) was added to a solution of sodium (25 mg.) in deuteromethanol (1 ml.) and the mixture refluxed for 1 hour. The solution was poured into deuterium oxide (1 ml.) and the oily suspension extracted into ether and the ethereal solution dried. A semicrystalline product (16 mg.) was obtained on removal of solvent in vacuo. The N.M.R. spectrum of this deuterated ketone is reported in the appendix.

3α-methylcholestan-3β-ol 0.110g. (17%) was recrystallised from ethanol to give white needles. m.p. 145-151°C. A mixed melting point with an authentic sample of 3α-methylcholestan-3β-ol gave no depression.
A solution of $4',4'$-dimethylcholestan-3-one (2.0g.) and potassium cyanide (15.0g.) in ethanol (120 ml.) was cooled to $0^\circ$C. Glacial acetic acid (10 ml.) was added over 3 hours to the stirred solution. The solution was poured into water and the crystalline suspension extracted into ether. The ether layer was washed with water and dried. White crystals of $3\beta$-cyano-$4',4'$-dimethylcholestan-3-ol (2.0g.) $\lambda_{\text{max}}$ 3600, 2700 cm$^{-1}$ were obtained when the solvent was removed. The cyanohydrin was dissolved in a solution of pyridine (10 ml.) and acetic anhydride (10 ml.) and the solution heated at $60^\circ$C for 18 hours. The solution was poured into water and the crystalline suspension extracted with ether. The ether layer was washed with sodium carbonate solution and dilute hydrochloric acid and dried. The solvent was removed in vacuo and the product was recrystallised from ethanol to give white plates of

$3\alpha$-acetoxy-$3\beta$-cyano-$4',4'$-dimethylcholestan (1.1g.), (55%), m.p. 195-202$^\circ$C, $[\alpha]_D +1^\circ$ (c, 0.32) (Found C = 79.9%, H = 10.8%
N. = 3.0%. $C_{32}H_{53}NO_2$ requires C = 79.5%, H = 11.0%, N = 2.9%),
$\lambda_{\text{max}}$ 1755, 1235, 1035 cm$^{-1}$ (acetate) 2250 cm$^{-1}$ (cyano).
**3β-Aminomethyl-4,4'-dimethylcholestan-3β-ol (38e)**

3α-acetoxy-3β-cyano-4,4'-dimethylcholestan (0.90 g.) and lithium aluminium hydride (0.90 g.) in anhydrous ether (50 ml.) were refluxed for 2 hours. The excess lithium aluminium hydride was destroyed, chloroform (50 ml.) added, the ether solution washed with 10% sodium hydroxide solution and dried. A white crystalline material (\( \lambda_{\text{max}} 3450, 3600 \text{ cm}^{-1} \)) was obtained when the solvent was removed in vacuo. This material was insoluble in acetone and the acetonide could not be formed. The material was soluble in hot acetic acid but on cooling gave white plates of 4,4'-dimethylcholestan-3α-ol, m.p. 156-158°C, 0.175 g (20%), melting point undepressed on admixture with an authentic sample. The filtrate, a solution of 3β-aminomethyl-4,4'-dimethylcholestan-3β-ol in acetic acid, was used in the next experiment.

**The action of nitrous acid on 3β-aminomethyl-4,4'-dimethylcholestan-3β-ol (Fig. 1)**

The solution of 3β-aminomethyl-4,4'-dimethylcholestan-3β-ol (0.73 g.) in acetic acid (10 ml.) and ether (4 ml.) were cooled to -10°C. A solution of sodium nitrite (2 g.) in water (7 ml.) was added to the reaction mixture over 3 hours so that the temperature did not exceed 0°C. The resultant suspension was extracted with ether and the ether layer washed with sodium carbonate solution and dried. A brown oil (0.79 g., \( \lambda_{\text{max}} 1695 \text{ cm}^{-1} \)) was obtained when the solvents were removed in vacuo. Chromatography of this/
this oil on alumina gave 4a,4a'-dimethyl-A-homocholestan-3-one (0.30g., 60% material after chromatography) which was recrystallised from ethanol to give white prisms 0.23g., m.p. 99-104°C $\left[\alpha\right]_D^{10} + 10^0$ (c, 0.30) (Found C = 83.6% H = 12.1% C$_{30}$H$_{52}$O requires C = 84.0% H = 12.2%), $\nu_{\text{max}}$ 1695 cm$^{-1}$, N.M.R. spectrum: two doublets centred on 7.42, 7.70 $\tau$. ($J_{\text{AB}} = 7$ cps. methylene protons at $C - 3$) G.L.C. indicated one component with a retention with respect to cholestane: (3.56). The remainder of the material after chromatography consisted of a series of oils with no definite absorption in the infra red.

4a, 4a'-dimethyl-A-homocholestan-3-one (35 mg.) was dissolved in a solution of sodium (35mg.) in deuteromethanol (2 ml.) and refluxed for 1 hour. On cooling white prisms of tetra-D-4a,4a'-dimethyl-A-homocholestan-3-one m.p. 115-118°C, $\nu_{\text{max}}$ 1695 cm$^{-1}$, N.M.R. spectrum: no signals in 7 - 8 $\tau$ region. (See appendix) were obtained.

c) Exocyclic steroid epoxides

3α-Methyl-3α,3'-oxidocholestanate (50)

