TRANSFORMATIONS OF HECOGENIN ACETATE

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by

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1965
ABSTRACT

The \( \triangleleft{}^{13,17}a \)-C-nor-D-homo-spirostan-3-ene olefin has been characterised. The epoxides derived from this olefin, and from the isomeric \( \triangleleft{}^{17}a,18 \)-olefin have been made and their configurations determined, by the study of the tert-alcohols derived by reduction with lithium aluminium hydride. The boron trifluoride and perchloric acid catalysed reactions of these four epoxides have been studied.

An attempt was made to synthesise and study the boron trifluoride catalysed rearrangements of the analogous C-nor-D-homo pregnene epoxides.

The epoxides of 12-methylene tigogenin acetate have been made and their configurations determined by the study of the dehydration reactions of the tert-alcohols formed by reduction of the epoxides with lithium aluminium hydride. The Grignard reaction of the C\(_{12}\) ketone of hecogenin acetate was shown to proceed from the \( \beta \) -face. Dehydration of this alcohol gave the \( \triangleleft{}^{11,12} \) olefin from which the \( 12\beta \)-methyl-11\( \alpha \),12\( \alpha \) -epoxide was made. The boron trifluoride and perchloric acid catalysed rearrangements of this epoxide, along with the two 12,12\( \alpha \)-epoxides, was studied.
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PART I
INTRODUCTION

Spiroketal C-nor-D-homo-olefins

The C-nor-D-homo-steroidal system was first obtained from the normal steroid skeleton during attempts at the conversion of the 12-keto group of hecogenin into $\Delta^{11,12}$ olefins. Subsequent work has been directed towards the synthesis of jervine-like structures, jervine being a C-nor-D-homo-steroidal alkaloid.

The base catalysed rearrangement of the p-toluenesulphonyl hydrazone$^1,2$ of hecogenin acetate has been shown to give a mixture of three olefins: $\Delta^{11,12}$ (1), $\Delta^{17,17a}$ (2), and $\Delta^{17a,18}$ (3). The $\Delta^{17a,18}$ olefin (3) has also been synthesised by base catalysed rearrangement of the $12_{\beta}$-mesylate (4a) derived from hecogenin$^1$ (5).

Hydroxylation of the $\Delta^{17a,18}$-olefin (3, 3-0H) with osmic acid$^1$ gave a triol which in turn gave a diacetate on room temperature acetylation with acetic anhydride-pyridine. Periodic acid oxidation of the triol produced formaldehyde together with a quantitative yield of a norketone. The latter possessed normal carbonyl absorption at 1712 cm$^{-1}$, in the infrared spectrum characteristic of a six-membered ring ketone. The olefin (3) was thereby shown to contain a methylene group exocyclic to a six-membered ring.

An alternative structure (6), is the product of an improbable
two stage Wagner Meerwein rearrangement involving successively the \( \text{C}_{13}-\text{CH}_3 \) and \( \text{C}_{12}-\text{H} \). If structure (6) were to be formed it would more probably arise from the \( 12\alpha -\text{mesylate} \) rather than from the \( 12\beta -\text{mesylate} \). This was shown not to be the case as the \( \alpha -\text{mesylate} \) under the rearrangement conditions gives largely unchanged starting material together with a small amount of \( \triangle^{11} \((12)\)-olefin (1). Jones\(^3\) and his associates have demonstrated that ketones possessing \( \alpha -\text{methylene} \) groups exhibit a characteristic band in the infrared due to \( \alpha -\text{methylene} \) bending. This band appears at \( 1400-1440 \text{cm}^{-1} \) for a six-ring ketone and disappears after deuterium exchange with \( \alpha -\text{hydrogen} \) atoms. Hecogenin (5) exhibits an intense band at \( 1429 \text{cm}^{-1} \) which disappears after deuterium exchange. The ketone obtained from olefin (3) did not exhibit absorption in the region \( 1370-1453 \text{cm}^{-1} \). This evidence would support the C-nor-D-homo-structure (3) relative to the alternative structure (6).

Olefin (2), the second olefin produced from the decomposition of the \( 12\beta -\text{mesylate} \) (4a), was found to be the endocyclic \( \triangle^{13} (17a) - \) or \( \triangle^{17} (17a) - \) double bond isomer of (3). This was established by the conversion of (3) to (2) with formic acid at room temperature.\(^4\) Both olefins were hydrogenated to give the same compound.\(^4\)

It has been found\(^5\) that when the \( 12\beta -\text{tosylate} \) (4b), was refluxed with potassium \( \text{tert-butoxide} \) in \( \text{tert-butanol} \)
for 4 hours, the products were identical to those obtained under similar conditions from the 12β-mesylate.

Similarly, the same products were formed when the 12β-tosylate (4b) was refluxed in pyridine for 7 hours. It has been assumed that expulsion of a tosylate anion from the 12β-tosylate (4b) proceeds with formation of the intermediate carbonium ion (7) and elimination of a proton (some from a, b, and c: 7) gives the olefin (8). If the attack of a hydride ion occurs on the intermediate carbonium ion (7) before elimination of a proton, the product is expected to be the saturated material (9).

Rockogenin-3-acetate-12-tosylate (4b) in ether refluxed with lithium aluminium hydride for 5 hours, gave besides the exocyclic olefin (3) and the endocyclic olefin (2) a small amount of saturated C-nor-D-homo sapogenin (9). This evidence supports the above mechanism.

In the case of the 12β-mesylate or 12β-tosylate the C₁₂-O is equatorial and the condition for Wagner Meerwein rearrangement of coplanarity is satisfied by the chains O-C₁₂-C₁₃-C₁₄ and O-C₁₂-C₁₁-C₉. Involvement of the C₉-C₁₁ bond with C₁₂-O, would mean the transitory formation of a primary carbonium ion at C₁₄ which would be less favoured than the tertiary carbonium ion at C₁₃ formed from involvement of the C₁₃-C₁₄ bond.

Endocyclic olefin (2) was the major product formed from the alkaline decomposition of the p-toluene sulphonyl
hydrazone of hecogenin (10). It has been argued\(^2\) that under the influence of base initial double bond migration occurs to give the azo form (11) (which may well exist only transitorily), and this undergoes decomposition and rearrangement through the conventional carbonium ion intermediates. In such a double bond rearrangement, the newly formed single bond between C\(_{12}\) and N will be predominately in the more stable equatorial (i.e., \(\beta\) -) configuration and the geometric factors will be similar to the \(12\beta\) - mesylate (1a).

To account for the formation of some \(\Lambda^{11\beta,12\beta}\) olefin (1) during the hydrazone decomposition it has been suggested\(^2\) that a proportion of the azo intermediate has the C\(_{12}\)-N bond in the axial \(\alpha\) -configuration (12) which would be suitably disposed for involvement of the \(11\beta\) -hydrogen atom.

It is known\(^6\) that camphor p-toluene sulphonyl hydrazone (13) undergoes Wagner Meerwein rearrangement during decomposition with alkali (sodium in ethylene glycol) to give camphene (15). The decomposition of diazo camphene (16) gives tricyclene (17), via a carbene intermediate.\(^7\) By analogy with the postulated mechanism for camphor p-toluene sulphonyl hydrazone decomposition (13, 14, 15), the mechanism (18, 19, 20) has been suggested\(^6\) for the alkaline decomposition of the hydrazone of hecogenin (10). The anti-parallel disposition of the
C18-methyl group with respect to the hydrazone residue makes unlikely a concerted pathway with the involvement of a C18=H atom. Consequently olefin (3) should not arise in significant amounts, as was observed to be the case.

In an attempt to find the position of the double bond of olefin (2, 3-OH),2 the triol formed with osmic acid was treated with sodium metaperiodate and the resulting dicarbonyl compound examined. The infrared spectrum showed a methyl ketone (1714 cm⁻¹) and a five-membered ring ketone (1740 cm⁻¹). These results would agree with the starting olefin being either Δ₁₃,(17a),, or Δ₁₇,(17a),, however favour was found for Δ₁₇,(17a) structure (2) as the cleavage product from this olefin would be a potential α'-ketol and possess weak reducing properties. The dicarbonyl compound gave a weak positive test with Fehlings solution.

Epoxides and alcohols from spiroketal C-nor-D-homo-olefins

A separable mixture of two epoxides 'P' and 'Q' (1:2) was obtained on epoxidation of the endocyclic olefin (2) with monoperphthalic acid.2 Both epoxides were reduced with lithium aluminium hydride. Subsequent acetylation at C₃ with acetic anhydride-pyridine gave the tert-alcohols named 'P'' and 'Q'' respectively. Both these tert-alcohols on dehydration with phosphorous oxychloride-pyridine gave the original olefin (2).
Reaction of the exocyclic olefin (3) with perbenzoic acid\(^1\) gave a separable mixture (3:1) of epoxides named 'A' and 'B'. The epoxide B was reduced with lithium aluminium hydride to give a diol. Mild acetylation of this diol gave the tert-alcohol 'B' different from both P' and Q'. Dehydration of this alcohol B' gave the exocyclic olefin (3).

The authors\(^1,2\) did not assign configurations to the epoxides or alcohols, and the evidence presented was insufficient to allow this to be attempted.

**Preparation of C-nor-D-homo-pregnane derivatives**

For many years synthetic routes\(^3\) have been known for the degradation of the spiroketal side chain of hecogenin to 12-oxygenated-pregnane. While the initial interest in this field has been largely concerned with the production of cortisone from readily available naturally occurring steroids, the possibility of obtaining C-nor-D-homo-pregnanes has held some interest.

Rearrangement of the tosyl hydrazone of 3\(\beta\),20\(\beta\)-dihydroxy-5\(\alpha\)-pregnan-12-one (21) with sodium in ethylene glycol has been reported\(^9\) to give 3\(\beta\),20\(\beta\)-dihydroxy-C-nor-D-homo-5\(\alpha\)-pregn-13,17\(\alpha\)-ene (22) in 30\% yield. Heating this olefin (22) with selenium gave Jacobs hydrocarbon (23), hence confirming the C-nor-D-homo skeleton.

Rearrangement of the tosyl hydrazone of 3\(\beta\),11\(\beta\)-dihydroxy-5\(\alpha\)-pregnan-12-one (24) under the same
conditions, followed by mild acetylation, gave $3\beta$-acetoxy-$11\beta$-hydroxy-C-nor-D-homo-$5\alpha$-pregn-13,17a-ene (25) in 65% yield. The position of the double bond was confirmed by chromium trioxide-pyridine oxidation of the $11\beta$-hydroxy group to give a conjugated ketone chromophore having a strong absorption at 255m$\mu$.

It was hoped that the rearrangement of the $12\beta$-mesylate and $12\beta$-tosylate of $3\beta$-acetoxy-$12\beta$-hydroxy-$5\alpha$-pregnan-11-one (26) with potassium tert-butoxide in tert-butanol would give $3\beta,11\beta$-dihydroxy-C-nor-D-homo-$5\alpha$-pregn-13,17a-ene, however both reactions gave after mild acetylation only $3\beta$-acetoxy-$11\beta$-hydroxy-$12$-keto-pregn-9,11(11)-ene (27).

Boron trifluoride catalysed rearrangements of steroidal epoxides

Steroidal epoxides fall into three classes:

(i) tetra-substituted
(ii) tri-substituted
(iii) di-substituted

An extensive study of boron trifluoride diethyl etherate catalysed rearrangements of $4,5$- and $5,6$- tri-substituted epoxides$^{10,11,12,13,14}$ and the tetra-substituted $4$-methyl-$4,5$-epoxy- and $6$-methyl-$5,6$-epoxy-epoxy-cholestanes has been made$^{15,16,17,18}$ (Table 1). Apart from these epoxide rearrangements, only isolated
<table>
<thead>
<tr>
<th>epoxide</th>
<th>non polar and unsat. products</th>
<th>C(_2)-O</th>
<th>ketonic products</th>
<th>C(_5)-O</th>
<th>hydroxy products</th>
<th>time</th>
<th>product</th>
<th>ref.</th>
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<td><img src="image5" alt="Product C5-O" /></td>
<td><img src="image6" alt="Hydroxy Product" /></td>
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<td>10</td>
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<td><img src="image3" alt="ketonic products 1" /></td>
<td><img src="image4" alt="hydroxy products 1" /></td>
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<td>5h.</td>
<td>95%</td>
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**TABLE 1 (contu.)**
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<th>Epoxide</th>
<th>Non polar and unsat products</th>
<th>Ketonic products</th>
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<td><img src="image3.png" alt="Image" /></td>
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<td>14 h.</td>
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<td>2 h.</td>
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<td>30 m.</td>
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<td>epoxide</td>
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<td>ketonic products</td>
<td>hydroxy products</td>
<td>reaction time</td>
<td>product accounted</td>
<td>ref.</td>
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<td><img src="image" alt="epoxide" /></td>
<td><img src="image" alt="non polar and unsat. products" /></td>
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<td><img src="image" alt="hydroxy products" /></td>
<td>20 m. 83%</td>
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* structure unknown.
examples are in the literature, there being no reported examples of boron trifluoride catalysed rearrangement of exocyclic epoxides in the steroid series. From an analysis of the results of studies on the 4,5- and 5,6- epoxides (see Table 1) it is apparent, that though extremely complex, various trends do develop.

A consideration of tri-substituted epoxides shows that boron trifluoride coordination with the epoxide oxygen tends to weaken the C-O bond from the more highly substituted tert-centre, where carbonium ion development is relatively favourable. All the ketonic products formed from the 4,5- and 5,6- tri-substituted epoxides result from C5-O bond cleavage.

Substituents at C3 exert both a steric and an electronic effect upon the course of the reaction. A conformational change which involves an increase in non-bonded repulsive interactions, such as a change from equatorial to axial conformation of a bulky substituent will be unfavourable. When such a path is the only way to form a ketone, the steric repulsion may be so great that a diaxial fluorohydrin is formed.

Various keto- and ketal- substituted epoxides have been studied in order to consider the electronic effect alone, on the course of the reaction.

While it has been possible to find various clear trends for tri-substituted epoxides, tetr subs...
epoxides are more complex in that cleavage of either C-O bond will lead to an equally favourable carbonium ion. For example, $4\alpha, 5\alpha$-epoxy cholestan-4-one$^{10}$ by $C_3-0$ cleavage whereas $4\beta$-methyl-$4\alpha, 5\alpha$-epoxy cholestan$^{15}$ shows $C_4-0$ cleavage to give $A$-nor-$B$-homo-$5\beta$-cholesta-6a-one. A qualitative attempt has been made by Hartshorn and Kirk$^{20}$ to account for the large variations in total yields of ketonic products (which have been found to vary from zero to over 90%) as distinct from hydroxylic and olefinic compounds formed from tetra-substituted epoxides.

The distribution of the epoxide among the various reaction products, provided that the rearrangement reactions are effectively irreversible must be determined initially by the energy levels of the corresponding transition state. The boron trifluoride catalysed rearrangement of an epoxide is believed to proceed through a transition state of considerable ionic character,$^{21}$ although the degree of development of positive charge at the reaction centre probably varies for different epoxides and reaction paths. When the stereochemistry of the epoxide permits migration of a group to be concerted with rupture of the epoxide the transition state need not involve a fully developed carbonium ion, and such a process should be strongly preferred over a non-concerted process requiring the formation of a discrete carbonium ion. It must be emphasised that the transition state should involve the minimum of
unfavourable non-bonded interactions.

It is possible with epoxides to have "axial" (28), or "equatorial cleavage" (29), depending on the resulting conformation of the oxygen atom.²⁰ It is assumed that axial cleavage (28) of an epoxide presents a reaction pathway having lower energy requirements than 'equatorial cleavage' (29), and only in special cases where structural features are present which specifically oppose the axial mode of cleavage of a particular epoxide are products found resulting from equatorial cleavage. The preference for axial cleavage was regarded as an extension of the generalisation that nucleophilic attack upon an epoxy-cyclohexane (or a protonated or Lewis acid coordinated epoxy-cyclohexane) gives the products of diaxial opening of the epoxide.²²
DISCUSSION

The C-nor-D-homo-$\Delta^{17a,18}$-olefin

3$\beta$-Acetoxy-C-nor-D-homo-$5\alpha$,25D-spirost-17a,18-ene

(3) has been prepared by base catalysed rearrangement of the 3$\beta$-succinate-12$\beta$-mesylate derived from hecogenin. Since the succinic-methyl-ester was found to hydrolyse readily, being relatively unstable even in methanol, it was considered desirable to protect the C$\beta$-hydroxyl group of hecogenin as a benzoate rather than as a succinate.

Chromatography and crystallisation enabled ready separation of the 3,12-isomeric diacetates derived by reduction and subsequent acetylation of hecogenin acetate. Hydrolysis of the more polar diacetate gave hecogenin, which it was found could be selectively benzoylated at C$\beta$.

Subsequent tosylation at C12 and rearrangement under basic conditions (potassium tert-butoxide in tert-butanol) gave the $\Delta^{17a,18}$-olefin (3).

The configuration of hydrogen atoms at C14, C16, and C17 of the $\Delta^{17a,18}$-olefin (3) must necessarily have the same configuration as in hecogenin (5). It is not possible on mechanistic grounds to assign the configuration at C13. To determine this configuration 3$\beta$-hydroxy-C-nor-D-homo-$5\alpha$,25D-spirost-17a,18-ene was hydroxylated with osmic acid, and the resulting triol (30) cleaved with
periodic acid to give $3\beta$-hydroxy-C-nor-D-homo-5\(\alpha\),25D-spirost-17a-one (31) and formaldehyde. The 'Cotton Curve' (a -29) for this 17a-ketone (31) supports the $13\alpha$-hydrogen configuration (32), rather than the $13\beta$-hydrogen (33), which would by application of the 'Octant Rule' be expected to exhibit a positive 'Cotton Curve'.