A dispersion of sodium hydride in oil (0.60g.) was added to a solution of trimethylsulphoxonium iodide (3.3g.) in dimethylsulphoxide (50ml.) The solution was slightly warmed so that all the sodium hydride dissolved. Cholestan-3-one (5.0g.) in anhydrous ether (30ml.) was added/
added to this solution and the mixture refluxed for 3 hours. The solution was poured into slightly acidified water and ether (100 ml.) was added. The ether layer was washed well with water and dried. A white crystalline material was obtained when the solvents were removed in vacuo. This material was recrystallised from ethanol to give white colourless plates of 3β-methyl-3α,3′-oxidocholestane, m.p. 130-135.5°C, [α]D + 22° (c, 0.38) (Found: C = 83.9%, H = 11.8%, C28H48O requires C = 83.9%, H = 12.0%) \( \nu_{\text{max}}^{\text{max}} \) 935 cm\(^{-1}\), N.M.R. spectrum: signal at 7.64 \( \tau \) (3′-methylene protons)

3β-Methylcholestan-3α-ol (52)

3β-methyl-3α,3′-oxidocholestane (0.40g.) and lithium aluminium hydride (0.40g) in anhydrous ether (25ml.) were refluxed for 2 hours. The excess lithium aluminium hydride was destroyed and the suspension poured into dilute hydrochloric acid. The steroid was extracted into ether and the ethereal solution washed with dilute hydrochloric acid and dried. A white crystalline product was obtained when the solvent was removed in vacuo. Crystallisation from acetone gave white prisms of 3β-methylcholestan-3α-ol, 0.25g. (60%) m.p. 125-128°C lit. 126-127°C, [α]D + 25° (c, 0.35) lit. + 28°, \( \nu_{\text{max}}^{\text{max}} \) 3600,920 cm\(^{-1}\) (hydroxyl) N.M.R. spectrum signal at 8.81 \( \tau \) (3β-methyl protons)
3-Methylcholest-2-ene (53)

A solution of 3β-methylcholestan-3α-ol (0.10g.) and phosphorus oxychloride (1.5 ml.) in pyridine (10 ml.) was allowed to stand at room temperature for 24 hours. The solution was poured into water and the resultant suspension extracted into ether. The ethereal solution was washed with dilute hydrochloric acid and dried. A semi-crystalline product was obtained when the solvent was removed in vacuo. Recrystallisation from ethyl acetate gave crystals of 3-methylcholest-2-ene, 0.055g (55%) m.p. 79-81°C lit. 82-83°C, $[\alpha]_D^0 + 69^0$ (c, 0.25) lit. + 74° max 790 cm$^{-1}$ (double bond)

The action of sodamide on 3β-methyl-3α,3'-oxidocholestane

A solution of 3β-methyl-3α,3'-oxidocholestane (0.60g.) in anhydrous ether (20 ml.) was added to sodamide (prepared from 0.10g sodium) in liquid ammonia (20ml.) The mixture was vigourously stirred for 5 hours. The ammonia was removed and the ethereal solution washed with water and dried. White crystalline starting material m.p. 129-132°C, $\nu_{max} 935$ cm$^{-1}$, was obtained when the solvent was removed.

The experiment was repeated in exactly the same manner using dry tetrahydrofuran (20ml.) A small aliquot of solution was withdrawn after 5 hours. Examination of the I.R. spectrum of this material showed that the reaction had proceeded partially or not at all. The ammonia was removed and the suspension in tetrahydrofuran refluxed for 8 hours. Ether (40 ml.) was added and the ether solution washed with water and dried. Unreacted starting material, m.p. 129-132°C, was obtained when the solvent was removed.
The action of lithamide on \(3\beta\)-methyl-\(3\alpha,3'\)-oxidocholestanol

The experiments using sodamide were repeated in an identical manner using instead lithamide. No reaction was observed.

A solution of \(3\beta\)-methyl-\(3\alpha,3'\)-oxidocholestanol (0.20g) and lithamide (0.50g) in dimethylformamide (20 ml.) was stirred at 80°C for 20 hours. The solution was poured into water and the suspension extracted into ether. The starting material was recovered unchanged when the solvent was removed in vacuo. The same result was obtained when dimethylsulphoxide was used as solvent.

\(3\beta\)-Methyl-\(3\alpha,3'\)-oxidoandrostan-17\(\alpha\)-ol\(33\) (50)

A dispersion of sodium hydride (0.10g.) was added to a solution of trimethylsulphoxonium iodide (0.55g.) in dimethyl sulphoxide (10 ml.). The solution was warmed slightly so that all the sodium hydride dissolved. Androstan-17\(\alpha\)-ol-3-one (0.10g.) in anhydrous ether (5 ml.) and benzene (5 ml.) was added to this solution and the mixture refluxed for 3 hours. The solution was poured into slightly acidified water and ether (20 ml.) was added. The ether layer was washed with water and dried. The solvent was removed in vacuo and the product recrystallised from acetone to give white needles of \(3\beta\)-methyl-\(3\alpha,3'\)-oxidoandrostan-17\(\beta\)-ol, m.p. 163-168°C, (lit. 173-175°C) \([\alpha]_D^0 + 10^\circ \) (c, 0.30) lit. + 7\% N.M.R. spectrum signal at 7.40 \(h\) (3'-methylene protons), 0.075g. (75%).
The action of sodamide on 3β-methyl-3α,3'-oxidoandrostan-17β-ol

A solution of 3β-methyl-3α,3'-oxidoandrostan-17β-ol (30mg.) in dioxan (10 ml.) was added to sodamide (prepared from 0.5g. sodium) in liquid ammonia (30 ml.). The mixture was vigourously stirred for 36 hours. The ammonia was removed and the ethereal solution washed with water and dried. A glass was obtained after the solvent had been removed in vacuo. This product ($\nu_{\text{max}} 3300, 1100\text{cm}^{-1}$) did not form an acetonide on refluxing with acetone. It was then dissolved in acetic acid and ether (3ml.) and cooled to $-10^\circ C$. A solution of sodium nitrite (0.5g) in water (2ml.) was added over 1½ hours to this solution so that the temperature did not exceed $-5^\circ C$. The solution was poured into water and the aqueous suspension extracted with ether. The ethereal solution was washed with sodium carbonate solution and dried. A product with an identical I.R. spectrum to the starting material ($\nu_{\text{max}} 3300, 1100\text{cm}^{-1}$) was obtained.