Osmium tetroxide attacks the $\Lambda^{17a,18}$-olefin (3) exclusively from the rear, $\alpha$-face, to give the 17a $\alpha$,18-dihydroxy (30) steroid. Acetylation of the triol (30) by reaction with acetic anhydride-pyridine followed by subsequent dehydration with thionyl chloride-pyridine gave the enol acetate (34) of the 18-aldehyde (35). The enol acetate (34) was a gum, and the splitting of several peaks in the NMR (\(\delta\) 7.89, 7.86 $\zeta$-CH-OAc; \(\delta\) 3.13, 3.02 $\gamma$-CH-OAc) suggested that it was probably a mixture of geometrical isomers at C$_{18}$ in the ratio 3:1. The product was readily hydrolysed by mild alkaline treatment to give the more stable 17a $\alpha$-18-aldehyde (35). Infrared absorption bands at 2703 and 1736 cm$^{-1}$ and NMR bands at \(\delta\) 0.21 (J = 2 c/s) confirm the presence of the aldehyde function. Examination of 'Dreiding' models show that ring D, cis fused to two five-membered rings will assume a boat conformation. The 17a$\beta$-hydroxy compound (36) would allow facile elimination$^{23}$ towards C$_{13}$ or C$_{17}$, however the 17a$\alpha$-hydroxy compound (37) to eliminate towards C$_{13}$ or C$_{17}$ would require unfavourable skew elimination, and in fact
elimination towards C\textsubscript{18} would be preferred. Since exo-
cyclic (enol acetate) rather than endocyclic olefin was
formed this can be regarded as establishing the 17α,\textsubscript{17a} -
configuration of the hydroxy compound (30).

The C-nor-D-homo-Δ\textsubscript{13},17α-olefin

It is known that the base catalysed rearrangement
(sodium in ethylene glycol) of the p-toluene sulphonyl
hydrazone of hecogenin acetate (10) derived by reaction of
p-toluene sulphonyl hydrazide and hecogenin acetate in
acetic acid, gave an endocyclic olefin, previously assigned
the Δ\textsubscript{17},17α structure (2). Evidence in favour of the
Δ\textsubscript{13},17α-structure (38) was first obtained from the NMR
spectrum of the olefin in which the 16α-proton appeared as
a multiplet (probably an octet) of total width 25 c/s
centered at 5.82. The chemical shift of the 16α-proton
signal agrees closely with data collected for related
spirostane derivatives, including the C-nor-D-homo-Δ\textsubscript{17α,18-}
olefin (3), and the multiplicity can best be explained as a
result of spin-spin coupling of the 16α-proton with the
three adjacent protons, namely, the 15α, 15β, and 17α
protons in the Δ\textsubscript{13},17α-structure.

Additional support for the Δ\textsubscript{13},17α structure was
obtained from the NMR spectrum of the diketone (39) derived
by oxidation of the olefin (38, 3-OH) with osmic acid,
followed by cleavage of the triol by reaction with periodic acid. The infrared spectrum for this diketone showed the presence of a five-membered ring ketone (1740 cm\(^{-1}\)) and an acetyl group (1724 and 1355 cm\(^{-1}\)). Either the \(\Delta^{13,17a}\) or the \(\Delta^{17,17a}\) structure for the parent olefin would account for this spectrum, however a low field signal in the NMR spectrum, equivalent to one proton at \(\tau\ 5.43\) was assigned to the 16\(\alpha\)-proton in the 13,17a seco structure (39). Spin-spin coupling with adjacent protons split the signal into a multiplet (sextet or octet) of total width 23.5 c/s. The alternative dicarbonyl compound (40) from a parent \(\Delta^{17,17a}\)-olefin could only give rise to a quadruplet for the 16\(\alpha\)-proton.

Treatment of the diketone (39) with toluene p-sulphonic acid in refluxing acetic acid, followed by alkaline hydrolysis gave an amorphous product which still exhibited the infrared absorption of a five-membered ring ketone (1740 cm\(^{-1}\)), although bands associated with the spiroketal system (926 and 909 cm\(^{-1}\)) were no longer present. This is only consistent with the starting olefin being the \(\Delta^{13,17a}\) isomer as the cleaved 17-keto compound (40) from the alternative \(\Delta^{17,17a}\)-olefin would not retain the characteristics of a five-membered ring ketone after rupture of the spiroketal system.

The boron trifluoride catalysed rearrangement in benzene of the \(\alpha\)-epoxide derived from the endocyclic
olefin (38) gave hecogenin acetate (18–20%). This can only
be explained in terms of a 13\(\alpha\),17a-epoxy structure, which
suffers cleavage at C 17a with rupture of the 13,14β-bond
to regenerate the normal steroid skeleton.

While various mechanisms have been proposed\(^1,2\) (see
Introduction) for the base catalysed (sodium in ethylene
glycol) decomposition of the hydrazone of hecogenin
acetate (10) it has been found that decomposition in the
aprotic solvent, diglyme, at 155° with sodium methoxide as
base gave after acetylation 3\(\beta\)-acetoxy-5\(\alpha\),25D-spirost-
11,12-ene (1) in 60% yield. This same olefin (1) is formed
as a minor product (20%) in the sodium-ethylene glycol
decomposition of the hydrazone (10).\(^2\) It was suggested
that this \(\Delta^{11,12}\) -olefin (1) may be formed \textit{via} a 12\(\alpha\) -azo
intermediate (12).\(^2\) Since in aprotic solvents the
decomposition of hydrazones is known to proceed \textit{via} a
carbenoid type intermediate\(^2\) it would seem probable that
the \(\Delta^{11,12}\) -olefin (1) may arise by a similar intermediate
when the system is sodium in ethylene glycol. It was not
possible, due to the insolubility of the hydrazone (10) in
ethylene glycol or diglyme at room temperature to study
the light catalysed reaction. It was also not possible by
gas chromatography or thin layer chromatography to analyse
the mother liquors after crystallisation of the \(\Delta^{11,12}\)
olefin (1) from the reaction product of the sodium methoxide-
diglyme decomposition of the hydrazone (10).
Configuration of epoxides and alcohols from
\[ \Delta^{13,17a} \text{ and } \Delta^{17a,18} \text{-nor-D-homo-olefin} \]

Reaction of the \[ \Delta^{13,17a} \text{-olefin (38)} \] with monoper-
phthalic acid gave a separable mixture of two epoxides
(P, 41; and Q, 42), separated by chromatography in the
ratio 1:2. Each epoxide, however, can be isolated by
separate routes. Perchloric acid hydrolysis of the mixed
epoxides (P and Q) was found to give only one diol, namely,
the \[ 13\alpha,17a,\beta \text{-diol (43)} \] which by reaction with thionyl
chloride in pyridine gave the minor epoxide P (41) in high
yield. This dehydration presumably proceeds with the
initial formation of the \[ 13\alpha \text{-chloro-sulphite ester} \]. Loss
of the ester group in the form of sulphur dioxide and
chloride ion would be concerted with trans-attack of the
\[ 17a,\beta \text{-hydroxy group}. \]

Epoxide Q (42) could be prepared by treatment of the
\[ \Delta^{13,17a} \text{-olefin (38)} \] with aqueous hypobromous acid to give
the bromo-hydrin (44) which by mild alkaline hydrolysis and
acetylation with acetic anhydride-pyridine gave epoxide Q
(42). The bromohydrin is formulated as the \[ 17a,\beta \text{-bromo-}
13\alpha \text{-hydroxy compound (44)} \] formed by stereospecific trans
addition. The NMR spectrum confirms the 17\alpha-location of
the bromo atom, for the 18-methyl signal appears as a sharp
peak at \[ \delta 8.18 \]. Attempts to convert epoxide Q (42) to the
bromohydrin with hydrobromic acid under mild conditions
were unsuccessful, and prolonged treatment caused rupture of
the spiroketal system.

Reaction of the $\Delta^{17a,18}$-olefin (3) with monoper-
phthalic acid gave a separable mixture of epoxides A (45)
and B (46).

The four epoxides A, B, P and Q were reduced with
lithium aluminium hydride followed by mild acetylation to
give the tert-alcohols; A', B', P' and Q' respectively.
It was found that alcohols A' and P' were identical (47),
and since A' is formed from a $\Delta^{17a,18}$-epoxide and P' from
a $\Delta^{13,17a}$ epoxide the alcohol must contain a 17a-hydroxyl
group. The $\Delta^{17a,18}$-olefin (3) and the derived epoxides
have the $13\chi$-hydrogen configuration, hence alcohol A' (47)
has the $13\chi$-hydrogen configuration, so that the identical
alcohol P', derived by trans attack of hydride ion on
epoxide P must have the 17a,\beta-hydroxyl group. Consequently
epoxides A and P must be the 17a,\beta,18- (45) and 13,\beta,17a,\beta-
epoxides (41) respectively. By exclusion, epoxides B and Q
must be the 17a,\alpha,18- (46) and 13,\alpha,17a,\alpha-epoxides (42)
respectively. Alcohol B' (48) would have the 13,\alpha-hydrogen-
17a,\alpha-hydroxy structure, and alcohol Q' which is not
identical with B' could have the 13,\alpha-hydrogen-17a,\alpha-
hydroxy or the 13,\alpha-hydroxy-17a,\beta-hydrogen structure. The
second of these structures was assigned to Q' (49). The
assumption is made that the same C-O bond is broken in the
lithium aluminium hydride reduction as is broken by acid-
catalysed hydrolysis, and that both reactions proceed by
trans addition. Reduction of \( P \) (41) gave the 13\( \alpha \)-hydrogen-17\( \alpha \beta \)-hydroxy compound by C\( _{13} \rightarrow O \) cleavage, hence acid hydrolysis of \( P \) must give the 13\( \alpha \),17\( \alpha \beta \)-diol (\( P' \)), 43). Acid hydrolysis of \( Q \) (42) gave the same 13\( \alpha \),17\( \alpha \beta \)-diol (\( P'' \)), 43) by C\( _{17} \rightarrow O \) cleavage, hence reduction of \( Q \) (42) must give the 13\( \alpha \)-hydroxy-17\( \alpha \beta \)-hydrogen compound (\( Q' \)).

A comparison of the NMR spectra of \( A' \), \( B' \), \( Q' \), and \( P'' \) supports the assignment of alcohol \( Q' \) as the 13\( \alpha \)-hydroxy structure (49). In all spectra, signals equivalent to six protons were analysed\(^{25} \) as a sharp singlet \[ \tilde{v} 9.17 \) (\( A' \), \( B' \)), 9.20 (\( P'' \)), 9.15 (\( Q' \)) : C\( _{19} \) methyl\] superimposed on a doublet \[ \tilde{v} 9.23, 9.17 \) : C\( _{27} \) methyl\]. Spectra of alcohols \( A' \) and \( B' \) and diol \( P'' \) showed peaks due to six protons analysed as a singlet \[ \tilde{v} 8.85 \) (\( A' \), \( B' \)), 8.77 (\( P'' \)) : C\( _{18} \) methyl\], superimposed on a doublet \[ \tilde{v} 8.93, 8.85 \) : C\( _{21} \) methyl\]. However the spectra of alcohol \( Q' \) in the same region showed only two broad bands \( \tilde{v} 8.93, 8.87 \) equivalent to six protons. There was no sharp singlet associated with the \( \tilde{> C(OH)} - C(18)H_3 \) structure, and the doublet was interpreted as the superposition of two doublets arising from the \( \tilde{> CH} - C(21)H_3 \) and \( \tilde{> CH} - C(18)H_3 \) structure.

The thionyl chloride-pyridine dehydration reactions of the alcohols \( A' \), \( B' \), and \( Q' \) were such as would be expected for trans diaxial elimination of water from the alcohols of the constrained boat ring D. The structure of
alcohol A' (50) would allow facile trans elimination\(^{23}\) of water towards either C\(_{13}\) or C\(_{17}\). Only the \(\Delta^{13,17a}\)-olefin was isolated from this reaction. Alcohol B' (51) to eliminate water towards either C\(_{13}\) or C\(_{17}\) would require cis or skew elimination, so that, in fact, elimination towards C\(_{18}\) is preferred. The only product isolated was the \(\Delta^{17a,18}\)-olefin. Finally the structure of Q' (52) is such as to allow trans elimination towards C\(_{17}\) to give the observed product, the \(\Delta^{13,17a}\)-olefin.

**Boron trifluoride catalysed rearrangements of \(\Delta^{13,17a}\)-epoxides**

The boron-trifluoride-diethyl-etherate used for these reactions was freshly distilled. The most suitable reaction time was chosen by following the course of the reaction polarimetrically and by thin layer chromatography.

It has already been mentioned that rearrangement of the \(13\alpha,17a\alpha\)-epoxide (42) with boron trifluoride gave hecogenin acetate in 20% yield, an observation which helped confirm the \(\Delta^{13,17a}\)-structure of the parent olefin.

Chromatographic separation of the other products gave a conjugated diene, a carbonyl fraction, and fluorohyrdrin. The \(\Delta^{8(14),13(17a)}\)-structure (53) is assigned to the diene on the basis of its ultra violet absorption (\(\lambda_{\text{max}}\) 259) and its NMR spectrum. This showed the absence of olefinic protons, but a band at \(\gamma\) 8.25 (3 protons) is assigned to
the 18-methyl group at the end of the conjugated system, and the 19-methyl signal showed an up-field shift to $\tau$ 9.43 compared with its normal position at $\tau$ 9.2 in related compounds in this series. This shift is attributed to shielding by the unsaturated system, and indicates a $\Delta^8,14$ component of the diene. The carbonyl fraction was a gum, apparently homogeneous by thin layer chromatography, but the NMR spectrum indicated that it was a mixture of two compounds in unequal amounts. The major component (ca. 85%) of the mixture was assigned the 13$\alpha$-acetyl- C-nor-structure (54). The acetyl group was revealed by the infrared absorption 1356 cm$^{-1}$ and by a peak equivalent to three protons at $\tau$ 7.85 in the NMR spectrum. This peak was quite distinct from the acetoxy methyl signal ($\tau$ 7.98) which disappeared after alkaline hydrolysis of a sample. Inspection of the model shows that migration of the 17,17a-bond can occur most easily trans to the epoxide oxygen, and that the resulting 13-acetyl group should have the $\alpha$-configuration. The minor carbonyl compound (55) was isolated in impure condition by treating the mixture with benzaldehyde in alkaline solution to convert the acetyl compound into its benzylidene derivative. Chromatography then gave the minor product (55) which while showing the infrared characteristics of a six-membered ring ketone (1722 cm$^{-1}$) was distinctly different from hecogenin. The $13\alpha,17a\alpha$-epoxide (50) is prevented by virtue of the
attachment of ring D to two adjoining five-membered rings from undergoing purely axial cleavage since ring D cannot assume a chair form. The two carbonium ions accessible from the \(13,17a\)-epoxide are shown (56), the \(17a\)-carbonium ion being favourably orientated for migration of the \(13,14\)-bond giving hecogenin acetate. The \(13\)-carbonium ion which can give diene by elimination reactions initiated by loss of a \(14\)-hydrogen atom can also rearrange to give two ketonic products, by migration of the \(17,17a\)-bond or the \(18\)-methyl group respectively. The minor ketone above is thought to be the \(13,17\)-methyl-\(C\)-nor-\(D\)-homo-\(17\)-ketone, produced by this \(18\)-methyl group migration. The structure is supported by its failure to form a benzylicene derivative, and by its infrared absorption at \(1722\text{ cm}^{-1}\). While the compound shows a negative 'Cotton Curve' a model shows ring D to be distorted and flexible in structure, hence preventing a clear application of the 'Octant Rule'. The low yield of the product of methyl migration may be due to the \(15\beta\)-hydrogen, \(18\)-methyl interaction which would arise in the transition state.

The final product, fluoro-hydridin (57) gave back the \(\alpha\)-epoxide on alkaline hydrolysis. The chemical shift of the \(18\)-methyl signal \(\delta 8.42\), in the NMR spectra supports the \(17a\)-fluoro structure as would be expected by analogy with the results of lithium aluminium hydride reduction and perchloric acid catalysed hydrolysis of the epoxide. This
fluoro-hydrin was the sole product when the reaction between the epoxide and boron trifluoride was carried out in ether solution.

When the fluoro-hydrin in benzene was treated with boron trifluoride the analysis of the reaction mixture proved almost identical to the boron trifluoride-epoxide-benzene reaction product mixture. The reaction was slow compared with the direct formation of these compounds from the epoxide in benzene, so it seems that a major part of the product mixture must be derived directly from the epoxide, only a minor proportion arising through the fluoro-hydrin in this case.

Rearrangement of the 13β,17αβ-epoxide (4) with boron trifluoride in benzene gave a single compound 3β-acetoxy-17αβ-hydroxy-5α,25D-spirostan-8,14-ene (58) in 96% yield. The location of the unsaturation at 8,(14) was revealed by the NMR spectrum, which showed no olefinic proton, but the 19-methyl signal was a sharp singlet at $\gamma$ 9.30, characteristic of an $\Delta^{8(14)}$-olefin. The hydroxyl group is at the 17a-position since the 18-methyl signal was a sharp singlet at $\gamma$ 8.92. The NMR and infrared spectra were normal in the region characteristic of the spiroketal system. The ultraviolet absorption exhibited the profile characteristic of a $\Delta^{8(14)}$-olefin and was quite different from the spectrum which would be expected from a $\Delta^{13,14}$-olefin which would show resemblance
to a 8(9)-olefin. Dehydration of this 17αβ-hydroxy-8,(14)-olefin (58) with thionyl chloride-pyridine gave the 8(14), 13(17a)-diene (53) identical to that formed from boron trifluoride on the α-epoxide. This supports the *trans* 13α-hydrogen,17αβ-hydroxyl configuration of this compound (58). Rearrangement presumably occurs with loss of the 8β-proton (59) with migration of the electrons to the 8,14-bond and synchronous 1,2-hydride shift of the 14β-hydrogen to the 13α-position with rupture of the C13-0 bond. The usual 15β-hydrogen,17α-*trans*-annular interaction of ring D existing as a boat would be avoided by considerable flattening of ring D by the olefinic bond. It is not possible to say why methyl migration to give the 17α-ketone does not compete.

Reaction of the 13β,17αβ-epoxide (41) with boron trifluoride in ether gave only 3β-acetoxy-13α-fluoro-17αβ-hydroxy-C-nor-D-homo-5α,25D-spirostan-5β,25D-spirostan (60) and unreacted epoxide. The position of the hydroxyl group at C17α is supported by the NMR spectrum, having a sharp singlet at 8 7.73 due to the 18-methyl group. Mild hydrolysis followed by acetylation with acetic anhydride-pyridine gave back the 13β,17αβ-epoxide (41). This fluorohydrin does not appear to be an intermediate in the reaction in benzene solution leading to the 17αβ-hydroxy-8,(14)-olefin (58) for similar reaction conditions caused
only slow degeneration of the fluorohydrin to give no identifiable products.

**Boron trifluoro catalysed rearrangements of the \( \Lambda^{17a,18\text{-epoxides}} \)**

Reaction of the \( 17a\alpha,18\text{-epoxide} \) with boron trifluoride in benzene gave one major product (60% yield) which is assigned the \( 17a\alpha-18\text{-aldehyde} \). This was identical to the aldehyde formed by hydrolysis of the enol acetate (34) formed by dehydration of the \( 3\beta,18\text{-diaoctoxy-}17a\alpha\text{-hydroxy-}C\text{-nor-D-homo-}5\alpha,25\text{D-spirostan}e \) (37). The aldehyde (61) was not epimerised by base confirming the \( \alpha \)-configuration of the aldehyde group assuming the pseudo equatorial conformation in a boat-like ring D. The aldehyde would presumably arise by cis 1,2-hydride shift of the 18-hydrogen to position 17a with formation of the 18-aldehyde(62).

Two minor products isolated from the reaction had suffered rupture of the spiroketal system and new structures remain unknown. The \( 17a\alpha,18\text{-epoxide} \) was not affected by treatment with boron trifluoride in ether solution for 1 hour.

The reaction of the \( 17a\beta,18\text{-epoxide} \) with boron trifluoride in benzene was unusual. Three products were formed and separated by chromatography. The least polar, the major product, was a compound isomeric with the epoxide, but having no unsaturation, hydroxyl or carbonyl functions
as shown by spectra, and chemical properties. The infrared and NMR spectra, however, gave indications of ether linkages additional to those in the spiroketal system, and on the basis of the evidence available the cyclic structure (63) seems the most likely. The NMR spectrum had a doublet equivalent to two protons at $\nu 6.28$ ($J = 2c/s$) which is attributed to the CH$_2$O moiety at C$_{18}$. The absence of any other signal (except those due to the $3\alpha$, $16\alpha$, and $26\alpha$-protons) in this region showed the other point of attachment of the ether to be a tertiary centre. The signal at $\nu 6.88$ is attributed to the $16\alpha$ proton, however in this compound it appears as an approximate triplet (1,2,1) of total band width 11 c/s. Examination of a model of this compound shows that the two 15-protons would couple with the $16\alpha$ proton to give a doublet ($J = 5c/s$). This doublet would be further split by the $17\alpha$ proton to give a triplet of band width 10 c/s. The stability of the ether to prolonged treatment with lithium-ammonia or to lithium aluminium hydride is consistent with the cyclic ether ring structure, and together with the chemical shift of the C-18 protons eliminates the possibility of a four-membered ring involving C-13. Acidic reagents (hydrobromic acid in acetic acid or borontrifluoride-acetic anhydride) rapidly attacked both the ether bridge and the spiroketal system giving no recognisable products. This can be rationalised on the basis of structure (63), for protonation of the ether
bridge with rupture of the C₁₅-0 bond would lead to unsaturation at 8₉(14) or 14₄(15). The resulting activation of the C₁₆-0 bond would allow collapse of the spiroketal side chain. A possible mechanism (64) to explain the formation of cyclic ether involves a two-step process involving an initial four-membered ring as an unstable intermediate. This intermediate can either give the cyclic ether, or by loss of the 17α-proton give the 18-hydroxy-Δ₁₃,17a-olefin (65).

The second product of the epoxide-boron trifluoride reaction was a fluoro-alcohol probably the 17α-fluoro-18-hydroxy compound (66). The fluoro-alcohol was completely stable to vigorous alkaline treatment, however, the structure is supported by its conversion to the 18-acetate which showed infrared absorption at the unusually high frequency of 1760 cm⁻¹, probably resulting from the proximity of the fluorine atom. The difficulty in forming the epoxide from the fluorohydrin may be due to steric difficulties in assuming the trans conformation required for the formation of 17α,18-epoxide. The presence of a trace (4-5%) of 18-hydroxy-Δ₁₃,17a-olefin (65) in the hydroxylic fraction was demonstrated by oxidation of the residues (using 2,3-dichloro-5,6-dicyano-benzoquinone) after crystallisation of the fluorohydrin. The unsaturated alcohol was oxidised selectively to give 3β-acetoxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene 18-aldehyde (67) characterised by
infrared absorption bands at 2740 cm\(^{-1}\) (\(-\text{CHO}\)) and 1689 cm\(^{-1}\) (\(\text{C=O-CHO}\)), and separated from the unreacted fluoro-alcohol by chromatography.

Boron trifluoride catalysed rearrangement of the \(17a-\beta\)-epoxide (45) in ether gave a mixture of cyclic ether (63) and 18-hydroxy-\(\Lambda^{13,17a}\)-olefin (65). The structure of this 18-hydroxy-olefin followed from the reduction of its acetate by lithium-ethylamine to give \(3\beta\text{-acetox}-\text{C-nor-D-homo-5}x,25D\text{-spirost}-13,17a\text{-ene (38)}\). It could also be converted to the \(\Lambda^{13,17a}\text{-18-aldheyde (67)}\) by oxidation with 2,3-dichloro-5,6-dicyano-benzoquinone. The \(\text{C}_{18}\) protons appeared as a doublet at \(\tau\) 5.92 but in other respects the NMR spectra was very similar to that of the \(\Delta^{13,17a}\text{-hydrocarbon. The absence of any fluoro-alcohol in this product is another remarkable feature of this epoxide reaction.}\n
Rearrangement of the 17a,18-epoxides with perchloric acid

Reaction of the \(17\alpha\text{-18-epoxide (46)}\) with perchloric acid in aqueous acetone-methylene chloride gave the 18-aldheyde (61) in higher yield (85\%) than from the boron trifluoride catalysed rearrangement of the same epoxide. The remainder of the product was the 18-hydroxy-\(\Delta^{13,17a}\)-olefin (65).

The reaction of the \(17\beta\text{-18-epoxide (45)}\) with
perchloric acid in aqueous acetone-methane chloride gave
the 18-hydroxy-$\Delta^{13,17a}$-olefin (65) in 66% yield.

Table of chemical shifts of protons at C-18, C-19, and C-21
in NMR spectra of
C-nor-D-homo-spirostan $\tau$ values

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-18protons</th>
<th>19-Me</th>
<th>21-Me</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17a$\alpha$-methyl series</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 $\beta$-acetoxy 17a$\alpha$-methyl-C-nor-5$\alpha$,25D-spirostan (parent compound)</td>
<td>9.19(5e/s)</td>
<td>9.18</td>
<td>9.03(6 e/s)</td>
</tr>
<tr>
<td>17a$\beta$-OH</td>
<td>(47)</td>
<td>8.85</td>
<td>9.19</td>
</tr>
<tr>
<td>17a$\beta$-OH - $\Delta$8 (1H)</td>
<td>(58)</td>
<td>8.92</td>
<td>9.30</td>
</tr>
<tr>
<td>13$\alpha$-OH</td>
<td>(49)</td>
<td>8.90(4)</td>
<td>9.25</td>
</tr>
<tr>
<td>13$\alpha$-OH, 17a$\beta$-OH</td>
<td>(43)</td>
<td>8.77</td>
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<tr>
<td>13$\alpha$-OH, 17a$\beta$-F</td>
<td>(57)</td>
<td>8.42</td>
<td>9.20</td>
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<tr>
<td>13$\alpha$-OH, 17a$\beta$-Br</td>
<td>(1H)</td>
<td>8.18</td>
<td>9.13</td>
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<tr>
<td>13$\alpha$-F, 17a$\beta$-OH</td>
<td>(60)</td>
<td>8.73</td>
<td>9.20</td>
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<tr>
<td><strong>17a$\delta$-methyl series</strong></td>
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<td></td>
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</tr>
<tr>
<td>3 $\beta$-acetoxy-17a,$\delta$-methyl-7-nor-D-homo-5$\alpha$,25D-spirostan (parent compound)</td>
<td>9.12(4)</td>
<td>9.18</td>
<td>9.03(6)</td>
</tr>
<tr>
<td>17a$\alpha$-OH</td>
<td>(48)</td>
<td>8.85</td>
<td>9.18</td>
</tr>
<tr>
<td>Compound</td>
<td>C-18protons</td>
<td>19-Me</td>
<td>21-Me</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>-------</td>
<td>-------</td>
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<tr>
<td><strong>Δ13(17a)-series</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3β-acetoxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (parent compound)</td>
<td>8.33</td>
<td>9.22</td>
<td>8.87(6.5)</td>
</tr>
<tr>
<td>8(14),13(17a)-diene</td>
<td>8.25</td>
<td>9.43</td>
<td>8.88(6.5)</td>
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<tr>
<td>18-OH</td>
<td>5.82</td>
<td>9.22</td>
<td>8.80(6)</td>
</tr>
<tr>
<td>18-oAc</td>
<td>5.45</td>
<td>9.22</td>
<td>8.92(6)</td>
</tr>
<tr>
<td><strong>Epoxides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13β,17αβ-</td>
<td>8.65</td>
<td>9.17</td>
<td>8.87(6)</td>
</tr>
<tr>
<td>13α,17αα-</td>
<td>8.68</td>
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<tr>
<td>17α/β,18-</td>
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</tr>
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<td>17αα,18-</td>
<td>7.27</td>
<td>9.22</td>
<td>9.07(7)</td>
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<td><strong>Miscellaneous</strong></td>
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<tr>
<td>Δ17α(18)-olefin</td>
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<td>9.20</td>
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<td>18-OH0</td>
<td>0.21(7)</td>
<td>9.25</td>
<td>9.02(7)</td>
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<td>cyclic ether</td>
<td>6.23</td>
<td>9.16</td>
<td>8.98(6)</td>
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<td>13α-acetyl compound</td>
<td>7.85</td>
<td>9.15</td>
<td>8.98(5.5)</td>
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<tr>
<td>17α-ketone</td>
<td>8.80</td>
<td>9.22</td>
<td>8.97(6.5)</td>
</tr>
<tr>
<td>17αα,18-diol</td>
<td>6.33</td>
<td>9.22</td>
<td>8.95(6.5)</td>
</tr>
<tr>
<td>enol acetate</td>
<td>3.13,3.02</td>
<td>9.22</td>
<td>9.05(6.5)</td>
</tr>
<tr>
<td>17α-F,18-OH</td>
<td>6.40</td>
<td>9.05</td>
<td>8.90(6.0)</td>
</tr>
<tr>
<td>17α-OH,18-oAc</td>
<td>5.96</td>
<td>9.25</td>
<td>9.02(6.0)</td>
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</tbody>
</table>
**Pregnane C-nor-D-homo-olefins**

The previous study of the boron trifluoride catalysed rearrangements of ring D epoxides of the C-nor-D-homo spirostane series led to interest in analogous compounds having the conformationally restraining ring E of the spiroketal side chain removed.

Hecogenin acetate was converted to the 12-oxygenated pregnane derivative by methods improved from the original method of Marker. Hecogenin acetate (68) was converted first into pseudo-hecogenin acetate (69) by heating under reflux with methylamine hydrochloride in acetic anhydride. Hydrogen peroxide oxidation, followed by subsequent hydrolysis of the resulting $\beta$-ester (70) by heating under reflux with acetic acid, gave the $\Lambda,16,17$-pregnan-12,20-dione (71). Hydrogenation of the olefin (71) proceeded from the least hindered $\alpha$-face to give $\Sigma$-pregnan-12,20-dione (72). Before reduction of the 20-ketone could be attempted it was necessary to protect the 12-ketone as the ethylene-dioxy-compound (73) made by selective reaction of the 12-ketone with ethylene glycol-boron trifluoride. Subsequent reduction of the 20-ketone using the method of Huang Minlon, followed by hydrolysis gave $5\alpha$-pregnan-12-one (74).

By analogy with the base catalysed rearrangement of the p-toluene sulphonyl hydrazone of $3\beta,20\beta$-dihydroxy-5$\alpha$-pregnan-12-one (21), $3\beta,11\beta,20\beta$-tri-hydroxy-5$\alpha$-pregnan-12-one$^9$ (24) and hecogenin acetate (68) which give the
respectively \( \Lambda^{13,17a} \)-C-nor-D-homo compounds, it was thought likely that similar rearrangement of the hydrazone of 3\(\beta\)-benzoxyl-5\(\chi\)-pregnan-12-one (74, 3-oBz) would give 3\(\beta\)-hydroxy-C-nor-D-homo-5\(\chi\)-pregn-13,17a-ene (75).

The 12-hydrazone of 3\(\beta\)-benzoxyl-5\(\chi\)-pregnan-12-one made by reaction of the 12-ketone with p-toluene sulphonyl hydrazide in acetic acid was decomposed at 150\(^\circ\) with sodium in ethylene glycol. The resulting olefin, assigned the C-nor-D-homo-\(\Lambda^{13,17a}\)-olefin (75) was formed in 60\% yield and was characterised as the 3-benzoate. A band at \(\gamma\) 8.43, equivalent to three protons, in the NMR spectrum is assigned to the 18-methyl adjacent to the \(\Lambda^{13,17a}\)-double bond.

Oxidation of the hydroxy olefin (75) with osmic acid followed by cleavage of the triol with lead tetraacetate in acetic acid-tert butanol gave a di-carbonyl compound (76) as an oil. The infrared spectrum showed the presence of a five-membered ring ketone (1748 cm\(^{-1}\)) and an acetyl group (1721 and 1360 cm\(^{-1}\)). The NMR spectrum showed the three protons of the acetyl group as a sharp singlet at \(\gamma\) 8.91. This is only consistent with the starting olefin being the C-nor-D-homo-\(\Lambda^{13,17a}\) compound (75).

By analogy with the base catalysed rearrangement of the 12/\(\beta\)-tosylate in the spirostane series which gave the C-nor-D-homo-\(\Lambda^{17a,18}\)-olefin (3), it was considered likely
that rearrangement of the 12β-tosylate (77a), derived from
the tosylate of the 12β-alcohol (77b) formed by reduction
of 5α-pregn-12-one (74), might give the C-nor-D-homo-
\[\Delta^17a,18\]-pregnene (78).

Reduction of 3β-benzoxy-5α-pregn-12-one (74, 3-oBz) with lithium borohydride gave the two C12-epimeric
alcohols separated by chromatography in the ratio 3:2. The
least polar alcohol, the major product, is assigned the
β-configuration (77b) on the basis of its NMR spectrum.
The 12α, axial hydrogen atom appears as a quartet,
centered at \(\gamma\) 6.52, while the 12β, equatorial hydrogen
atom of the 12α-alcohol (77c), the minor product, appears
as a triplet centred at \(\gamma\) 7.84. It is known that in six-
membered ring systems the axial protons absorb at a higher
field than do their epimeric equatorial counterparts.

The configuration of these epimeric alcohols is
further consistent with the splitting pattern to be expected
for the 12-axial and equatorial hydrogen atoms respect-
ively. The 12α-hydrogen atom of the 12β-alcohol appears
as a quartet of all four peaks equivalent and with a total
width 15cps. This arises by the spin-spin interaction of
the 12α-hydrogen with the C11 axial and equatorial protons.
Various attempts by Karplus,\(^{32}\) and more recently by
Williamson and Johnson,\(^{33}\) have been made to calculate the
dependence of coupling constants, between vicinal protons
with dihedral angle \(\phi\). The results are summarised as:-
Application of this data to the 12α-hydrogen atom confirms that it will appear as a quartet, the bands having equal intensity and the experimentally found coupling constants of $J_{aa}=10\text{c/s}$ and $J_{ae}=5\text{c/s}$ are within the expected limits.

The epimeric 12α-alcohol (77c) shows the 12β-equatorial hydrogen atom as a triplet with a total bandwidth of 5c/s. This is the result of spin-spin coupling of the 12β-hydrogen atom with the 11-axial and equatorial protons. Since the 12β-hydrogen is symmetrically disposed at an angle of 60° to both the C11 hydrogen atoms it would be expected from the above table to exist as a triplet. The experimental coupling constant $J_{ae}$ was found to be 2.5 c/s.

The 12α-tosylate (77d) made from the 12α-alcohol (77c) by reaction of p-toluene sulphonyl chloride in pyridine, was unchanged after heating under reflux with potassium tert-butoxide in tert-butanol.

The 12β-tosylate (77a) made from the 12β-alcohol (77b) gave on similar base treatment and rebenzoylation of the 3-hydroxyl group, 3β-benzoyl-C-nor-D-homo-5α-pregnane-13α,7α-ene (75, 3-oBz) by direct crystallisation.
Chromatography of the mother liquors gave a solid which melted at 92-93°. This solid was shown to be a mixture of the C-nor-D-homo-Δ^{13,17α}-olefin (75, 3-oBz) and the C-nor-D-homo-Δ^{17,17α}-olefin (79, 3-oBz). Infrared spectrum analysis excluded the possibility of the exocyclic olefin (78) being present.

A sample of the above olefin mixture (79), after hydrolysis of the C_3-benzoate, was hydroxylated with osmic acid, and the resulting triol cleaved with lead tetra acetate. The infrared spectrum of the resulting oil showed strong acetyl absorption (1721 and 1360cm^{-1}) and the presence of some five-membered ring ketone 1748cm^{-1}. This suggested the presence of the Δ^{13,17α}-olefin in the original olefin mixture. There was no aldehyde absorption at 2700cm^{-1} indicating that no pregnan-11,12-ene was in the olefin mixture. The NMR spectrum of the di-carbonyl compound showed the presence of two acetyl bands at \( \delta \) 7.87 and \( \delta \) 7.91 in the ratio 2:1. The band at \( \delta \) 7.91 has been assigned to the acetyl group derived by cleavage of the Δ^{13,17α}-olefin. Evidence consistent with the major component of the olefin mixture being the C-nor-D-homo-Δ^{17,17α}-olefin is that a triplet centred \( \delta \) 9.07 \( J=7.0 \)cps is assigned to the terminal methyl of the ethyl side-chain split by the methylene group adjacent to the Δ^{17,17α} double bond. The equivalent terminal methyl in pent-2-ene appears as a triplet centred \( \delta \) 9.01 \( J=7.0 \)cps.
The methyl group adjacent to the double bond in pent-2-ene appears as multiplet centred \( \tau \ 8.35 \), while the 18 methyl group of the \( \Lambda^{17,17a} \)-olefin appears as a singlet at \( \tau \ 8.38 \).