3β-Ethoxymethylcholestan-3α-ol (63)

3β-methyl-3α,3'-oxidocholestane (0.50g.) and potassium hydroxide (2.0g) were dissolved in ethanol (20 ml.) and water (3ml) and the solution was refluxed for 36 hours. The solution was poured into water and the suspension obtained extracted into ether. The ether layer was washed with water, dried and the solvent removed in vacuo. A white crystalline product was obtained which was purified by filtration through/
through alumina and recrystallised from ethanol/methanol to give white plates of 3β-ethoxymethylcholestan-3β-ol, m.p. 89 - 90°C 

\[ \delta^D + 25{^o} \text{C} \] (c, 0.32), (Found C = 80.4%, H = 12.1%, \( \text{C}_{30}\text{H}_{54}\text{O}_2 \) requires C = 80.6%, H = 12.2%), \( \nu_{\text{max}} \) 3550, 1130cm\(^{-1}\)  N.M.R. spectrum: quartet centred on 6.37\( \gamma \) (J = 7 cps.) singlet at 6.79\( \gamma \) and triplet centred on 7.69\( \gamma \)(J = 8 cps.)

Acetylation:

(a) 3β-ethoxymethylcholestan-3β-ol (0.07g.) was dissolved in a solution of pyridine (5ml.) and acetic anhydride (5 ml.) and the solution left to stand for 18 hours. The solution was poured into water and the suspension obtained extracted into ether. The ether layer was washed with dilute sodium carbonate solution and dilute hydrochloric acid, dried, and the solvent removed in vacuo.

Crystallisation from methanol gave the unchanged starting material m.p. 87-89°C \( \nu_{\text{max}} \) 3550,1130cm\(^{-1}\)

(b) 3β-ethoxymethylcholestan-3β-ol (0.07g.) was dissolved in ethyl acetate (1.5ml.) and acetic anhydride (0.5 ml.) and perchloric acid (2 drops) was added. The solution was left for 5 mins. and then poured into water. The suspension obtained was extracted with ether. The ether layer was washed with dilute sodium carbonate solution, dried, and the solvent removed in vacuo. An oil was obtained which, when crystallised from acetone, gave colourless needles/
needles 30mg. (43%) m.p. 123-133°C, $\nu_{\text{max}}$ 1765, 1250, 1215, 1020, 990cm$^{-1}$ (acetate) N.M.R. spectrum, signal at 7.93 (5-6 protons).

Action of sodium metaperiodate:

A solution of sodium metaperiodate (0.25g.) in water (1.5ml.) was added to 3β-ethoxymethylcholestan-3α-ol (0.75g.) and the mixture left to stand at room temperature for 60 hours. The solution was then poured into water and the suspension extracted into ether. The ether layer was dried and the solvent removed in vacuo. Crystallisation from methanol gave unchanged starting material m.p. 85-88°C, $\nu_{\text{max}}$ 3550, 1130cm$^{-1}$.

The action of perchloric acid on 3β-methyl-3α,3'-oxidocholestan

To a solution of 3β-methyl-3α,3'-oxidocholestan (0.50g.) in acetone (25ml.) and ether (5ml.) was added 0.6ml. 7% perchloric acid. This solution was allowed to stand at room temperature for 16 hours and then poured into water. The oily suspension was extracted into ether and the ether layer washed with water, dried, and the solvent removed in vacuo. The oil obtained ($\nu_{\text{max}}$ 1725, 2700, (aldehyde) 1075, 887cm$^{-1}$) could not be fractionated on alumina. Examination of the product by gas chromatography on an S.E.30 column at 260°C showed that it contained three components with relative retention times of 5.85 7.30, 12.04 min. in the approximate ratio 1:0.75:1.
The acetolysis of 3α-methyl-3α,3'-oxidocholestane

A solution of 3α-methyl-3α,3'-oxidocholestane (0.27g.) in glacial acetic acid (10ml.) was refluxed for 3 hours. A light colouration occurred during this time. The solution was poured into water and the suspension obtained extracted into ether. The ether layer was washed with sodium carbonate solution, dried, and the solvent removed in vacuo. The crude product was chromatographed on alumina to give two crystalline fractions in the order indicated:

3β-acetoxy-3α-acetoxy methylcholestane: 60mg. (22%) \[\text{max} 1745, 1240;
1055\text{cm}^{-1} \text{ (acetate). N.M.R. spectrum: singlet at 5.54} \nu \text{. (2-3 protons; 3α-methylene protons) 2 signals at about 7.95} \nu \text{. (5-6 protons; acetate)}\]

3β-acetoxy-3α-hydroxy methylcholestane: 140mg. (52%) \[\text{max} 1745, 1240,
1059\text{cm}^{-1} \text{ (acetate) 3550, 3450\text{cm}^{-1} \text{ (hydroxy)}}, 
\text{N.M.R. spectrum: two signals at 5.85} \nu \text{. and 6.01} \nu \text{. (3α-methylene protons) 7.89, 7.91} \nu \text{. (acetate protons). The signals at 6.07, 7.91} \nu \text{. had about a third of the amplitude of the signals at 5.85, 7.89} \nu \text{. and this result was interpreted as non-stereoselectivity of acetolysis. A suitable solvent for crystallisation of these two fractions was not found.} \]

3α-Hydroxymethylcholestan-3β-ol (62b)

The crude 3β-acetoxy-3α-hydroxymethylcholestane (0.095g.) and lithium aluminium hydride (0.20g.) in anhydrous ether (10ml.) were refluxed for 1\frac{1}{2} hours. The excess lithium aluminium hydride was destroyed and the ether solution/
solution washed with dilute hydrochloric acid and dried. This material was recrystallised from ethanol to give colourless needles of 3\(\alpha\)-hydroxymethylcholestan-3\(\beta\)-ol m.p. 190-196\(^\circ\)C, \(\nu_{\text{max}}\) 3500, 3550, 1060 cm\(^{-1}\) (hydroxyl), N.M.R. spectrum: singlet at 6.40 (3 methylene protons) broad band 6.3-6.7 (hydroxyl: signals disappear on addition of deuterium oxide).