Reaction of 3\(\beta\)-benzoxo-C-nor-D-homo-5\(\alpha\)-pregnan-13,17a-ene (75, 3-oBz) with monoperphthalic acid gave a mixture of two epoxides separated by chromatography in the ratio 1:8. The least polar epoxide, formed as the minor product, has been assigned the \( \beta \) -epoxide \( \Lambda(80) \). The \( \beta \) -face is more hindered to electrophilic attack than the \( \alpha \) -face. The formulation of the major reaction product as the \( \alpha \) -epoxide \( \Lambda(81) \) is consistent with the NMR spectrum of the diol \( \Lambda(82) \) formed by lithium aluminium hydride reduction of the epoxide, which shows the 18-methyl group as a singlet at \( \tau \ 8.83 \). Unlike the reduction of the 13\(\alpha\),17a\(\alpha\)-epoxide \( \Lambda(42) \) in the C-nor-D-homo spirostane series, which gave the 13\(\alpha\) -hydroxy-17a\(\beta\)-hydrogen compound \( \Lambda(49) \), the reduction of the 13\(\alpha\),17a\(\alpha\)-epoxide \( \Lambda(81) \) in the pregnane series, ring D no longer being constrained into a boat conformation by fusion to ring \( \Lambda \), an alternative trans diaxial opening of the epoxide is possible to give the 13\(\beta\) -hydrogen-17a\(\alpha\) -hydroxy compound \( \Lambda(82) \), ring D existing in the more stable chair conformation. Had the epoxide been assigned the alternative \( \beta \) -configuration, similar \( \beta \) -face diaxial opening would have given the 13\(\beta\)-hydroxy-17a\(\alpha\) -hydrogen compound \( \Lambda(83) \), in which the NMR absorption of the 18-methyl group would be a doublet.
Boron trifluoride catalysed rearrangement of the
13\(\alpha\),17a\(\alpha\)-epoxide

The boron trifluoride catalysed rearrangement of 3\(\beta\)-benzoxyl-13\(\alpha\),17a\(\alpha\)-epoxy-C-nor-D-homo-5\(\alpha\)-pregnane (81) in benzene gave three products, which were separated by chromatography. The first compound was a hydrocarbon isolated as an oil. Kept overnight this clear oil turned a deep orange, suggesting the hydrocarbon was decomposing. The second compound has been assigned the \(\Delta^8,14\)-17a-hydroxy structure (84) on the basis of the following evidence. The infrared spectrum shows the presence of a hydroxy-group at 3571 cm\(^{-1}\). The NMR spectrum did not show the presence of a proton adjacent to a hydroxy group, showing the hydroxy-group to be tertiary. There was no olefinic protons in the NMR spectrum, and the 19-methyl signal had shifted from \(\tau\) 9.18 in the parent epoxide to \(\tau\) 9.25, consistent with shielding associated with the \(\Delta^8,(14)\)-double bond.\(^{27}\) The 18-methyl signal appeared as a sharp singlet at \(\tau\) 8.85, consistent with the assigned 17a-hydroxy structure.

The structure of the third compound, an olefinic alcohol remains unknown. The infrared spectrum shows the presence of a hydroxyl group by absorption at 3597 and 3460 cm\(^{-1}\). The NMR spectrum suggested this alcohol to be tertiary since no absorption was apparent due to a proton adjacent to a hydroxy group. The spectrum also showed an
olefinic proton (7.4.75), a methyl group adjacent to a
double bond (7.8.42), and absorption due to two methyl
groups at 7.9.02 and 7.9.27 respectively.

Table of chemical shifts of protons at C-18, C-19 and C-21
in the NMR spectra of
pregnanes and C-nor-D-homo-pregnanes. (7 values)

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-19</th>
<th>C-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>5α pregnane series</td>
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<td></td>
</tr>
<tr>
<td>3β -O Bz 12 C=O (74, 3-O Bz)</td>
<td>9.07</td>
<td>9.03</td>
</tr>
<tr>
<td>3β -O Bz 12β-OH (77b)</td>
<td>9.11</td>
<td>9.36</td>
</tr>
<tr>
<td>3β -O Bz 12 α-OH (77c)</td>
<td>9.10</td>
<td>9.38</td>
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</table>

<table>
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<tr>
<th>C-nor-D-homo-5α-pregnane series</th>
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</tr>
</thead>
<tbody>
<tr>
<td>3β -O Bz △ 13,17a- (75, 3-O Bz)</td>
<td>9.23</td>
<td>8.47</td>
</tr>
<tr>
<td>3β -O Bz △ 17,17a- (impure)(79, 3-O Bz)</td>
<td>9.20</td>
<td>8.47</td>
</tr>
<tr>
<td>diketone from 3β-OH △ 13,17a- (76)</td>
<td>9.20</td>
<td>7.90</td>
</tr>
<tr>
<td>diketone from 3β-OH △ 17,17a- (impure)</td>
<td>9.22</td>
<td>7.85</td>
</tr>
<tr>
<td>3β -O Bz 13α,17a α-epoxide (81)</td>
<td>9.18</td>
<td>8.78</td>
</tr>
<tr>
<td>3β -O Bz 13β,17a β-epoxide (80)</td>
<td>9.25</td>
<td>8.78</td>
</tr>
<tr>
<td>3β -O H 13β-H 17a α-OH (82)</td>
<td>9.3</td>
<td>8.82</td>
</tr>
<tr>
<td>3β -O Bz △ 8(14)- 17a α-OH (84)</td>
<td>9.25</td>
<td>8.85</td>
</tr>
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</table>
EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured in chloroform in a 1dm. polarimeter tube at room temperature. Micro-analyses were carried out at the University of Otago. Infrared absorption measurements were in carbon disulphide solutions and were recorded with a Perkin-Elmer Model 221 double-beam instrument equipped with a sodium chloride prism. Ultra violet absorption data was obtained with methanol solutions, and recorded with a Beckman DK 2-A spectrophotometer. Nuclear magnetic resonance measurements were obtained with a Varian A-60 instrument at 60Mc in deuterochloroform solution, using tetramethylsilane as an internal reference. Alumina used for chromatography was P. Spence Grade 'H'; deactivated alumina refers to grade 'H' to which 5% of 10% aqueous acetic acid has been added. Silica gel used for chromatography was J. Crosfield and Sons. Light petroleum refers to the fraction of b.p. 50-70°. The phrase 'isolated in the usual manner' implies that the reaction mixture was poured into ether-water, and the organic phase washed to neutrality with aqueous sulphuric acid and, or, aqueous sodium bicarbonate and water. The organic phase was then dried with anhydrous magnesium sulphate, and after filtration to remove the magnesium sulphate, the solvents were removed in vacuo on a water bath.
Reduction of hecogenin acetate$^{34}$

Hecogenin acetate (100g) in methanol (1.5l) was heated under reflux with sodium hydroxide (50g) and water (60ml) for 1 hr. A suspension of sodium borohydride (6.0g) in aqueous methanol (90%, 48ml) containing sodium hydroxide (2g) was added dropwise over 2hr. Heating was continued for a further 2 hr. The product, isolated via chloroform, was acetylated by treatment with pyridine (40ml) and acetic anhydride (300ml) at 100° for 2 hr. Isolation of the steroidal material and crystallisation from methylene chloride-methanol gave the 3β,12β-diacetate (48g), m.p. 210-211°, [α]$^D$ -64.5° (c 1.2l). (Lit.$^{34}$ m.p. 200-202°, [α]$^D$ -64° (c 0.5 in acetone)).

The mother liquors were evaporated to dryness and the steroidal material adsorbed onto alumina (1.5kg). The 12β-isomer was eluted with light petroleum-benzene (2:1) (21g), m.p. 152-155°, [α]$^D$ -16° (c 1.02). Elution with benzene gave further 12β-acetate (25g), m.p. and m.m.p. 210-211°.

Hydrolysis of 3β,12β-diacetoxy-5α,25D-spirostan.$^{35}$

A solution of 3β,12β-diacetoxy-5α,25D-spirostan (78g), potassium hydroxide (100g) in aqueous methanol (11, 90%) was heated under reflux for 5 hr. Isolation in the usual manner gave hecogenin (61g), m.p. 218-220°, [α]$^D$ -64° (c 1.03). (Lit.$^{35}$ m.p. 218.5-220.5°, [α]$^D$ -63.8° (c 1.05 in acetone)).
3β-Benzoyloxy-12β-hydroxy-5α,25D-spirostan

To a stirred solution of rockogenin (61g) in dry benzene (300ml) and pyridine (60ml) was added over 30 min. benzoyl chloride (19.5ml; 1.3 mole) in benzene (20ml). The reaction mixture was allowed to stand for a further 1 hr. Isolation of the steroidal material in the usual manner and crystallisation from methanol gave 3β-benzoyl-12β-hydroxy-5α,25D-spirostan: as needles (47g), m.p. 224-226°, [α]D-5hO (c 1.08), λmax. 3610, 1727 and 1274cm⁻¹. (Found: C, 76.1; H, 9.2. C34H48O5 requires C, 76.1; H, 9.0%).

3β-Benzoyloxy-12β-tosyl-5α,25D-spirostan

A solution of 3β-benzoyl-12β-tosyl-5α,25D-spirostan (20g) in pyridine (100ml) was added to a solution of p-toluene sulphonyl chloride (20g) in pyridine (50ml). The resulting solution was protected from atmospheric moisture and kept at room temperature for 5 days. The excess toluene sulphonyl chloride was decomposed by gradual transfer of the reaction mixture to an excess of ice-water. The resulting white solid was filtered, dried and recrystallised from ether to give 3β-benzoyloxy-12β-tosyl-5α,25D-spirostan: as needles (21g), m.p. 132-135° (decomp.), λmax. 1724, 1241 and 1176cm⁻¹.
Base catalysed rearrangement of

3β-benzyloxy-12β-tosyl-5α,25D-spirostan

To a solution of potassium tert-butoxide in tert-butanol (potassium, 12g; tert-butanol, 3l.) was added
3β-benzyloxy-12β-tosyl-5α,25D-spirostan (35.5g), and the mixture heated under reflux, in a nitrogen atmosphere for
18 hr. The solvent was removed in vacuo, water being added periodically to aid in the removal of tert-butanol. The
residue, in pyridine (100ml) and acetic anhydride (40ml) was kept on a steam bath for 1 hr. Isolation of the
steroidal material in the usual manner and crystallisation from hexane gave 3β-acetoxy-C-nor-D-homo-5α,25D-spirost-
17a,18-ene (10.5g), m.p. 223-225°, [α]D -66° (c 1.14).
(Lit.1 m.p. 221-225°, [α]D -80.6°.) After the removal of
solvents from the mother liquors the steroidal residue was adsorbed onto alumina (600g). Elution with light petroleum-
benzene (2:1) gave further 3β-acetoxy-C-nor-D-homo-5α,25D-
spirost-17a,18-ene (4.9g), m.p. and m.m.p. 223-225°.

Hecogenin acetate toluene p-sulphonyl hydrazone

To a solution of hecogenin acetate (20g) in acetic acid (600ml) was added p-toluene sulphonyl hydrazone (20g).
After 2 min. solid began to separate, and after further standing for 1 hr. the solid was filtered, washed with
aqueous ethanol, and dried (24.5g), m.p. 264-265° (decomp.),
[α]D -15° (c 1.03). (Lit.2 m.p. 274° (decomp.), [α]D -15°)
Sodium (7.5g) was reacted with diethylene glycol (500ml) with warming. The solution was cooled to 50° and hecogenin acetate toluene p-sulphonyl hydrazone (24.5g) added. The mixture was heated to 130-140°C and kept at that temperature until no further gas evolution was apparent (6 hr). After being cooled to 60° the mixture was diluted with water when a white solid separated. This was filtered, washed with aqueous ethanol and dried.

Recrystallisation from methanol gave 3β-hydroxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (9.0g), m.p. 119-123°, [α]_D-41° (c 1.03). (Lit.² m.p. 120-125°, [α]_D-55°).

The mother liquors after evaporation to dryness were acetylated by treatment with acetic anhydride, pyridine (1:10) at room temperature, overnight, and the isolated steroidal material adsorbed onto alumina (500g). Elution with light petroleum gave after crystallisation from methanol 3β-acetoxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (3.9g), m.p. 141-144°, [α]_D-43° (c 1.01). (Lit.² m.p. 142-145°, [α]_D-57°).

Acetylation of 3β-hydroxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene

A solution of 3β-hydroxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (4g) in pyridine (20ml) and acetic anhydride (6ml) was kept at room temperature for 18 hr.
Isolation of the steroidal material in the usual manner and crystallisation from methanol gave \(3\beta\)-acetoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan-13,17a-ene (3.5g), m.p. 142-145\(^\circ\), \([\alpha]\)_D -43\(^\circ\) (c 0.91).

**Sodium methoxide decomposition of hecogenin acetate toluene p-sulphonyl hydrazone**

To a 1.0N suspension of sodium methoxide in diethylene glycol dimethyl ether (50ml) was added hecogenin acetate toluene p-sulphonyl hydrazone (2g) and the resulting mixture heated, under nitrogen, at 155\(^\circ\) until no further gas evolution was apparent, (2 hr). The solution was cooled and poured into water. The steroidal material was isolated via ether. After removal of solvents the steroidal material was acetylated by reaction with pyridine-acetic anhydride (10:1) at 100\(^\circ\) for 1 hr. Isolation in the usual manner, and crystallisation from methanol gave 3\(\beta\)-acetoxy-5\(\alpha\),25D-spirostan-13,12-ene as needles (865mg), m.p. 204-208\(^\circ\), \([\alpha]\)_D -33\(^\circ\) (c 0.94). (Lit.\(^2\) m.p. 206-210\(^\circ\), \([\alpha]\)_D -44\(^\circ\)).

**Hydroxylation of 3\(\beta\)-hydroxy-C-nor-D-homo-5\(\alpha\),25D-spirostan-13,17a-ene**

A solution of 3\(\beta\)-hydroxy-C-nor-D-homo-5\(\alpha\),25D-spirostan-13,17a-ene (2g) and osmium tetroxide (1g) in pyridine (60ml) was kept at room temperature for 3 days. A solution of sodium sulphite (4g) in water (60ml) was added,
and the resulting solution stirred for 30 min. The steroidal material was extracted via chloroform, and after removal of solvents was adsorbed onto deactivated alumina (50g). Elution with benzene gave unchanged starting material (600mg), m.p. and m.m.p. 120-125°. Elution with ether gave triol which was crystallised from ethyl acetate as needles (1.14g), m.p. 228-229°, \([\alpha]_D^{21} = 32°\) (c 1.12). (Lit.\(^2\) m.p. 229-233°, \([\alpha]_D^{1} = 40°\)).

**Cleavage of triol\(^2\)**

A solution of triol (600mg) in methanol (50ml) was added to an aqueous solution of periodic acid (7ml; 10%), and the resulting mixture kept at room temperature for 2 days. Water was then slowly added and the flocculent white precipitate filtered and dried (555mg). Recrystallisation from aqueous methanol gave 13,17a-seco steroidal as fine needles (400mg), m.p. 157.5-160°, \([\alpha]_D^{31} = 31°\) (c 0.83), \(\nu_{\text{max.}}\) 3636 cm\(^{-1}\) (OH), 1748 cm\(^{-1}\). (5-membered ring ketone), 1724 and 1355 cm\(^{-1}\) (COCH\(_3\)). (Lit.\(^2\) m.p. 157-160°, \([\alpha]_D^{21} = 21°\)).

**Rupture of spirotetral side-chain**

A solution of 13,17a-seco steroid (50mg) and p-toluene sulphonie acid (30mg) in acetic acid (10ml) was refluxed for 6 hr. The solution was poured into water and the steroidal material extracted into ether, washed with
aqueous sodium bicarbonate and water, and dried. After the removal of solvents the resulting oil was hydrolysed by treatment with ethanolic aqueous potassium hydroxide for 18 hr. at room temperature. Isolation of the steroidal material in the usual manner gave an oil (40 mg), $J_{\text{max.}}$ 3636 cm$^{-1}$, 1748 cm$^{-1}$ (5-membered ring ketone). There was no absorption in the infrared spectrum at 1724 or 1355 cm$^{-1}$ (COCH$_3$) or in the normal spiroketal absorption region.

Hydroxylation of 3\(_\beta\)-acetoxy-C-nor-D-homo-5\(\alpha\),25D-spirost-17a,18-ene

A solution containing 3\(_\beta\)-acetoxy-C-nor-D-homo-5\(\alpha\),25D-spirost-17a,18-ene (500 mg), osmium tetroxide (500 mg), pyridine (0.3 ml), benzene (12.5 ml) and dioxan (10 ml) was kept at room temperature for 6 days. A solution of sodium sulphite (2 g) in water (30 ml) and pyridine (35 ml) was added and the resulting mixture stirred until the solution became orange (1 hr). The steroidal material was isolated via chloroform and after removal of solvents was adsorbed onto deactivated alumina (20 g). Elution with light petroleum-benzene (1:1) gave unreacted starting olefin (80 mg). Elution with ether gave 3\(_\beta\)-acetoxy-17a\(\alpha\),18-diol (410 mg), m.p. 215-216$^\circ$, $[\alpha]_D$-33$^0$ (c 1.132), $J_{\text{max.}}$ 3558, 3448, 1742 and 1244 cm$^{-1}$. (Found: C, 70.9; H, 9.4.

C$_{29}$H$_{46}$O$_6$ requires C, 71.0; H, 9.45%).
Periodic acid cleavage of $3\beta$-acetoxy-17a,18-diol

To a solution of $3\beta$-acetoxy-17a,18-diol (60mg) in ethanol (5ml) was added aqueous periodic acid (periodic acid, 3mg; water, 0.3ml) and the resulting mixture kept at room temperature for 1½ hr. The solution was poured into water and the steroidal material isolated via ether. Crystallisation from methanol gave $3\beta$-acetoxy-18-nor-C-nor-D-homo-5,25D-spirostan-17a-one (4mg), m.p. 232-235°, $\left[\alpha\right]_D^{20} = -81^0$ (c 1.0), R.D. in methanol: $\left[\psi\right]_D^{20} = 298 -2815^0$; $\left[\psi\right]_D^{26} = 263 +90^0$. (Lit. $^1$ m.p. 227-232°, $\left[\alpha\right]_D^{20} = -95.1^0$).

Acetylation of the $3\beta$-acetoxy-17a,18-diol

A solution of $3\beta$-acetoxy-17a,18-diol (300mg) in pyridine (2ml) and acetic anhydride (0.3ml) was kept at room temperature for 18 hr. After isolation of the steroidal material, crystallisation from methanol gave $3\beta,18$-diacetoxy-17a,18-dihydroxy-C-nor-D-homo-5,25D-spirostan as needles, (260mg), m.p. 218-219°, $\left[\alpha\right]_D^{20} = -22^0$ (c 0.90), $\left[\psi\right]_D^{20} = 3584$, 1742 and 1342 cm$^{-1}$. (Found: C, 70.1; H, 9.3. C$_{31}$H$_{48}$O$_{7}$ requires C, 69.9; H, 9.1%). (Lit. $^1$ m.p. 212-219°).
Dehydration of 3β,18-diacectoxy-17α,5α,25D-spirostane

To a solution of 3β,18-diacectoxy-17α,5α,25D-spirostane (200mg) in pyridine (10ml) at -20° was added thionyl chloride (0.2ml). The resulting mixture was allowed to come to room temperature over 15 min., then poured into water. The steroidal material, isolated via pentane, was adsorbed onto deactivated alumina. Elution with light petroleum-benzene (2:1) gave the enol acetate of the 18-aldehyde as an oil (158mg), $\delta$ D-60° (g 1.54), $\nu_{\text{max}}$ 1763, 1742, 1242 and 1219 cm$^{-1}$.

Hydrolysis of this enol acetate (80mg) in aqueous ethanol (10ml) with potassium hydroxide (300mg) gave the 3β-hydroxy-18-aldehyde (60mg), m.p. 166-167°, $\delta$ D-47.5° (g 1.03), $\nu_{\text{max}}$ 2703, 1736 cm$^{-1}$ (RH). (Found: C, 74.8; H, 9.8. C$_{27}$H$_{42}$O$_4$ requires C, 75.3; H, 9.8%).

Preparation of 13,17a-epoxides

To a solution of 3β-acet oxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (5g) in chloroform (200ml) was added an ethereal solution of monoperphthalic acid (105ml; 0.4N). The solution was kept at room temperature for 40 min, poured into aqueous sodium bicarbonate and the steroidal material isolated via ether. After removal of solvents the residue was adsorbed onto alumina (150g). Elution with light petroleum-benzene (2:1) gave after crystallisation from
methanol $3_B^\beta$-acetoxy-$13\beta,17\alpha^\beta$-epoxy-C-nor-D-homo-5$\alpha$,25D-spirostan as needles (1.1g), m.p. 187.5-189$^\circ$, $[\alpha]_D$-57.5 ($c$ 1.06). (Lit.$^2$ m.p. 189-190$^\circ$, $[\alpha]_D$-66$^\circ$). Elution with light petroleum-benzene (1:1) gave after crystallisation from methanol $3_B^\beta$-acetoxy-$13\alpha,17\alpha^\beta$-epoxy-C-nor-D-homo-5$\alpha$,25D-spirostan (3.2g), m.p. 194-195$^\circ$, $[\alpha]_D$-54$^\circ$ ($c$ 1.04). (Lit.$^2$ m.p. 194-195$^\circ$, $[\alpha]_D$-63$^\circ$).

**Acid hydrolysis of $13\beta,17\alpha^\beta$-epoxide**

A solution of $3_B^\beta$-acetoxy-$13\beta,17\alpha^\beta$-epoxy-C-nor-D-homo-5$\alpha$,25D-spirostan (100 mg) in acetone (4ml) containing perchloric acid (4ml; 1.5M) was kept at 20$^\circ$ for 1$\frac{1}{2}$ hr.

Isolation, and crystallisation of the crude product from light petroleum gave $3_B^\beta$-acetoxy-$13\alpha,17\alpha^\beta$-dihydroxy-C-nor-D-homo-5$\alpha$,25D-spirostan as needles (76mg), m.p. 221-222$^\circ$, $[\alpha]_D$-36$^\circ$ ($c$ 1.07), $\lambda_{\text{max.}}$ 3605, 1730 and 1238cm$^{-1}$.

(Found: C, 70.5; H, 9.6. C$_{29}$H$_{46}$O$_6$ requires C, 70.9; H, 9.4%).

**Acid hydrolysis of $13\alpha,17\alpha^\beta$-epoxide**

A solution of $3_B^\beta$-acetoxy-$13\alpha,17\alpha^\beta$-epoxy-C-nor-D-homo-5$\alpha$,25D-spirostan (200mg) in acetone (8ml) containing perchloric acid (8ml; 1.5M) was kept at 20$^\circ$ for 1$\frac{1}{2}$ hr.

Isolation, and crystallisation of the crude product from light petroleum gave $3_B^\beta$-acetoxy-$13\alpha,17\alpha^\beta$-dihydroxy-C-nor-D-homo-5$\alpha$,25D-spirostan (160mg), m.p. 221-222$^\circ$, $[\alpha]_D$-36$^\circ$ ($c$ 1.03).
Alternative preparation of 13β,17αβ-epoxide

A solution of 3β-acetoxy-13α,17αβ-dihydroxy-C-nor-D-homo-5α,25D-spirostan-13,17α-epoxides in pyridine (25ml) was treated at -10° with thionyl chloride (2.5ml) for 30 min. Isolation of the steroidal material via pentane and crystallisation from methanol gave the 13β,17αβ-epoxide (2.2g), m.p. 187.5-189°, which was identical in all respects with an authentic sample.

Alternative preparation of 13α,17αα-epoxide

A solution of 3β-acetoxy-C-nor-D-homo-5α,25D-spirost-13,17α-ene (500mg) in dioxan (80ml) was treated with aqueous hydrobromic acid (14ml; 0.1M) at room temperature for 40 min. Water was added and the precipitate filtered, dried and recrystallised from light petroleum to give the 17αβ-bromo-13αα-hydroxy compound (480mg), m.p. 130-131°, [α]D -36° (c 0.5), λ max. 3600, 1726 and 1247 cm^-1.

(Found: C, 63.3; H, 8.4; Br, 14.3. C_{29}H_{45}O_{5}Br requires C, 62.9; H, 8.2; Br, 14.4%).

The bromohydrin (135mg) in aqueous ethanol (10ml) was treated with potassium hydroxide (150mg) for 18 hr. at room temperature. The isolated product was acetylated by reaction with acetic anhydride-pyridine (1:10) at room temperature over night. The isolated material was crystallised to give 3β-acetoxy-13α,17αα-epoxy-C-nor-D-homo-
5\(\alpha\),25D-spirostan (70mg), m.p. 194–196\(^\circ\), identical in all respects with an authentic sample.

**Preparation of 17\(a\),18-epoxides**

To a solution of 3\(\beta\)-acetoxy-C-nor-D-homo-5\(\alpha\),25D-spirost-17\(a\),18-ene (7g) in dry benzene (400ml) was added an ethereal solution of monoperphthalic acid (50ml; 0.7N) and the solution kept at room temperature overnight. After isolation of the steroidal material in the usual manner the product was adsorbed onto alumina (300g). Elution with light petroleum-benzene (2:1) gave after crystallisation from acetone 3\(\beta\)-acetoxy-17\(a\)\(\beta\),18\(\alpha\)-epoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan: (4.5g), m.p. 238–239\(^\circ\), \([\alpha]_D^{-61}\) (c 1.02). (Lit.\(^1\) m.p. 234.5–238\(^\circ\), \([\alpha]_D^{-79}\).)

Elution with benzene, benzene-ether gave 3\(\beta\)-acetoxy-17\(a\)\(\alpha\),18\(\alpha\)-epoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan: crystallised from methanol as needles (2.2g), m.p. 210–214\(^\circ\), \([\alpha]_D^{-56}\) (c 1.01). (Lit.\(^1\) m.p. 206–213\(^\circ\), \([\alpha]_D^{-57}\).)

**Reduction of 3\(\beta\)-acetoxy-13\(\beta\),17\(a\)\(\beta\)-epoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan**

To a solution of 13\(\beta\),17\(a\)\(\beta\)-epoxide (330mg) in dry tetrahydrofuran (40ml) was added lithium aluminium hydride (350mg) and the resulting suspension heated under reflux for 4 hr. After the careful addition of ethyl acetate the steroidal material was isolated via ether. The solvents were removed in vacuo and the residue dissolved in pyridine
(10ml) and acetic anhydride (1ml) and kept at room temperature overnight. Isolation of the steroidal material in the usual manner and crystallisation from methanol gave 3\(\beta\)-acetoxy-17\(\alpha\)\(\beta\)-hydroxy-C-nor-D-homo-5\(\alpha\),25D-spirostan as needles (293mg), m.p. 196-197\(^\circ\), \([\alpha]\)_D -55\(^\circ\) (c 1.02).

(Lit.\(^2\) m.p. 192-194\(^\circ\), \([\alpha]\)_D -63\(^\circ\).

**Reduction of 3\(\beta\)-acetoxy-13\(\alpha\),17\(\alpha\)\(\alpha\)-epoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan**

To a solution of 13\(\alpha\),17\(\alpha\)\(\alpha\)-epoxide (400mg) in dry tetrahydrofuran (40ml) was added lithium aluminium hydride (400mg) and the resulting solution heated under reflux for 4 hr. After the careful addition of ethyl acetate the steroidal material was isolated via ether. The solvents were removed in vacuo and the product acetylated by reaction with acetic anhydride-pyridine (1:10) overnight at room temperature. Isolation of the steroidal material in the usual manner and crystallisation from hexane gave 3\(\beta\)-acetoxy-13\(\alpha\)-hydroxy-C-nor-D-homo-5\(\alpha\),25D-spirostan as needles (320mg), m.p. 159-163\(^\circ\), \([\alpha]\)_D -48\(^\circ\) (c 1.05).

(Lit.\(^2\) m.p. 170-171\(^\circ\), \([\alpha]\)_D -53\(^\circ\).

**Reduction of 3\(\beta\)-acetoxy-17\(\alpha\)\(\beta\),18\(\alpha\)-epoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan**

To a solution of epoxide (400mg) in dry tetrahydrofuran (40ml) was added lithium aluminium hydride (400mg),
and the resulting suspension heated under reflux for 4 hr. After the careful addition of ethyl acetate the steroidal material was isolated via ether. The solvents were removed in vacuo and the product dissolved in pyridine (10ml) and acetic anhydride (1ml) and kept at room temperature overnight. Isolation of the steroidal material in the usual manner and crystallisation from methanol gave 3β-acetoxy-17α,β-hydroxy-C-nor-D-homo-5α,25D-spirostan as needles (320mg), m.p. 196-197°, [α]D -55° (c 1.07), identical in all respects to the tert-alcohol formed by reduction of 13β,17αβ-epoxide.

Reduction of 3β-acetoxy-17α,18α-epoxy-C-nor-D-homo-5α,25D-spirostan

To a solution of 17α,18α-epoxide (300mg) in dry tetrahydrofuran (30ml) was added lithium aluminium hydride (300mg) and the resulting mixture heated under reflux for 4 hr. After the careful addition of ethyl acetate the steroidal material was isolated via ether. The solvents were removed in vacuo and the residue, dissolved in pyridine (10ml) and acetic anhydride (1ml) was kept at room temperature overnight. Isolation of the steroidal material in the usual manner and crystallisation from light petroleum gave 3β-acetoxy-17α-hydroxy-C-nor-D-homo-5α,25D-spirostan as flakes (217mg), m.p. 187-188°, [α]D -58 (c 1.01). (Lit.1 m.p. 185-188°).
Dehydration of 3β-acetoxy-17αβ-hydroxy-
C-nor-D-homo-5α,25D-spirostan-13,17a-ene

A solution of 17αβ-hydroxy steroid (140mg) in pyridine (2ml) and thionyl chloride (0.06ml) was kept at -20° for 12 hr. After isolation via pentane and adsorption onto alumina (10g) elution with light petroleum-benzene (6:1) and crystallisation from methanol gave 3β-acetoxy-
C-nor-D-homo-5α,25D-spirostan-13,17a-ene (96mg), m.p. and m.m.p. with authentic sample 141-144°, [α]D -44° (c 0.94).

Dehydration of 3β-acetoxy-13α-hydroxy-
C-nor-D-homo-5α,25D-spirostan-13,17a-ene

A solution of the 13α-hydroxy steroid (56mg) in pyridine (1ml) and thionyl chloride (0.025ml) was kept at -20° for 30 min. Isolation of the steroidal material via pentane and crystallisation from methanol gave 3β-acetoxy-
C-nor-D-homo-5α,25D-spirostan-13,17a-ene (22mg), m.p. and m.m.p. with an authentic sample 141-144°, [α]D -42° (c 1.09). The residue from the above crystallisation was shown (infrared spectrum) to consist largely of starting material.

Dehydration of 3β-acetoxy-17α-hydroxy-C-nor-D-homo-
5α,25D-spirostan-13,17a-ene

A solution of the alcohol (137mg) in pyridine (2ml) and thionyl chloride (0.06ml) was kept at -20° for 40 min.
Isolation via pentane and crystallisation from methanol gave $3\beta$-acetoxy-C-nor-D-homo-5α,25D-spirost-17α,18-ene (60mg), m.p. and m.m.p. with an authentic sample 223-224°, $[\alpha]_D^{-65^0}$ (c 1.12). The residue from the above crystallisation was shown to consist (infrared spectrum) largely of starting material.

**Reaction of $3\beta$-acetoxy-13α,17α-epoxy-C-nor-D-homo-5α,25D-spirostane with boron trifluoride in benzene**

A solution of 13α,17α-epoxide (1g) in anhydrous benzene (100ml) and boron trifluoride-etherate (1ml) was kept at room temperature for 30 sec. then ether was added and the solution washed with aqueous sodium bicarbonate and water. After removal of solvents the product was adsorbed onto alumina (80g).

Elution with light petroleum-benzene (8:1) gave $3\beta$-acetoxy-C-nor-D-homo-5α,25D-spirost-8(14),13(17α)-diene (330mg), which was crystallised first from pentane then from methanol as cubes, m.p. 160-162°, $[\alpha]_D^{-62^0}$ (c 1.17); λ max. 259m μ. (ε 23,000), λ max. 1726 and 1234cm⁻¹. (Found: C, 76.3; H, 9.35. C₂₉H₄₂O₂ requires C, 76.6; H, 9.3%).

A gum (300mg), eluted by light petroleum-benzene (1:1) consisted mainly of 13-acetyl-C-nor-compound, $[\alpha]_D^{-53^0}$ (c 1.33), λ max. 1726, 1234 (oAc), 1696 and
1356 cm\(^{-1}\) (COCH\(_3\)), but was contaminated with C-nor-D-homo-17α-ketone (see below). R.D. in methanol (of crude material): \([\psi]\) \(_{400}^{\pm} -405^\circ; \([\psi]\) \(_{310}^{\pm} -1720^\circ; \([\psi]\) \(_{270}^{\pm} +430^\circ\). Elution with benzene gave hexogenin acetate (180mg), m.p. 250–252\(^\circ\), \([\alpha]_D^{\pm} -7^\circ (c 1.01)\), identical in all respects with an authentic sample.

Finally, elution with ether gave 3β-acetoxy-13α-hydroxy-17α/β-fluoro-C-nor-D-homo-5α,25O-spirostane crystallised as needles from hexane (128mg), m.p. 176–177\(^\circ\), \([\alpha]_D^{\pm} -62^\circ (c 0.73)\), \(\nu_{\text{max.}}\) 3602, 1726 and 1238 cm\(^{-1}\). (Found: C, 70.5; H, 9.3; F, 3.6. \(C_{29}H_{45}O_5F\) requires C, 70.7; H, 9.2; F, 3.9%).

A portion of 13-acetyl-C-nor-compound, contaminated with C-nor-D-homo-17α-ketone (175mg) was treated with benzaldehyde (0.5ml) in ethanol (10ml) containing potassium hydroxide (60mg) at room temperature for 18 hr. The product, isolated via ether, was adsorbed onto alumina (20g). Elution with benzene gave the benzylidene derivative of the 13-acetyl compound as a gum (14.3mg), \([\alpha]_D^{\pm} -38^\circ (c 0.93)\), \(\nu_{\text{max.}}\) 3584 and 1695 cm\(^{-1}\), \(\lambda_{\text{max.}}\) 221\(\mu\) (ε 11,000), 226\(\mu\) (ε 11,000) and 290\(\mu\) (ε 19,600). Elution with ether gave the 3β-hydroxy-13β-methyl-C-nor-D-homo-17α-ketone, (29mg) as a gum, \([\alpha]_D^{\pm} -42^\circ (c 1.12)\), \(\nu_{\text{max.}}\) 3597 and 1722 cm\(^{-1}\), R.D. in methanol: \([\psi]\) \(_{400}^{\pm} -195^\circ; \([\psi]\) \(_{305}^{\pm} -2140^\circ; \([\psi]\) \(_{268}^{\pm} +3600^\circ; \([\psi]\) \(_{221}^{\pm} +1950^\circ.\)
Hydrolysis of $3\beta$-acetoxyl-13$\alpha$-hydroxy-17$\alpha$/3-fluoro-C-nor-D-homo-5$\alpha$,25$\beta$-spirostane

A solution of fluorohydrin (100mg), potassium hydroxide (100mg) in aqueous ethanol (25ml; 90%) was heated under reflux for 4 hr. to give the $3\beta$-hydroxy-13$\alpha$,17$\alpha$-epoxide, m.p. 215-218°, which was acetylated by reaction with acetic anhydride-pyridine (1:10) for 18 hr. at 20°, to give the $3\beta$-acetoxyl-13$\alpha$,17$\alpha$-epoxide, m.p. and m.m.p. with an authentic sample 194-196°.