**Attempted synthesis of the tetrahydropyranyl ether of 3\(\beta\)-cyanocholestan-3\(\alpha\)-ol.**

A solution of 3\(\beta\)-cyanocholestan-3\(\alpha\)-ol in dihydropyran (10 ml.) and phosphorus oxychloride (2 drops) was refluxed for 1 hour. The solution turned a dark brown colour. Ether (10 ml.) was added and the brown solution obtained washed with water and dried. The solvent was removed in vacuo to give a dark brown oil. The oil was filtered through alumina in a mixture of hexane and benzene in equal amounts. A white crystalline product was obtained which, when crystallised from ethanol, gave white prisms of cholestan-3-one, 0.75 g., m.p. 125-128\(^\circ\)C \(\nu_{\text{max}}\) 1708 cm\(^{-1}\).

**The hydrolysis of 3\(\alpha\)-acetoxy-3\(\beta\)-cyanocholestanol.**

The solution of 3\(\alpha\)-acetoxy-3\(\beta\)-cyanocholestanol (1.0 g.) in ethanol (10 ml.) and dilute hydrochloric acid (5 ml.) was refluxed for 30 minutes. The solution was poured into water and the oily suspension extracted into ether. The ether layer was washed with water, dried, and the solvent removed in vacuo. An oil, \(\nu_{\text{max}}\) 3550, 3400, 2250, 1750, 1230, 1040 cm\(^{-1}\), was obtained.
Section 3: The acid catalysed reactions of diazomethane with some alpha beta
unsaturated ketones

A-homocholest-4a-en-3-one (18)

To a stirred solution of cholest-4-en-3-one (5.0g.) in anhydrous
methylene chloride solution containing 0.3 ml. boron trifluoride catalyst
solution*, was added over a period of 30 mins. a solution of diazomethane
(0.2M) in methylene chloride (200ml.). Vigorous nitrogen evolution
occurred on addition of diazomethane and white flocculent polymethylene
was precipitated. The solution was stirred for a further hour at 0°C
and then filtered. The filtrate was washed with sodium carbonate solution
and dried. The oil (\(\nu_{\text{max}}\) 1710, 1690 cm\(^{-1}\)) obtained when the solvent was
removed in vacuo was chromatographed on Florisil. Elution was carried
out using benzene/ether mixtures. Crystalline fractions were obtained in
the following order.

A-homocholest-4a-en-3-one, 2.92g. 60% was recrystallised from acetone to
give white prisms 2.0g. m.p. 88-94°C lit. 94-95°C \([\alpha]_D +40^\circ\) (c, 0.35)
lit. +48° \(\nu_{\text{max}}\) 1710 cm\(^{-1}\)

* A solution of 1 ml. freshly distilled boron trifluoride etherate in
25 ml. anhydrous 3:1 ether methylene chloride solution.
Cholest-\textsubscript{4-en-3-one} 1.2g (24\%) was recrystallised from ethanol to give white prisms 0.70g. m.p. 79-81°C.

A-homocholest-4\textsubscript{a-en-3-one} (30mg.) in a 10\% solution of anhydrous oxalic acid in ethanol (2ml.) was refluxed for 30 minutes. The solution was poured into water and the suspension extracted into ether. The ether solution was washed with water, dried, and the solvent removed into vacuo. The homo-ketone was recovered unchanged. $\lambda_{\text{max}}$ 1710 cm\textsuperscript{-1}.

The acid catalysed reaction of diazomethane with cholest-1-en-3-one (Fig. 8)

To a stirred solution of cholest-1-en-3-one (1.0g.) in anhydrous methylene chloride containing 0.15ml. boron trifluoride catalyst solution* was added over a period of 20 minutes, a saturated solution of diazomethane in methylene chloride (20ml.) at 0°C. Nitrogen evolution occurred on addition of diazomethane and white polymethylene was precipitated. The yellow colour of the diazomethane still persisted and further 0.15ml. of catalyst solution was added and the solution stirred at 0°C for 30 minutes. The solution was filtered to remove the polymethylene and the filtrate was washed with sodium carbonate solution and dried.

* A solution of 1ml. freshly diluted boron trifluoride etherate in 25ml. anhydrous 3:1 ether methylene chloride solution.
The oil \( (\nu_{\text{max}} 1705, 1680\text{cm}^{-1}) \) obtained when the solvent was removed in vacuo, was chromatographed on alumina (Woelm neutral, activity grade 3) and crystalline fractions were obtained in the following order.

A-homocholest-1-en-4-one (100mg., 10%) was recrystallised from ethanol to give a white amorphous powder (60mg.) m.p. 95-100°C, \( \nu_{\text{max}} 1708 \) (carbonyl) 720 cm\(^{-1}\). N.M.R. spectrum: a complicated series of signals in the 4.1-4.6 \( \tau \) region (vinyl protons) unresolved multiplets at 6.25, 6.60 \( \tau \) (protons allylic to double bond and alpha to carbonyl) a series of signals lying between 7.0-7.75 \( \tau \) (protons alpha to carbonyl). A yellow colour was obtained when this compound was dissolved in tetranitromethane. G.L.C. indicated one component, with a retention time with respect to cholest-1-en-3-one (1.24)

Cholest-1-en-3-one (400mg.) 40%, was recrystallised from acetone to give white plates 0.25g., m.p. 98-100°C, \( \nu_{\text{max}} 1680\text{cm}^{-1} \).