Reaction of $3\beta$-acetoxyl-13$\alpha$,17$\alpha$-epoxy-C-nor-D-homo-5$\alpha$,25$\beta$-spirostane with boron trifluoride in ether

The 13$\alpha$,17$\alpha$-epoxide (800mg), and boron trifluoride-etherate (0.8ml) were allowed to react in anhydrous ether (80ml) for 1 hr. Isolation of the steroidal material, and crystallisation from hexane gave $3\beta$-acetoxyl-13$\alpha$-hydroxy-17$\alpha$-fluoro-C-nor-D-homo-5$\alpha$,25$\beta$-spirostane (646mg), m.p. and m.m.p. 176-177°.

Reaction of $3\beta$-acetoxyl-13$\alpha$-hydroxy-17$\alpha$/3-fluoro-C-nor-D-homo-5$\alpha$,25$\beta$-spirostane with boron trifluoride in benzene

The fluorohydrin (140mg) and boron trifluoride-etherate (0.16ml) were allowed to react in anhydrous benzene (16ml) for 22 min. The ultra violet spectrum of the crude material, isolated in the usual manner, $\lambda_{\text{max.}}$, 251$\mu$
(ε 3200), indicated the presence of diene (14%). Crystallisation from methanol gave hecogenin acetate (20mg), m.p. 246-248°, and chromatography of the residues on alumina gave a ketonic fraction (53mg), consisting mainly of the 13α-acetyl compound, and unreacted fluorohydrin (43mg).

**Reaction of 3β-acetoxy-13α,17αβ-epoxy-C-nor-D-homo-5α,25D-spirostan-8,14-ene with boron trifluoride in benzene**

The 13β,17αβ-epoxide (500mg) in dry benzene (50ml) was treated with boron trifluoride-etherate (0.5ml) for 3 min. Ether was added and the solution washed with aqueous sodium bicarbonate and water. After removal of solvents 3β-acetoxy-17αβ-hydroxy-17αα-methyl-C-nor-D-homo-5α,25D-spirost-8,14-ene was crystallised as prisms from methanol (480mg), m.p. 170-171°, [α]D -94° (ε 1.03), λmax. 207m μ (ε 11,500), Ψmax. 3640, 1729 and 1237cm⁻¹.

(found: C, 73.2; H, 9.4. C25H₄₄O₅ requires C, 73.7; H, 9.4%).

**Dehydration of 3β-acetoxy-17αβ-hydroxy-17αα-methyl-C-nor-D-homo-5α,25D-spirost-8,14-ene**

Thionyl chloride (0.045ml) was added to a solution of the 17αβ-hydroxy-Δ8(14)-olefin (100mg) in pyridine (1.5ml) at -30°. The solution was allowed to come to room temperature over 15 min. and the product was isolated by use of ether and purified by chromatography on deactivated
algumina. The 8(14), 13(17a)-dienes (60mg), crystallised as cubes from methanol, was identical to the previous sample, m.p. and m.m.p. 160-162°.

Reaction of 3β-acetoxy-13β,17αβ-epoxy-C-nor-D-homo-5α,25D-spirostane with boron trifluoride in ether

The 13β,17αβ-epoxide (500mg) and boron trifluoride-etherate were allowed to react in ether (50ml) for 1 hr. The steroidal material was isolated in the usual manner. Crystallisation from light petroleum gave 3β-acetoxy-13α-fluoro-17β-hydroxy-17αα-methyl-C-nor-D-homo-5α,25D-spirostane as needles (195mg), m.p. 130-137° (decomp.), [α]D -50° (c 0.96), νmax 3608, 1726 and 1235cm⁻¹. (Found: C, 70.5; H, 9.3; F, 3.6. C29H45O5F requires C, 70.7; H, 9.2; F, 3.9%). The residue crystallised from methanol to give unreacted epoxide (250mg).

Hydrolysis of the fluorohydrin (50mg) with potassium hydroxide (50 mg) in refluxing aqueous ethanol (20ml; 90%) for 4 hr. gave the 3β-hydroxy-13β,17αβ-epoxide, m.p. 128-140°, [α]D -60.5° (c 1.02), which was acetylated by reaction with acetic anhydride-pyridine overnight at room temperature to give 3β-acetoxy-13β,17αβ-epoxy-C-nor-D-homo-5α,25D-spirostane, m.p. and m.m.p. with authentic sample 187-189°.
Reaction of 3\(\beta\)-acetoxy-17a,18-epoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan with boron trifluoride in ether

The 17a\(\alpha\),18-epoxide (1.3g) and boron trifluoride-etherate (1.3ml) were allowed to react in benzene (130ml) for 15 min. The products were isolated via ether and crystallisation from light petroleum gave 3\(\beta\)-acetoxy-C-nor-D-homo-5\(\alpha\),25D-spirostan-18-aldehyde as prisms (250mg), m.p. 186-188\(\circ\), \([\alpha]_D^{20} -63^{\circ} (c \ 0.92), \) \(\cup \) max 2703, 1721 (CHO), 1736 and 1241 cm\(^{-1}\) (oAc). (Found: C, 73.9; H, 9.8.
\(C_{29}H_{40}O_5 \) requires C, 73.7; H, 9.4%)

Chromatography of the residues on deactivated alumina (75g) gave two products of unknown structure both lacking the spectral features of the spiroketal system. The first compound (210mg), eluted by light petroleum-benzene (10:1) crystallised from pentane as needles, m.p. 167-173\(\circ\), \([\alpha]_D^{20} -46^{\circ} (c \ 1.22), \) \(\cup \) max 1731, 1672, 1242 and 1029 cm\(^{-1}\).
UV: \(\varepsilon \ 220 \ 4580, \varepsilon \ 210 \ 4920. \) (Found: C, 75.45; H, 9.0%).

The second compound, eluted by light petroleum-benzene (20:3) gave on crystallisation from methanol, needles (210mg), m.p. 187-190\(\circ\), \([\alpha]_D^{20} -9^{\circ} (c \ 1.0), \) \(\cup \) max 1712, 1242, 1028 cm\(^{-1}\). UV: \(\varepsilon \ 220 \ 4160, \varepsilon \ 210 \ 7450. \) (Found: C, 76.0; H, 9.0%). A further quantity (330mg) of the 18-aldehyde was eluted by the same solvent.
Alkaline hydrolysis of the 18-aldehyde

The aldehyde (100mg) and potassium hydroxide (100mg) were dissolved in aqueous ethanol (10ml, 90%) and kept at room temperature for 18 hr. The product, crystallised from light petroleum, was 3-hydroxy-18-aldehyde (70mg), m.p. 168-170, $[\alpha]_D^{27} -47^\circ$ (c 0.95), vmax, 2703, 1736 cm$^{-1}$ (CHO) (Found: C, 74.8; H, 9.8. C$_{27}$H$_{42}$O$_4$ requires C, 75.3; H, 9.8%). Reacetylation of the hydroxy-aldehyde by reaction with acetic anhydride-pyridine gave back the starting acetoxyl-aldehyde, m.p. and m.m.p. 186-188$^\circ$.

Rearrangement of 3,3'-acetoxyl-17a,18-epoxy-C-nor-D-homo-5a,25D-spirostane with perchloric acid

A solution of the 17a,18-epoxide (1.2g) in methylene chloride (60ml) and acetone (120ml) was treated with aqueous perchloric acid (1.2ml; 1.5M). After 10 min. at 20$^\circ$ the solution was diluted with water and the organic phase washed neutral. After removal of solvents the product was adsorbed onto deactivated alumina (50g). Elution with benzene gave the 18-aldehyde (1.009 g), m.p. and m.m.p. 186-188$^\circ$, identical in all respects with the product obtained from the above boron trifluoride catalysed reaction. Elution with ether gave 3,3'-acetoxyl-18-hydroxy-C-nor-D-homo-spirostane-13,17a-one (150mg) which was crystallised from light petroleum as needles, m.p. 204-206$^\circ$. 
\[ \alpha \] \text{D} -64^\circ (c 1.20), \upsilon_{\text{max}} = 3597, 1745 \text{ and } 1241 \text{cm}^{-1}.

(Found: C, 73.3; H, 9.6. \text{C}_{29}\text{H}_{40}O_5 \text{ requires C, 73.7; H, 9.4%).}

**Conversion of the 3\beta\text{acetoxy-18-hydroxy-C-nor-D-homo-}
spirost-13,17a-ene into 3\beta\text{acetoxy-C-nor-D-homo-}
5\alpha,25\alpha\text{spirost-13,17a-ene}

The 18-hydroxy olefin (200mg) in acetic anhydride (0.4ml) and pyridine (4ml) was kept at 20\degree \text{C} for 18 hr., and the product isolated via ether. Crystallisation from light petroleum gave 3\beta,18-di\text{acetoxy-C-nor-D-homo-5\alpha,25\alpha}
spirost-13,17a-ene as needles, m.p. 159-163\degree \text{C}, \alpha \text{D} -48^\circ
(c 0.87), \upsilon_{\text{max}} = 1745 \text{ and } 1239 \text{cm}^{-1}. \text{(Found: C, 72.3; H, 9.3. \text{C}_{31}\text{H}_{46}O_6 \text{ requires C, 72.3; H, 9.0).}

The 3,18-di\text{acetate (60mg) in ethylamine (20ml) was}
stirred during the addition of small pieces of lithium until there was a permanent blue colour in the solution (45 min.). After a further 30 min. stirring solid ammonium chloride was added, followed by ether and water, and the residue, after washing and evaporating the ether, was treated with acetic anhydride-pyridine for 18 hr. at 20\degree \text{C}. The product, isolated by use of ether and crystallised from methanol was 3\beta\text{-acetoxy-C-nor-D-homo-5\alpha,25\alpha-spirost-}
13,17a-ene, (35mg), m.p. 141-145\degree \text{C identical in all respects with an authentic sample.}
Reaction of \(3\beta\)-acetoxy-17\(a\),18\(\beta\)-epoxy-C-nor-D-homo-5\(\alpha\),25\(\alpha\)-spirostan with boron trifluoride in benzene

The 17\(a\),18\(\beta\)-epoxide (2.3 g) in benzene (230 ml) was treated with boron trifluoride-etherate (23 ml) for 30 sec., then the product was isolated by use of ether. After removal of solvents the residue was adsorbed onto deactivated alumina (60 g). Elution with light petroleum-benzene (1:1) gave a gum (1.5 g) which crystallised from methanol to give a cyclic ether as needles, m.p. 209-210\(^0\), \([\alpha]_D\) -62.5\(^\circ\) \((c\ 0.83), \upsilon_{\text{max.}}\ 1742, 1242 (\text{oAc}), 1081, 1055, 1031, 1023, 957 and 943 cm\(^{-1}\). No ultra violet absorption in the region to 360-202m\(\mu\). (Found: C, 73.4\%; H, 9.2. \(C_{29}H_{44}O_5\) requires C, 73.7; H, 9.4\%). Benzene eluted 3\(\beta\)-acetoxy-17\(a\)-fluoro-18-hydroxy-C-nor-D-homo-5\(\alpha\), 25\(\alpha\)-spirostan which crystallised from methanol as needles (340 mg), m.p. 206-209\(^0\), \([\alpha]_D\) -64\(^\circ\) \((c\ 1.0), \upsilon_{\text{max.}}\ 3610, 3184 (-OH), 1745 and 1241 cm\(^{-1}\). (Found: C, 70.4; H, 9.4; F, 3.9. \(C_{29}H_{45}O_5F\) requires C, 70.7; H, 9.2; F, 3.9\%). The residues (398 mg) from the fractions which gave the fluoro-hydriin were dissolved in dioxan (5 ml) and treated with 2,3-dichloro-5,6-dicyanobenzoquinone (400 mg) for 18 hr. at 20\(^0\). The resulting solution was poured into ether and washed with aqueous sodium hydroxide. The product was adsorbed onto deactivated alumina (40 g), from which benzene-ether eluted 3\(\beta\)-acetoxy-C-nor-D-homo-5\(\alpha\),25\(\alpha\)-spirostan-13,17\(a\)-ene 18-aldehyde (90 mg) which crystallised from methanol,
m.p. 197-199°, $\left[\alpha\right]_D -41^\circ$ (c 0.98), $\lambda_{\text{max}}$ 2740 (CHO), 1742, and 1241 cm$^{-1}$ (oAc), and 1689 cm$^{-1}$ (C=O-CHO), $\lambda_{\text{max}}$ 257m$\mu$ (c 12,650), (Found: C, 73.6; H, 8.9. C$_{29}$H$_{42}$O$_5$ requires C, 74.0; H, 9.0%). Ether eluted a further quantity of fluorohydrin (250mg), m.p. 206-209°.

$3\beta$ 18-Diacetoxy-17$\alpha$-fluoro-C-nor-D-homo-5$\alpha$,25D-spirostan was prepared from the fluorohydrin by reaction with acetic anhydride-pyridine at 20° for 18 hr. The isolated product was an oil, $\left[\alpha\right]_D -55^\circ$ (c 1.18), $\lambda_{\text{max}}$ 1760, 1745 and 1235 cm$^{-1}$.

$3\beta$-Acetoxy-17$\alpha$-fluoro-18-benzoxy-C-nor-D-homo-5$\alpha$,25D-spirostan prepared by reaction of the fluorohydrin with benzoyl chloride-pyridine, was also an oil, $\left[\alpha\right]_D -52^\circ$ (c 0.87), $\lambda_{\text{max}}$ 1733, 1269 and 1242 cm$^{-1}$.

Alkaline hydrolysis of $3\beta$-acetoxy-17$\alpha$-fluoro-18-hydroxy-C-nor-D-homo-5$\alpha$,25D-spirostan:

The 17$\alpha$-fluoro-18-hydroxy steroid (50mg), and potassium hydroxide (50mg), were dissolved in aqueous ethanol (10ml) and heated under reflux for 4 hr. Isolation of the steroidal material in the usual manner and crystallisation from methanol gave $3\beta$-hydroxy-fluorohydrin as needles (32mg), m.p. 258-259°, $\left[\alpha\right]_D -63^\circ$ (c 0.77), $\lambda_{\text{max}}$ (CH$_2$Cl$_2$) 3610 cm$^{-1}$. (Found: C, 71.6; H, 9.2; F, 4.0. C$_{27}$H$_{45}$O$_{14}$F requires C, 72.0; H, 9.6; F, 4.2%).

An attempt to convert the fluorohydrin into the
17α,18-epoxide by reaction with potassium tert.-butoxide in tert.-butanol also gave the 3β-hydroxy-fluorohydrin.

Reaction of 3β-acetoxy-17αβ,18β-epoxy-C-nor-D-homo-5α,25D-spirostan: with boron trifluoride in ether

The 17α/β,18β-epoxide (1.97g) in anhydrous ether (200ml) was treated with boron trifluoride-etherate (2ml) for 1½ hr. Isolation of the steroidal material in the usual manner and removal of solvents gave product which was adsorbed onto deactivated alumina. Elution with light petroleum benzene (1:1) gave cyclic ether (769mg) m.p. and m.m.p. 209-211°. Elution with ether gave 3β-acetoxy-18-hydroxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (1.17g), m.p. and m.m.p. 204-206°.

Rearrangement of 3α-acetoxy-17αβ,18β-epoxy-C-nor-
D-homo-5α,25D-spirostan: with perchloric acid

The 17α/β,18-epoxide (500mg) in methylene chloride (16ml) and acetone (32ml) was treated with aqueous perchloric acid (1.5M; 0.5ml) for 10 min. at 20°. The product, which crystallised from light petroleum, was 3β-acetoxy-18-hydroxy-C-nor-D-homo-5α,25D-spirost-13,17a-ene (332mg), m.p. and m.m.p. 202-206°, identical in all respects with the sample obtained from the α-epoxide.
Reduction of 3β-acetoxy-C-nor-D-homo-5α,25D-spirostan-18-aldehyde to give 3β-acetoxy-17αα-methyl-C-nor-D-homo-5α,25D-spirostan:

The 18-aldehyde (250mg) and hydrazine hydrate (60%, 1.5ml) were heated in ethylene glycol (10ml) at 120° for 1 hr., then potassium hydroxide (1g) was added and the solution heated to 200° in a slow stream of nitrogen for 2 hr. The product isolated by use of ether, was treated with acetic anhydride (0.2ml) in pyridine (10ml) at 100° for 30 min. The product was crystallised from methanol to give 3β-acetoxy-17αα-methyl-C-nor-D-homo-5α,25D-spirostan as needles (206mg), m.p. 154-155°, $[\alpha]_D -60°$ (c 0.85), $\nu_{\text{max.}}$ 1712 and 1242 cm$^{-1}$. (Found: C, 75.6; H, 10.3. C$_{29}$H$_{46}$O$_4$ requires C, 75.9; H, 10.1%).

Preparation of 3β-acetoxy-17αβ-methyl-C-nor-D-homo-5α,25D-spirostan:

A solution of 3β-acetoxy-C-nor-D-homo-5α,25D-spirostan-17α,18-ene (250mg) in acetic acid (10ml) was hydrogenated at atmospheric pressure over a Pd-c catalyst (10%, 150mg) for 7 hrs. The filtered solution was evaporated to dryness at 20mm. and the residue crystallised from methanol to give 3β-acetoxy-17αβ-methyl-C-nor-D-homo-5α,25D-spirostan: (222mg), m.p. 175-176°, $[\alpha]_D -49.5°$ (c 1.07), $\nu_{\text{max.}}$ 1712 and 1242 cm$^{-1}$. (Found: C, 75.5; H, 10.4. C$_{29}$H$_{46}$O$_4$ requires C, 75.9; H, 10.1%) (Lit. m.p. 179-181°, $[\alpha]_D -112°$)
Degradation of the Spiroketal side-chain

To a solution of hecogenin acetate (120g) in pyridine (120ml) and acetic anhydride (240ml), was added methylamine hydrochloride (41g, azeotropically dried with benzene) and the resulting suspension heated under reflux for 2 hr. The solution was distilled till the boiling point reached 118°, then heated under reflux for 3 hr. The solution was poured into water and the steroidal material, isolated via methylene chloride, was washed with dilute sulphuric acid dried, and the solvents removed to give pseudo hecogenin acetate as an oil, \( \lambda_{\text{max}} 1725 \text{cm}^{-1} \) (broad band).

A solution of pseudo hecogenin acetate (14g) in acetic acid (210ml) and hydrogen peroxide (30%; 28ml) was kept at room temperature overnight. The solution was poured into water and the steroidal material isolated via ether. After the removal of solvents the residue was dissolved in acetic acid (150ml) and acetic anhydride (7.5ml) and heated under reflux for 2 hr. The solvents were removed in vacuo and the residue taken up in ether, washed with aqueous sodium bicarbonate, water, and dried. After the removal of solvents the residue was adsorbed onto alumina. Elution with light petroleum-benzene (1:1) and crystallisation from methanol gave 3\( \beta \)-acetoxy \( \Lambda_{16,17} \)-pregnan-12,20-dione (6g), m.p. 179-180°, \([\alpha]_D +64 \) (c 1.02). (Lit. m.p. 178-180°, \([\alpha]_D +128°\).)
Hydrogenation of \(3\beta\)-acetoxy-\(\Delta^{16,17}\)-pregnan-12,20-dione\(^{31}\)

To a solution of \(3\beta\)-acetoxy-\(\Delta^{16,17}\)-pregnan-12,20-dione (24g) in ethanol (625ml) was added palladium on charcoal (0.6g; 5%) and the resulting suspension stirred vigorously in a hydrogen atmosphere till 1 mole of hydrogen had been adsorbed. After filtration and reduction in volume, \(3\beta\)-acetoxy-5\(\alpha\)-pregnan-12,20-dione crystallised as chunks (22.3g), m.p. 194-195\(^0\) \([\alpha]_D +135^0\) (c 1.02).

(Lit.\(^{30}\) m.p. 188-190\(^0\), \([\alpha]_D +140^0\)).

3\(\beta\)-Acetoxy-12:12-ethylene dioxy-5\(\alpha\)-pregnan-20-one\(^{31}\)

A solution of \(3\beta\)-acetoxy-5\(\alpha\)-pregnan-12,20-dione (44g) in freshly distilled ethylene glycol (320ml) and boron-trifluoride-etherate (65ml) was kept at room temperature, with occasional swirling for 3 days. The solution was poured into aqueous sodium bicarbonate and the steroidal material extracted \textit{via} ether.

The residue in pyridine (100ml) and acetic anhydride (100ml) was kept at 100\(^0\) for 45 min. Isolation of the steroidal material in the usual manner gave \(3\beta\)-acetoxy-12:12-ethylene dioxy-5\(\alpha\)-pregnan-20-one (40.3g), m.p. 160-162\(^0\), \([\alpha]_D +98^0\) (c 1.04).

(Lit.\(^{31}\) m.p. 159-162\(^0\), \([\alpha]_D +99^0\) (c 0.62)).
"Huang Minlon" reduction of 20-keto group

$3\beta$-Acetoxy-12:12-ethylene dioxo-5$\alpha$-pregnan-20-one (37g) was added to a solution of sodium hydroxide (59.5g), diethylene glycol (595ml) and hydrazine hydrate (90ml; 60% w/v), and heated under reflux for 1 hr. The reaction mixture was distilled until a temperature of 195$^\circ$ was reached, and then kept at that temperature for 4 hr. After cooling, water was slowly added, and the steroidal material extracted via chloroform. After washing with water and drying, the solvents were removed in vacuo and the residue in acetic acid (90%) heated at 100$^\circ$ for 2 hr. The acetic acid was removed in vacuo and the residue, in ether, was washed with water. Removal of solvents and crystallisation from methanol gave $3\beta$-hydroxy-5$\alpha$-pregnan-12-one (25.1g), m.p. 184-185$^\circ$, $[\alpha]_D^\text{20}$ +82.5$^\circ$ (c 0.50). (Lit. 9 m.p. 186$^\circ$.)

$3\beta$-Benzoxy-5$\alpha$-pregnan-12-one

A solution of $3\beta$-hydroxy-5$\alpha$-pregnan-12-one (25g) in dry benzene (200ml), pyridine (30ml) and benzoyl chloride (26ml) was kept at room temperature overnight. The steroidal material isolated via methylene chloride-ether was crystallised from methanol to give $3\beta$-benzoxy-5$\alpha$-pregnan-12-one as needles (33g), m.p. 215-217$^\circ$, $[\alpha]_D^\text{20}$ +90$^\circ$ (c 1.125), $\nu_{\text{max}}$ 1712cm$^{-1}$ (broad), 1274cm$^{-1}$. (Found: C, 79.3; H, 9.1. C$_{28}$H$_{38}$O$_3$ requires C, 79.6; H, 9.1%).
Reduction of 3β-benzoxy-5α-pregn-12-one

A suspension of 3β-benzoxy-5α-pregn-12-one (15g) and lithium borohydride (4g) in tetrahydrofuran was stirred at room temperature for 3½ hr. After isolation of the steroidal material via methylene chloride-ether, and removal of solvents, the residue was adsorbed onto deactivated alumina (1kg). Elution with light petroleum-benzene (1:1) gave after crystallisation from hexane 3β-benzoxy-12β-hydroxy-5α-pregnane (7.9g), m.p. 191-191.5°, [α]D +20° (c 1.12), λ max. 3597, 1724 and 1274cm⁻¹. (Found: C, 78.6; H, 9.6. C₂₈H₄₀O₃ requires C, 79.2; H, 9.5%).

Further elution with the same solvent gave after crystallisation from methanol 3β-benzoxy-12α-hydroxy-5α-pregnane (6.0g), m.p. 165-166°, [α]D +27° (c 1.15), λ max. 3610, 1724 and 1274cm⁻¹. (Found: C, 78.8; H, 9.6. C₂₈H₄₀O₃ requires C, 79.2; H, 9.5%).

3β-Benzoxyl-12β-tosyl-5α-pregnane

To a solution of 3β-benzoxy-12β-hydroxy-5α-pregnane (7.1g) in pyridine (36ml) was added a solution of p-toluene sulphonyl chloride (10g) in pyridine (36ml) and the resulting solution kept at room temperature for 4 days. The solution was poured into ether and washed with dilute sulphuric acid, water, aqueous sodium bicarbonate and water. After removal of solvents the resulting oil showed infrared
absorption at 1724, 1274 and 1175 cm\(^{-1}\).

**Base catalysed rearrangement of 3\(\beta\)-benzoxyl-
12\(\beta\)-tosyl-5\(\alpha\)-pregnane**

To a solution of potassium tert-butoxide in tert-butanol (potassium 3g, tert-butanol 400ml) was added 3\(\beta\)-benzoxyl-12\(\beta\)-tosyl-5\(\alpha\)-pregnane, and the mixture heated under reflux for 18 hr. in a nitrogen atmosphere. After cooling, tetrahydrofuran (48ml), water (30ml), and methanol (100ml) were added and the resulting solution heated under reflux for a further 6 hr. After isolation via ether, the steroidal material was dissolved in pyridine (100ml) and benzoyl chloride (8ml) and kept at room temperature for 30 min. The solution was poured into ether and washed with aqueous sodium hydroxide and water. Removal of solvents and crystallisation from acetone gave 3\(\beta\)-benzoxyl-\(C\)-nor-\(D\)-homo-5\(\alpha\)-pregnan-13,17a-ene as chunks (1.16g), m.p. 140-141\(^0\) (\(\alpha\) 1.03), \(\nu_{\text{max}}\) 1742 and 1274 cm\(^{-1}\).

(found: C, 83.3; H, 9.8. C\(_{28}\)H\(_{36}\)O\(_2\) requires C, 82.7; H, 9.4%).

The residue, after removal of solvents from the mother liquors, was adsorbed onto silica gel (250g). Elution with light petroleum and crystallisation from methanol gave a mixture of 3\(\beta\)-benzoxyl-\(C\)-nor-\(D\)-homo-5\(\alpha\)-pregnan-13,17a-ene and 3\(\beta\)-benzoxyl-\(C\)-nor-\(D\)-homo-5\(\alpha\)-pregnan-17,17a-ene (3g), m.p. 92-93\(^0\) (\(\alpha\) 0.78),
\( J \) \(_{\text{max.}} \) 1724 and 1274 cm\(^{-1}\). (Found: C, 82.4; H, 9.6. 
C\(_{28}\)H\(_{38}\)O\(_2\) requires C, 82.7; H, 9.4%).

3\(\beta\)-Benzoxy-12\(\alpha\)-tosyl-5\(\alpha\)-pregnane

To a solution of 3\(\beta\)-benzoxy-12\(\alpha\)-hydroxy-5\(\alpha\)-pregnane (500mg) in pyridine (2.5ml) was added a solution of p-toluene sulphonyl chloride (750mg) in pyridine (2.5ml) and the resulting solution kept at room temperature for 6 days. The solution was poured into ether and washed with dilute sulphuric acid, water, aqueous sodium bicarbonate and water. After removal of solvents, crystallisation from pentane gave 3\(\beta\)-benzoxy-12\(\alpha\)-tosyl-5\(\alpha\)-pregnane (550mg), m.p. 166-170\(\degree\) (decomp.), \( J \) \(_{\text{max.}} \) 1724, 1274 and 1175 cm\(^{-1}\).

Base catalysed rearrangement of 3\(\beta\)-benzoyl-12\(\alpha\)-tosyl
5\(\alpha\)-pregnane

To a solution of potassium tert-butoxide in tert-butanol (potassium 175mg; tert-butanol 35ml) was added 3\(\beta\)-benzoyl-12\(\alpha\)-tosyl-5\(\alpha\)-pregnane and the mixture heated under reflux for 18 hr. The solvents were removed in vacuo, water being added periodically to aid in the removal of tert-butanol. After isolation via ether the steroidal material (451mg) in pyridine (10ml) and benzoyl chloride (0.5ml) was kept at room temperature overnight. Isolation of the steroidal material in the usual manner and crystallisation from pentane gave unchanged starting material
Oxidation of 3β-benzoxy-12α-hydroxy-5α-pregnan

To a solution of 3β-benzoxy-12α-hydroxy-5α-pregnan (4.4g) in acetone (100ml) was added dropwise a solution of chromium trioxide, sulphuric acid and water (CrO₃, 24g; H₂SO₄, 23ml; H₂O, 100ml) until a permanent orange colour persisted. Sodium metabisulphite was added to neutralise the excess chromic acid, and the solution poured into water. The steroidal material, isolated via ether, was crystallised from methanol to give 3β-benzoxy-5α-pregnan-12-one as needles (4g), m.p. 215-217°, [α]D +90° (c 1.04).

3β-Benzoxy-5α-pregnan-12-one toluene p-sulphonyl hydrazone

To a solution of 3β-benzoxy-5α-pregnan-12-one (4.0g) in glacial acetic acid (240ml) was added p-toluene sulphonyl hydrazide, and the resulting mixture left overnight. The precipitated white solid 3β-benzoxy-5α-pregnan 12-one toluene p-sulphonyl hydrazone was filtered, washed with water, ethanol, and dried (5g), m.p. 225-230°, [α]D +27° (c 0.6), ν max. 3205 cm⁻¹ (N-H), 1724 and 1274 cm⁻¹.

Alkaline decomposition of the toluene p-sulphonyl hydrazone of 3α-benzoxy-5α-pregnan-12-one

Sodium (4g) was dissolved in diethylene glycol (160ml)
with warming. The solution was cooled to 50° and the hydra-
zone (5g) slowly added. The mixture was heated to 165°
and kept at that temperature until no further gas evolution
was apparent (2 hr). After being cooled to 60° the mixture
was diluted with water and the steroidal material isolated
via ether. After removal of solvents the residue in
pyridine (100 ml) and benzoyl chloride (4 ml) was kept at
room temperature for 30 min. After isolation of steroidal
material via ether and removal of solvents the residue was
adsorbed onto alumina (150g). Elution with light-petroleum-
benzene (9:1) and crystallisation from acetone gave
3β -benzoxy-C-nor-D-homo-5α-pregnan-13,17a-ene (2.4g) as
chunks, m.p. 140-141°, [α] D +17° (e 1.04).

Hydroxylation of 3β -hydroxy-C-nor-D-homo-5α-
pregnan-13,17a-ene

A solution of 3β -benzoxy-C-nor-D-homo-5α-pregnan-
13,17a-ene (500mg), potassium hydroxide (1g) in aqueous
ethanol (100ml) was heated under reflux for 6 hr. The
sterol material isolated in the usual manner was
dissolved in pyridine (20ml) and a solution of osmic acid
(500mg) in pyridine (20ml) added. The resulting solution
was kept at room temperature for 9 days. Hydrogen sulphide
was passed through the solution, and the precipitate of
osmium sulphide removed by filtration. After removal of
the solvents in vacuo the black residue was heated under
reflux for 6 hr. in a solution of ethanol (200ml) to which
a solution of sodium sulphite (2.2g) in water (50ml) had
been added. Isolation of the steroidal material in the
usual manner gave triol as an oil, \( J_{\text{max}} \) 3600 cm\(^{-1}\).

Cleavage of the cis diol from hydroxylation of
\( 3\beta\)-hydroxy-C-nor-5\( \alpha\)-pregnan-13,17a-ene

To a solution of triol (180mg) in tert-butanol
(20ml) and acetic acid (20ml), was added lead tetra acetate
(1g) and the resulting suspension stirred for 18 hr.
Ethylene glycol was added, and the resulting clear solution
poured into water. The steroidal material, isolated via
ether, was washed successively with water, aqueous sodium
bicarbonate and water. The solvents were removed to leave
an oil (150mg), \( J_{\text{max}} \) 3610 cm\(^{-1}\) (\( \text{OH} \)), 1748 cm\(^{-1}\) (5-
membered ring ketone), 1721 and 1360 cm\(^{-1}\) (COCH\(_3\)).

Hydroxylation of impure hydroxy isomer of \( 3\beta\)-benzoxy-
C-nor-D-homo-5\( \alpha\)-pregnan-17,17a-ene

A solution of the impure olefin (400mg; m.p. 92-93\(^{\circ}\)
and potassium hydroxide (600mg) in aqueous ethanol (100ml)
was heated under reflux for 6 hr. The steroidal material
isolated in the usual manner was dissolved in benzene (20ml)
and pyridine (3ml), and a solution of osmic acid (500mg) in
benzene (10ml) added. The resulting solution was kept at
room temperature for 6 days. Hydrogen sulphide was passed
through the solution, and the precipitated osmium sulphide removed by filtration. After removal of the solvents in vacuo the black residue was heated under reflux for 6 hr. in a solution of ethanol (200ml) to which a solution of sodium sulphite (2.2g) in water (50ml) had been added. Isolation of the steroidal material in the usual manner afforded an oil, $\nu_{\text{max}}$ 3610 cm$^{-1}$.

Cleavage of the impure cis triol

To a solution of the triol (175mg) in methanol (20ml) was added a solution of periodic acid (100mg) in water (5ml), and the resulting solution kept at room temperature for 18 hr. The steroidal material was isolated in the usual manner to give an oil, $\nu_{\text{max}}$ 3610 cm$^{-1}$ (-OH), 1748 cm$^{-1}$ (weak, 5-membered ring ketone) 1721, 1360 cm$^{-1}$ (COCH$_3$).

Epoxidation of $3\beta$-benzoxoy-C-nor-D-homo-5$\alpha$-pregnan-13,17a-ene

To a solution of $3\beta$-benzoxoy-C-nor-D-homo-5$\alpha$-pregnan-13,17a-ene (2g) in dry benzene (100ml) was added an ethereal solution of monoperphthalic acid (64ml; 0.45 M) and the resulting solution kept at room temperature for 1 hr. Isolation of the steroidal material in the usual manner and crystallisation from methanol gave $3\beta$-benzoxoy-13$\alpha$-17a$\alpha$-epoxy-C-nor-D-homo-5$\alpha$-pregnane (1.35g), m.p. 127-128°.
\[ [\alpha]_D \, 0.0^\circ \,(c \, 0.93), \, \lambda_{\text{max}} \, 1724 \, \text{and} \, 1274 \text{cm}^{-1}. \] (Found: C, 79.6; H, 9.3. \( \text{C}_{28}\text{H}_{38}\text{O}_3 \) requires C, 79.6, H, 9.1\%).

The mother liquors were evaporated to dryness and the residue adsorbed onto alumina (60g). Elution with light petroleum-benzene (10:1) gave \( 3\beta\)-benzoyl-13\( \beta\)-epoxy-\( \alpha \)-nor-\( \delta \)-homo-5\( \alpha \)-pregnane (252mg) crystallized from hexane as needles, m.p. 175-178\(^\circ\), \( [\alpha]_D \, +49^\circ \,(c \, 1.06), \, \lambda_{\text{max}} \, 1727 \, \text{and} \, 1275 \text{cm}^{-1}. \) (Found: C, 79.2; H, 9.3. \( \text{C}_{28}\text{H}_{38}\text{O}_3 \) requires C, 79.6; H, 9.1\%).

Further elution with benzene gave \( 3\beta\)-benzoyl-13\( \beta\), 17\( \alpha \)-epoxy-\( \alpha \)-nor-\( \delta \)-homo-5\( \alpha \)-pregnane (206mg), m.p. 127-128\(^\circ\), \( [\alpha]_D \, 0.0^\circ \).

**Reaction of 3\( \beta\)-benzoyl-13,17\( \alpha \)-epoxy-\( \alpha \)-nor-\( \delta \)-homo-5\( \alpha \)-pregnane with boron trifluoride in benzene**

The 13,17\( \alpha \)-epoxide (700mg) in anhydrous benzene (70ml) was allowed to react with boron trifluoride-etherate (0.7ml) for 45 sec. Ether was added and the organic phase washed successively with aqueous sodium bicarbonate, and water. After the removal of solvents in vacuo the product was adsorbed onto deactivated alumina (70g).

Elution with light petroleum-benzene (10:1) gave an unstable hydrocarbon as an oil (137mg), \( [\alpha]_D \, -13^\circ \,(c \, 1.29), \, \lambda_{\text{max}} \, 227^\circ \,(c \, 16,300), \, 248 \,(c \, 13,900), \, 257 \,(c \, 13,200), \, 267 \,(c \, 8,350), \, \lambda_{\text{max}} \, 1724 \, \text{and} \, 1274 \text{cm}^{-1}. \)
Elution with light petroleum-benzene (3:1) and crystallisation from acetone gave 3β-benzoxy-17α-hydroxy-C-nor-D-hom-5α-pregn-8(14)-ene as plates (245mg), m.p. 99-100°C, $[\alpha]_D^{26} = -26.0$ (c 1.23), $\lambda_{max}$ 3571, 1724 and 1274 cm$^{-1}$. (Found: C, 79.8; H, 9.1. C$_{28}$H$_{38}$O$_3$ requires C, 79.6; H, 9.1%).