The remainder of the material 0.20g. (20%) consisted of oils. These were combined and refractionated on alumina but no further crystalline material was obtained. The fractions were recombined and examination of this material showed that it contained a significant proportion of non-conjugated ketone \( \nu_{\text{max}} 1705\text{cm}^{-1} \). Gas chromatography of this oil at 260°C on an S.E. 30/Epon column indicated that it contained seven components in approximately equal amounts.
The isomerisation of A-homocholest-1-en-4-one.

A-homocholest-1-en-4-one (36 mg.) was dissolved in a 10% solution of anhydrous oxalic acid in ethanol (2 ml.) and refluxed for 45 min. The solution was poured into water and the suspension extracted into ether. The ether solution was washed with water, dried, and the solvent removed in vacuo. An oil, \( n_{\text{max}}^{\text{C}} 1705, 1685 \text{ cm}^{-1}, \lambda_{\text{max}} 229 \text{ m} \mu \), was obtained.

Attempted catalytic hydrogenation of A-homocholest-1-en-3-one

A-homocholest-1-en-3-one (20 mg.) in ethanol (2 ml.) and benzene (2 ml.) was hydrogenated at room temperature using prehydrogenated 10% Pd/C as catalyst. No hydrogen uptake was observed. The solution was filtered and the solvents removed in vacuo. The product was crystallised from ethanol to give A-homocholest-1-en-3-one (15 mg.) m.p. 95-100°C (melting point undepressed on admixture with an authentic sample).

The acid catalysed reaction of diazomethane with 4-methylcholest-4-en-3-one (Fig. 8)

To a stirred solution of 4-methylcholest-4-en-3-one (0.50 g.) in anhydrous methylene chloride (5 ml.) containing 0.15 ml. boron trifluoride catalyst solution was added over a period of 15 minutes, a saturated solution of diazomethane in methylene chloride (20 ml.) at 0°C. Nitrogen evolution occurred on addition of diazomethane and white polymethylene was precipitated. The solution was stirred at 0°C for a further hour and then filtered to remove the polymethylene. The filtrate was washed with sodium carbonate solution, dried, and the solvents removed in vacuo.
A pale yellow crystalline product $\nu_{\text{max}} = 1670, 1708\text{cm}^{-1}$ was obtained.

Chromatography of this material on alumina did not result in separation of the ketone $\nu_{\text{max}} = 1708\text{cm}^{-1}$ from the ketone $\nu_{\text{max}} = 1670\text{cm}^{-1}$. Crystallisation of the product from ethanol gave white prisms of 4-methylcholest-4-en-3-one m.p. 95-100°C. The amount of non-conjugated ketone formed during this reaction estimated on relative intensities of carbonyl frequencies, was less than 10%. (cf. homologation of cholest-1-en-3-one (50%) and cholest-4-en-3-one (75%).

Aluminium trichloride catalysed reaction of diazomethane and cholest-
1-en-3-one

A solution of cholest-1-en-3-one (0.05g.) and aluminium trichloride (0.01g.) was cooled to 0°C with stirring and an ice-cold solution of diazomethane (0.7M) in ether added over half an hour until the yellow colour of the diazomethane persisted. The solution was filtered to remove the polymethylene formed and the filtrate washed with sodium carbonate solution and dried. An oil ($\nu_{\text{max}} = 1705\text{cm}^{-1}$) was obtained when the solvent was removed in vacuo. This oil was examined by G.L.C. on a S.E. 30/Epon column at 255°C. A seven component mixture was obtained with a principal component at retention time, 2.73 (with respect to cholest-1-en-3-one) cf. A-homocholest-1-en-4-one - retention time 1.24 (with respect to cholest-1-en-3-one).
The reaction of aluminium trichloride and cholest-1-en-3-one

The previous experiment was carried out identically except that ether was added instead of the diazomethane solution. After isolation, the product obtained was an oil $\nu_{\text{max}} \text{1705 cm}^{-1}$.

5α-Cyanocholestan-3-one (82)

A solution of potassium cyanide (1.3g.) in water (4ml.) was added to a hot solution of cholest-4-en-3-one (4.0g.) in methanol (100ml.) This solution was refluxed for 6 hours and then allowed to cool slowly. White crystals of 5α-cyanocholestan-3-one (0.40g. m.p. 175-180°C) were obtained when the mixture was filtered. The filtrate was reduced in volume and the suspension obtained extracted into chloroform. The chloroform solution was washed well with water and an oil was obtained when the solvent was removed in vacuo. The oil was chromatographed on alumina and eluted with benzene -ether mixtures to give fractions in the following order.

5α-cyanocholestan-3-one: 0.25g. m.p. 179-182°C.

Cholest-4-en-3-one/5α-cyanocholestan-3-one: mixed crystals m.p. 115-25°C 0.95g.

Cholest-4-en-3-one: 0.20g. m.p. 75-79°C, $\nu_{\text{max}} \text{1680 cm}^{-1}$

Total yield of 5α-cyanocholestan-3-one = 0.65g. (33%) $\nu_{\text{max}} \text{1710, 2210 cm}^{-1}$

$[\alpha]_D + 45^\circ \text{ (c, 0.40) lit. + 47^0}$
Catalytic hydrogenation of 5α-cyanocholestan-3-one

A solution of 5α-cyanocholestan-3-one (0.10g.) in acetic acid (8ml.) was added to prehydrogenated Adam's catalyst (0.05g.) in acetic acid (2ml.) and the suspension shaken in an atmosphere of hydrogen for 3 hours. The catalyst was filtered off and the filtrate poured into sodium carbonate solution. The suspension obtained was extracted into ether. The ether solution was washed with sodium carbonate solution, dried and the solvent removed in vacuo. A glass, \( \nu_{ \text{max}} \) 3600, 1045 (hydroxyl) 2250 cm\(^{-1}\) (cyano), was obtained.

Oxidation

The glass (90mg.) was dissolved in acetone (25ml.). The 8 N chromic acid (1ml.) was added to this solution with stirring. After one minute methanol (10ml.) was added and a deep green precipitate was formed. Dilute hydrochloric acid (50ml.) was added and the suspension extracted into ether and the ether solution washed with dilute hydrochloric acid and dried. The solvent was removed in vacuo and recrystallisation of the product twice from ethanol gave 5α-cyanocholestan-3-one (50mg.) m.p. 170-175°C (undepressed on admixture with an authentic sample).

Formation of ethylene ketal of 5α-cyanocholestan-3-one (84)

A solution of 5α-cyanocholestan-3-one (0.1g.) and p.-toluenesulphonic acid (50mg.) in distilled ethylene glycol (10ml.) was heated to 60°C and the ethylene glycol slowly distilled at 60°C under reduced pressure until the volume was reduced by half. The ketal was precipitated during this time.
The suspension was poured into water and the ketal extracted into ether. The ether layer was washed with water and dried. The crystalline ketal was obtained when the solvent was removed into vacuo. Crystallisation from ethanol gave white crystals of 5α-cyanocholestan-3-one ethylene ketal 0.06g. (60%) m.p. 133-139°C, $[\alpha]_D^0 + 27^0$ (c, 0.28)

(Found C = 79.5% H = 10.8% N = 3.0%; $C_{30}H_{49}NO_2$ requires C = 79.1% H = 10.8% N = 3.1%) $\lambda_{\text{max}}$ 1110, 2250cm$^{-1}$. N.M.R. spectrum; signals at 8.75 (C-19 protons) 8.20, 8.30 (C-4 protons) multiplet centred on 6.0 (ethylene ketal protons).

**Lithium aluminium hydride reduction of 5α-cyanocholestan-3-one-ethylene ketal**

The ketal (0.10g.) and lithium aluminium hydride (0.10g.) in anhydrous ether (10ml.) were refluxed for half an hour. The excess lithium aluminium hydride was destroyed and the mixture partitioned between 10% sodium hydroxide solution and ether. The ether layer was washed with 10% sodium hydroxide solution and water, dried, and the solvent/
solvent removed in vacuo. An oil (80mg.) was obtained which had practically the same absorption as the starting material \( \nu_{\text{max}} \) 1110cm\(^{-1}\); and slight absorption at \( \nu_{\text{max}} \) 3400cm\(^{-1}\).

Removal of ethylene ketal:

The oil (80mg.) in a solution of ethanol (10 ml.) and concentrated hydrochloric acid (1ml.) was refluxed for 2 hours. The solution was poured into water and the suspension obtained extracted with ether. The ether solution was washed with water and dried, and the solvent removed in vacuo. A glass \( \nu_{\text{max}} \) 1680, 1750, 3400, 3600cm\(^{-1}\), was obtained.

**Lithium aluminium hydride reduction of 5\(\alpha\)-cyanocholestan-3-one**

5\(\alpha\)-cyanocholestan-3-one (0.10g.) and lithium aluminium hydride (0.10g.) in anhydrous ether (10ml.) were refluxed for one hour. The excess lithium aluminium hydride was destroyed and the mixture partitioned between 10% sodium hydroxide solution and ether. The ether layer was washed with 10% sodium hydroxide solution and water, dried, and the solvent removed in vacuo. An oil (80mg.) \( \nu_{\text{max}} \) 3400, 3600, 1050, 1210cm\(^{-1}\) was obtained.

**Oxidation:**
Oxidation:

The oil (80mg.) was dissolved in acetone (10ml.) and 1 ml. 8N. chromic acid added. After 1 minute, methanol (10ml.) was added and a dark green precipitate was formed. The suspension was poured into dilute hydrochloric acid and the steroid extracted into ether. The ether solution was washed with dilute hydrochloric acid, dried, and the solvent removed in vacuo. An oil $\nu_{\text{max}} 1710\text{cm}^{-1}$ (5α-cyanocholestan-3-one); 1750, 3600cm$^{-1}$ ($\delta -$ lactone).

Section 4: Rearrangements of exocyclic ethyl and isopropyl side chains

3α-Ethynylcholestan-3-ol (87)

A solution of cholestan-3-one (1.0g.) in dry benzene (2.5ml.) was added to a solution of potassium (1g.) in t-amylalcohol and the air displaced with nitrogen. A slow stream of purified acetylene was passed through this solution for 20 hours. The solution was then neutralised with dilute hydrochloric acid and the amyl alcohol removed by steam distillation. The suspension obtained was extracted with ether. The ether solution was washed with water, dried, and the solvent removed in vacuo. A pale yellow crystalline solid $\nu_{\text{max}}$ 3575, 1040 (hydroxyl) 3400cm$^{-1}$ (ethynyl) N.M.R. spectrum: signal at 7.55 $\tau$. (1 ethynyl proton) was obtained which could not be crystallised from usual solvents.

Acetylation: /
Acetylation:

(a) \(3\beta\)-ethynylcholestan-3\(\beta\)-ol (0.5g.) and p-toluene-sulphonic acid (1.0g.) were dissolved in acetic acid and refluxed for 3 hours. The solution turned very brown. The solution was poured into water and the suspended oil extracted into ether. The ether layer was washed with sodium carbonate solution and dried. The solvent was removed in vacuo and the dark coloured oil obtained chromatographed on alumina. The pale yellow crystalline material (0.25g.) obtained was recrystallised from methanol to give plates of \(3\)-acetylcholest-2-ene m.p. 91-93°C \(\lambda_{\text{max}}\) 242 m\(\mu\), \(\lambda_{\text{max}}\) 1625, 1671 cm\(^{-1}\) N.M.R. spectrum: signals at 7.75 (acetyl protons) (Found C = 63.7%; H = 11.4%; \(C_{29}H_{48}O\) requires C = 64.4%, H = 11.7%)

(b) \(3\beta\)-ethynylcholestan-3\(\alpha\)-ol (0.5g.) was dissolved in a solution of pyridine (10 ml.) and acetic anhydride (15ml.) and the solution heated at 80°C for 15 hours. The solution was poured into water and the suspension extracted with ether. The ether solution was washed with dilute hydrochloric acid and sodium carbonate solution, dried and the solvent was removed in vacuo. The white crystalline product obtained was recrystallised from ethanol to give white prisms of \(3\alpha\)-acetoxy-\(3\beta\)-ethynylcholestan m.p. 110-114°C \(\lambda D\) + 23°C (c, 0.41) (Found C = 81.8, 81.6% H = 10.8, 10.7%, \(C_{31}H_{50}O_2\) requires C = 81.5% H = 11.5%).
3α-Acetoxy-3β-dibromoacetylcholestan (91)

3α-acetoxy-3β-ethinylcholestan (1.0g.) and sodium acetate (1.0g.) were dissolved with warming in acetic acid (50ml.) and water (5ml.). N-bromoacetamide (1.0g.) was added slowly to this solution and a white precipitate was obtained. Water (50ml.) was added slowly and the crystals filtered and washed with water until the filtrate was neutral to litmus. The crystals were dried in vacuo over phosphorus pentoxide.

3α-acetoxy-3β-dibromoacetylcholestan: yield 1.37g., $\lambda_{max}^{\text{nm}} 1745, 1235, 1025\text{cm}^{-1}$. N.M.R. spectrum: signals at 3.80 ppm (one proton), 7.92 ppm (three acetate protons).

A small sample was recrystallised from ethanol to give white needles m.p. 140-143°C (Found C = 59.5% H = 7.7% Br = 25.4%
$\text{C}_{31}\text{H}_{30}\text{O}_3\text{Br}_2$ requires C = 59.1% H = 7.9% Br = 25.3%), $[\alpha]_D^{10^\circ} (\text{C}, 0.28)$.

3α-Acetoxy-3β-acetylcholestan (92)

To a solution of sodium acetate (2.5g.) in acetic acid (50ml.) and water (5ml.) was added 3α-acetoxy-3β-dibromoacetylcholestan. The steroid did not dissolve and to the suspension was added a powdered zinc (0.75g.). The solution was heated at 90°C for 15 minutes and during/
during this time the steroid gradually dissolved. The hot solution was filtered and the filtrate poured into water. The suspension obtained was extracted into ether. The ether layer was washed with sodium carbonate solution, dried, and the solvent removed in vacuo. Crystallisation from ethanol gave white plates of 3α-acetoxy-3β-acetylcholestane (0.65g.) m.p. 145-150°C, [α]D +21° (c, 0.44) (Found C = 76.3, 76.1% H = 10.7, 10.9% C31H52O3 requires C = 76.7% H = 11.1%) νmax 1027, 1040, 1250, 1710, 1745 cm⁻¹ N.M.R. spectrum: signals at 7.95, 7.97 ℏ. (six acetyl and acetate protons).

Attempted preparation of the oxime of 3α-acetoxy-3β-acetylcholestane and reduction of the product.

(a) To a solution of 3α-acetoxy-3β-acetylcholestane (0.43g.) in pyridine (7ml.) was added hydroxylamine hydrochloride (0.5g.) and the mixture left at room temperature for 5 hours. The solution was poured into water and the aqueous suspension extracted into ether. The ether layer was washed well with dilute hydrochloric acid, dried, and the solvent removed in vacuo. A white crystalline product υmax 1745, 1245, 1030 cm⁻¹ (acetate) 3600, 3400 cm⁻¹ (weak absorption; oxime) 0.100g., was obtained.

(b) To a solution of 3α-acetoxy-3β-acetylcholestane (0.20g.) in pyridine (4ml.) was added hydroxylamine hydrochloride (0.20g.) and the/
the mixture heated at 80°C for 3 hours. The solution was poured into dilute hydrochloric acid and the white precipitate extracted with ether and chloroform. The ether and chloroform layer was washed with dilute hydrochloric acid, dried, and the solvent removed in vacuo. A white crystalline product $\nu_{\text{max}}^{\text{IR}} 3500, 3600\text{cm}^{-1}$ (oxime) (0.20g.) was obtained. Large hydrogenation

The oxime (0.20g.) prepared by method (b) was dissolved in acetic acid (10ml.). The solution was added to prehydrogenated Adam's catalyst (0.50g.) in acetic acid (2ml.) and the suspension shaken in an atmosphere of hydrogen for 3 hours. The catalyst was removed by filtration and the filtrate poured into sodium carbonate solution. The suspension obtained was extracted into ether. The ether solution was washed with sodium carbonate solution, dried, and the solvent removed in vacuo. The starting material $\nu_{\text{max}}^{\text{IR}} 3500, 3600\text{cm}^{-1}$ was obtained which was identified by comparison of infra-red spectra.

Lithium aluminium hydride reduction:

A solution of the oxime (0.20g.) prepared by method (b) and lithium aluminium hydride in anhydrous ether (10 ml.) was refluxed for one hour. The excess lithium aluminium hydride was destroyed and the suspension partitioned between 10% sodium hydroxide solution and ether. The/
The ether layer was washed with sodium hydroxide solution and water, dried, and the solvent removed in vacuo. A brown oil (0.20g.) with no characteristic absorption in the infra-red was obtained.

**Action of nitrous acid**:

The above oil (0.20g.) was dissolved in acetic acid (5 ml.) and cooled to -10°C. A saturated solution (5 ml.) of sodium nitrite in water was added over 1½ hours so that the temperature of the reaction did not exceed -5°C. The solution was poured into water and the suspension obtained extracted into ether. The ether layer was washed with sodium carbonate solution, dried, and the solvent removed in vacuo. Examination of the oil obtained showed that it had no carbonyl absorption in the infra-red and no absorption in the U.V. region.

**The action of Grignard reagent on 3α-acetoxy-3β-acetylcholestanec.**

Methyl magnesium iodide was prepared from magnesium turnings (0.20g.) and methyl iodide (1.0g.) in anhydrous ether (5 ml.). 3α-Acetoxy-3β-acetylcholestanec (0.20g.) was added and the solution refluxed for 2 hours. The solution was washed with ammonium chloride solution, dried, and the solvents removed in vacuo. Chromatography on alumina of the glass obtained gave a major crystalline fraction (0.10g.) $\nu_{\text{max}}^{\text{max}}$ 3550, 3400 cm$^{-1}$. No suitable solvent was found to crystallise/
crystallise this fraction and an acetonide could not be formed even after reflux in the presence of anhydrous copper sulphate.

Dehydration of product:

The glass (0.20g.) in pyridine (25ml.) was heated at 95°C for 1 hour with freshly distilled phosphorus oxychloride (2.5 ml.). The solution was poured into water and the suspension obtained extracted into ether. The ether layer was washed with dilute hydrochloric acid, dried, and the solvent removed in vacuo. Examination of the oil obtained showed that it had no carbonyl absorption in the infra red and no absorption in the U.V. region.

**The action of methyl lithium on 3α-acetoxy-3β-acetylcholestane**

Methyl lithium was prepared from lithium (0.10g.) and methyl iodide (2.0g.) in anhydrous ether (5ml.). 3α-acetoxy-3β-acetylcholestane (0.10g.) in anhydrous ether (5ml.) was added and the solution left to stand at room temperature for 5 hours. The ether solution was washed with dilute hydrochloric acid, dried, and the solvent removed in vacuo. The product obtained had absorption at ν max 1710, 1745 cm⁻¹ showing that no reaction had occurred.

**The action of ethanolic hydrochloric acid on 3α-acetoxy-3β-acetylcholestane**

3α-Acetoxy-3β-acetylcholestane (0.20g.) in ethanol (2ml.) and concentrated hydrochloric acid (0.2 ml.) were refluxed for one hour. The solution/
solution was poured into water and the suspension extracted into ether.
The ether solution was washed well with water and dried. An oil with
no characteristic I.R. absorption was obtained when the solvents were
removed in vacuo.
Appendix: N.M.R. spectra of steroid ketones and their alpha deuterated analogues

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Protons alpha to carbonyl (7-8 T)</th>
<th>Methyl Resonances (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestane-3-one</td>
<td>unresolved</td>
<td>8.98 9.09 9.18 9.32</td>
</tr>
<tr>
<td>A-homocholestane-3-one</td>
<td>unresolved</td>
<td>9.09 9.13 9.19 9.34</td>
</tr>
<tr>
<td>A-homocholestane-11-one</td>
<td>unresolved</td>
<td>8.93 9.04 9.08 9.18 9.31</td>
</tr>
<tr>
<td>2α-methylcholestan-3-one</td>
<td>unresolved</td>
<td>8.94 9.06 9.08 9.18 9.31</td>
</tr>
<tr>
<td>Tri-D-2α-methylcholestan-3-one</td>
<td>unresolved</td>
<td>8.94 9.00 9.08 9.18 9.31</td>
</tr>
<tr>
<td>2α-methyl-A-homocholestan-3-one</td>
<td>unresolved</td>
<td>8.93 9.05 9.09 9.18 9.35</td>
</tr>
<tr>
<td>2α-methyl-A-homocholestan-4-one</td>
<td>unresolved</td>
<td>8.98 9.09 9.12 9.17 9.34</td>
</tr>
<tr>
<td>Ketone</td>
<td>Protons alpha to carbonyl (7-8T)</td>
<td>Methyl Resonances (T)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>2,2'-dimethyl-cholestan-3-one</td>
<td>unresolved</td>
<td>8.88 8.95 9.01 9.07 9.18 9.32</td>
</tr>
<tr>
<td>Tetra-D-2,2'-dimethyl-A-homocholestan-4-one</td>
<td>- - -</td>
<td>8.97 9.02 9.09 9.16 9.19 9.34</td>
</tr>
<tr>
<td>4α-methylcholestan-3-one</td>
<td>unresolved</td>
<td>8.95 8.98 9.10 9.19 9.35</td>
</tr>
<tr>
<td>Tri-D-4α-methyl-cholestan-3-one</td>
<td>- - -</td>
<td>8.95 9.05 9.10 9.20 9.33</td>
</tr>
<tr>
<td>Tetra-D-4α-methyl-A-homocholestan-3-one</td>
<td>- - -</td>
<td>8.90 9.02 9.10 9.19 9.21 9.34</td>
</tr>
<tr>
<td>Ketone</td>
<td>Protons alpha to carbonyl (7-8T)</td>
<td>Methyl Resonances (T)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>4,4'-dimethyl-cholestan-3-one</td>
<td>unresolved</td>
<td>8.95 9.08 9.18 9.34</td>
</tr>
<tr>
<td>4α,4α'-dimethyl-A-homocholestan-3-one</td>
<td>7.37 7.48 7.65 7.75</td>
<td>8.98 9.08 9.15 9.18 9.35</td>
</tr>
<tr>
<td>Tetra-D-4α,4α'-dimethyl-A-homocholestan-3-one</td>
<td>-      -</td>
<td>8.98 9.08 (9.15-9.20) 9.34</td>
</tr>
</tbody>
</table>
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