Elution with benzene-ether (10:1) gave a second olefinic alcohol (210mg) crystallised from methanol as fine needles, m.p. 155-157°C, $[\alpha]_D^{26} = +38.0$ (c 0.88), $\lambda_{max}$ 3597, 3460, 1724 and 1274 cm$^{-1}$. (Found: C, 79.6; H, 9.1. C$_{28}$H$_{38}$O$_3$ requires C, 79.6; H, 9.1%).
PART II
As a result of the C-nor-D-homo-exocyclic epoxide studies it was considered of interest to study the boron trifluoride catalysed reactions of the 12,12'-exocyclic epoxides.

Steroidal methylene compounds have been made from ketones by the application of the Wittig reaction using butyl lithium and methyl tri-phenyl phosphonium bromide. Hecogenin has been shown to give 12-methylene tigogenin (85) in 51% yield.

An epoxide had been prepared from 12-methylene tigogenin (85) by reaction with perbenzoic acid. The assignment of the \( \beta \)-configuration (86) to this epoxide was based on the following evidence: the \( \text{tart} \)-alcohol (87) prepared by reduction of the epoxide with lithium aluminium hydride, followed by mild acetylation at C\(_3\), was shown to be identical to the alcohol formed from reaction of methyl lithium with 12-ketone. The formulation of the methyl lithium product as the 12/\( \beta \) -hydroxy-12\( \alpha \) -methyl (87) compound was based on "the preference of steroids to rear attack particularly in ring C." No direct proof of the above formulation was given. To account for the formulation of the 12/\( \beta \) -hydroxyl group on reduction of the epoxide it is necessary to assume the epoxide to be formed by \( \beta \) side
attack of the reactant species of perbenzoic acid. Since only one epoxide was formed and this necessarily by \( \beta \) -attack, the assumption for preferential \( \alpha \) -attack of the methyl anion on the ketone seems doubtful. The alternative supposition in which the alcohol has the \( 12\alpha \) -hydroxy-\( 12\beta \) -methyl configuration (88) and the epoxide the \( \alpha \) -configuration (89) was considered unlikely.

Reaction of hecogenin acetate with methyl magnesium bromide has been shown to give after mild acetylation, a tert-alcohol.\(^{39}\) It was realised that assignment of the \( \beta \)-configuration to this alcohol could not be confidently made from its mode of formation. Osmic acid hydroxylation of 12-methylene tigogenin 3-acetate followed by tosylation of the 12'-alcohol and subsequent reduction with lithium aluminium hydride gave a diol, which after mild acetylation gave an alcohol that was similar to that of the acetylated Grignard product, m.p. 213\(^0\), cf. m.p. 220\(^0\), but displayed distinctly different absorption in the regions 940, 925 and 850 cm\(^{-1}\). It was assumed that osmic acid would attack from the \( \alpha \)-face, hence the Grignard product was assigned the 12\( \beta \)-hydroxy-12 \( \alpha \)-methyl (87) structure.

It is known from a study of the dehydration reactions of 1-methyl cyclohexanol type compounds\(^ {23} \) with hot phosphorous pentachloride, leads, for equatorial alcohols to a preferential formation of exocyclic olefins, and for axial alcohols to endocyclic olefins. Dehydration of
3α-methyl cholestan-3β-ol (90) and 3β-methyl cholestan-3α-ol (91) give 3-methylene cholestan (92) and 3-methyl cholest-2-ene (93) respectively. Similarly, dehydration of 3α,4α-dimethyl cholestan-3β-ol (94) and 3β,4α-dimethyl cholestan-3α-ol (95) give 3-methylene-4α-methyl cholestan (96) and 3,4-dimethyl cholest-3-ene (97) respectively.

From such results it has been inferred that the course of phosphorous pentachloride dehydration of 1-methyl cyclohexanols involves a trans and coplanar four centre, hence concerted, reaction requiring the loss of a suitably disposed hydrogen atom.

To confirm the structures assigned to the C₁₂₂² epimeric alcohols a study was made of their dehydration reactions with thionyl chloride-pyridine. No attempt was made to separate pure substances from the reaction mixtures. The reaction mixtures were analysed, first, by elemental analysis for chlorine, then by infrared analysis. The β-alcohol was shown to give a product analysis of: chloro-product, 9%; exocyclic methylene (85), 35%; endocyclic olefin (98), 56%. The α-alcohol gave a product analysis of chloro-product, 21%; exocyclic methylene (85), 39%; endocyclic olefin (98), 40%. The olefins (85,98) were shown not to equilibrate under acid conditions.

The lack of stereospecificity of the dehydration reactions was not expected. The results were rationalised on the basis that trans diaxial dehydration of the axial
$\alpha$-alcohol to form the endo-olefin would require base attack on the highly hindered 11/$\delta$-hydrogen atom, and with either of the epimeric alcohols it was considered that there might be a strong driving force for ionization of the derived chloro sulphite ester leading to a $\text{tert}$-carbonium ion at C$_{12}$ (99). The formation of such a trivalent centre would it was claimed$^{39}$ be expected to reduce the axial character of the 11/$\delta$-hydrogen atom with the consequent release of compression energy. Such an intermediate, it was argued, could account for the near random production of olefinic products from the 12-methyl carbinols.
DISCUSSION

In view of the unsatisfactory evidence for the $\beta$-configuration of the epoxide, it was considered necessary to re-examine these compounds.

Application of the Wittig reaction\textsuperscript{36} to hecogenin acetate using a ten mole excess of Wittig reagent gave crude 12-methylene tigogenin (85), which was acetylated with acetic anhydride-pyridine to give after chromatography and crystallisation 12-methylene tigogenin 3-acetate in 90\% yield.

Reaction of 12-methylene tigogenin 3-acetate with monoperphthalic acid gave a separable mixture of two epoxides in the ratio 1:2. The minor epoxide, eluted first from an alumina column has been assigned the $12\beta', 12'\beta$-epoxide (86). The more polar epoxide has been assigned the $12\alpha', 12'\alpha$-epoxide (89). The physical properties of this $\alpha$-epoxide were identical to the literature values for the epoxide previously assigned as the $12\beta, 12'\alpha$-epoxide.\textsuperscript{38}

The assignment of the configuration of the epoxides is based on the thionyl chloride-pyridine dehydration reactions of the \textit{tert}-alcohols formed by lithium aluminium hydride reduction of the epoxides. The $\beta$-epoxide (86) after reduction with lithium aluminium hydride followed by mild acetylation with acetic anhydride-pyridine gave the \textit{tert}-alcohol, 12$\alpha$-hydroxy-12$\alpha$-methyl-tigogenin
3-acetate (87). This compound and the intermediate 3β,12β-diol while having similar physical properties to the corresponding 3β-acetate-12α-alcohol (88) and 3α,12α-diol formed by similar reduction and acetylation, of the 12α,12′-epoxide (89) were shown to be less polar by thin layer chromatography. The mixed melting points of the corresponding diols and mono hydroxy acetates were only slightly depressed. Applying the previously mentioned principles of conformational analysis to the dehydration reactions, the 12α-axial alcohol (100) will allow facile elimination towards C_11^+. It is not possible to exclude the possibility of elimination towards C_12^+. The thionyl chloride-pyridine dehydration reaction of the 12α-alcohol in fact gave the Δ^{11,12}-olefin (98) in 85% yield. The infrared spectrum of the mother liquors showed the presence of some exocyclic olefin (85).

The 12β-equatorial-alcohol (101), however, to eliminate towards C_11 would require cis or skew elimination, so that in fact elimination towards C_12^+ is preferred. The only product isolated from the thionyl chloride-pyridine dehydration of the 12β-alcohol was the Δ^{12,12′}-olefin (85), isolated in 78% yield. It is not possible to explain the dehydration reaction analysis of the previous workers.39

Interest has been shown in Δ^{11,12}-olefins as possible precursors to 11-oxygenated steroids.39
consequence it was desirable to re-examine the reaction of methyl magnesium bromide and hecogenin, with the possibility that the product would be the $12\alpha$-hydroxy-12$\beta$-methyl steroid (88), which on dehydration would give the $\Delta$ 11,12-olefin (98). The Grignard reaction was carried out under identical conditions to those used in the literature. After acetylation of the reaction product, $12\alpha$-hydroxy-12$\beta$-methyl tigogenin 3-acetate (88) was isolated in 82% yield. This compound was shown by its physical constants and by thin layer chromatography to be identical to the previously isolated $12\alpha$-hydroxy-12$\beta$-methyl (88) compound, and different from the $12\beta$-hydroxy-12$\alpha$-methyl isomer (87).

The previously known exocyclic epoxide, originally assigned the $\beta$-configuration, now known to be the $\alpha$-epoxide, has been shown on reduction and acetylation to give the same alcohol as formed by the action of methyl lithium on the 12-ketone. Methyl lithium must therefore attack from the $\beta$-face, analogous to the attack of methyl magnesium bromide.

Reaction of the $\Delta$ 11,12-olefin with monoperphthalic acid gave the $11\alpha,12\alpha$-epoxide (102) by direct crystallisation. The mother liquors, examined by thin layer chromatography, showed only a trace of a less polar compound which could be the $11\beta,12\beta$-epoxide (103).

The assignment of the configuration of the major epoxide as the $\alpha$-epoxide was based on its reduction with
lithium aluminium hydride to give the $3\beta,12\alpha$-dihydroxy-$12\beta$-methyl (88) compound identical with the diol obtained from the reduction of the $12\alpha,12\beta$-epoxide (89). The monoacetates of these two compounds were also identical.

The reactions of both 12-keto and 12-methylene steroids described above result in the formation, in high yield, of compounds derived by $\beta$-face attack on the $sp^2$ system of the carbonyl group or double bond. This is in conflict with the statement made by one of the earlier groups of workers that "ring C reactions occur by attack from the less hindered $\alpha$-face". It is apparent from the above work that this is not the case and that $\beta$-face attack on 12-ketones or the double bond of 12-methylene compounds is never insignificant and may in fact be the dominant steric course for the reaction of Grignards on 12-ketones give 85% yield of 12$\beta$-methyl compounds. The cause of this deviation from normal ring C chemistry is apparent from a consideration of the Dreiding models for both the 12-ketone and 12-methylene compounds. In both cases the contribution from the $C_{19}$-methyl to shielding of the $\beta$-face in the vicinity of the plane $C_{11}$, $C_{12}$, $C_{13}$, $C_{12}$ (or oxygen) is negligible; in fact the $C_{19}$-methyl group is not far removed from this plane.

The remaining main hindrance normally present to attack from the $\beta$-face at or around ring C is derived from the presence of the $C_{18}$ methyl group. Again
consideration of bonding models for both the 12-ketone and 12-methylene compounds clearly demonstrate that hindrance offered to an incoming reagent by C\textsubscript{18} to the $\beta$-face is almost balanced by the hindrance to the $\alpha$-face by the symmetrically disposed C\textsubscript{14} (with respect to the C\textsubscript{11}, C\textsubscript{12}, C\textsubscript{13}, C\textsubscript{12'} (or oxygen) plane). Having disposed of the normally dominant effects of the C\textsubscript{18}- and C\textsubscript{19}-methyl groups, the product ratios ($\alpha : \beta$) depend on the balance of non-bonded interactions of secondary importance resulting in energies of the various transition states differing by less than 1 kcal, mole$^{-1}$.

Consideration of a bonding model of the $\Delta^{14}$-olefin shows that C\textsubscript{8} and C\textsubscript{14} are symmetrically disposed above and below the plane C\textsubscript{9}, C\textsubscript{11}, C\textsubscript{12}, C\textsubscript{13}, C\textsubscript{12'} . There remains however the dominant overall shielding of the $\beta$-face of the double bond by the C\textsubscript{18}- and C\textsubscript{19}-methyl groups, in accordance with the statement of the earlier authors$^{38}$ with regard to normal ring C stereochemistry.

**Boron trifluoride catalysed rearrangement of 12,12'-steroid epoxides**

The reaction of both exocyclic epoxides with boron trifluoride is dominated by a 1,2-hydride shift with cleavage of the more substituted C\textsubscript{12}-O bond with the subsequent formation of aldehyde.
Reaction of the 12,12'-epoxide (86) with boron trifluoride in benzene gave three products, which could be separated by chromatography on deactivated alumina. The first compound was a hydrocarbon. The ultraviolet spectrum showed no absorption in the 360-230m\(\mu\) region, however, absorption in the 200-220m\(\mu\) region suggested the compound to be a non-conjugated diene. The NMR spectrum which showed no olefinic protons did reveal a methyl group adjacent to a double bond (\(\gamma\) 8.37). The 21-methyl group appeared as a doublet at \(\gamma\) 8.98 (\(J = 6\)o/s) while the 27-methyl group was hidden under an absorption due to the 19-methyl group at \(\gamma\) 9.26. If the assignment of the bands at \(\gamma\) 8.37 and \(\gamma\) 9.26 to the 18- and 19- methyl groups is correct then there is no evidence of the C\_12'-protons in the NMR spectrum.

The hydrocarbon, after mild alkaline hydrolysis of the C\_3-acetate, was oxidised with osmic acid and the resulting compound reacted with lead tetra-acetate in acetic acid-tert-butanol. A spectral study of the carbonyl compound from the above cleavage reaction did not give sufficient information to allow identification of the parent hydrocarbon. The infrared spectrum of the carbonyl compound showed the presence of a five-membered ring ketone (1742cm\(^{-1}\)) and an acetyl group (1718 and 1351cm\(^{-1}\)). The presence of the acetyl group was further confirmed by a three proton signal in the NMR spectrum at \(\tau\) 7.87. Apart
from the $C_{21}$- and $C_{27}$-methyl signals the only other three proton signal was at $\tau$ 9.22, presumably due to the $C_{49}$-methyl. Elemental analysis suggested this carbonyl compound had an approximate analysis of $C_{25}O_5$, i.e., three carbon atoms have been removed in the degradation.

The second compound, the $12\beta$-aldehyde (104) was the major product of this reaction. It is envisaged as arising by a cis 1,2-hydride shift of the $C_{12}$-hydrogen atom, concerted with the rupture of the $C_{12}$-O bond (105), to give the stable $12\beta$-aldehyde. The infrared spectrum and NMR spectrum showed the presence of the aldehyde proton at 2717 cm$^{-1}$ and $\tau$ 0.4 ($J=2c/s$) respectively.

The only other product formed was an unsaturated alcohol. The infrared spectrum showed the presence of an olefinic proton at $\tau$ 4.78 and the presence of two protons at $\tau$ 6.83. The compound gave a positive test for double bond with tetranitromethane, and the ultraviolet spectrum in the region 200-220 nm also suggested the presence of a double bond.40 While the above evidence suggests the compound to be the $\Delta^{11,12}$-hydroxy olefin (106) it could not be oxidised with 2,3-dichloro-5,6-dicyanobenzoquinone or with chromic acid.

The reaction of boron trifluoride with $12\beta,12$'-epoxide in ether gave hydrocarbon and $12\beta$-aldehyde in similar yields to those obtained from the reaction with benzene as solvent. There was a small amount (10%) of diol
formed. The infrared spectrum of this compound showed strong hydroxyl absorption (3610 and 3496 cm\(^{-1}\)), and the NMR spectrum showed the presence of the CH\(_2\)OH moiety as a singlet at \(\gamma\) 5.98. Acetylation of the diol with acetic anhydride-pyridine gave an oil, the infrared spectrum of which showed the presence of the \(\text{C}_{12}-\text{tert}-\text{hydroxyl group. It is probable that this diol results from hydrolysis of the boron-trifluoride-epoxide complex in the isolation procedure. Hydrolysis will occur at } \text{C}_{12}'\text{, analogous to lithium aluminium hydride reduction of the epoxide, to give the } \text{C}_{12}'\text{,12''-diol (107).}

Reaction of the \(12\alpha',12''\)-epoxide with boron trifluoride in benzene gave after direct crystallisation of the reaction product the \(12\alpha\text{-aldehyde (108). The infrared and NMR spectrum showed the presence of the aldehyde proton at 1725 cm\(^{-1}\) and } \gamma\text{ 0.15 (} \nu Internet\text{=30/s). This aldehyde must arise by the concerted rupture of the } \text{C}_{12}-0\text{ bond with a } \text{cis 1,2-hydride shift (109). Treatment of this aldehyde with alcoholic potassium hydroxide gave, after acetylation of the } \text{C}_{3}\text{-hydroxy group the more stable } \text{C}_{12}'\text{-aldehyde (104) identical with the major product of the rearrangement of the } \text{C}_{12}'\text{-epoxide with boron trifluoride. Chromatography on deactivated alumina of the mother liquors from which the } \text{C}_{12}\alpha\text{-aldehyde was crystallised gave } \text{C}_{12}'\text{-aldehyde (104). It was subsequently shown that the } \alpha\text{-aldehyde (108)
epimerised to the more stable $\beta$-aldehyde (104) on de-
activated alumina. The only other compounds obtained after
chromatography were oils. The first compound was a hydro-
carbon, which was not the same as the hydrocarbon obtained
from the $\beta$-epoxide rearrangement. The second oil was
shown by thin layer chromatography to be just one compound,
and its retention suggested it to be a diol.

Reaction of the $12\alpha,12^\prime$-epoxide with boron tri-
fluoride in ether gave largely aldehyde. Direct crystal-
lisation gave the $12\alpha$-aldehyde (108). Chromatography of
the mother liquors in addition to giving $12\beta$-aldehyde (104)
gave hydrocarbon identical to that obtained from the
$12\beta,12^\prime$-epoxide.

**Boron trifluoride catalysed rearrangement of the**
$11\alpha,12\alpha$-epoxide

Due to the ready availability of the $12$-methyl-
$\Delta^{11,12}$-olefin (98), by dehydration of the tert-alcohol
formed by the reaction of methyl magnesium bromide on
hecogenin acetate, it was considered of interest to convert
the olefin into the $11,12$-epoxides and to include the boron
trifluoride catalysed rearrangements of the epoxides in the
present study. Only the $\alpha$-epoxide (102) was in fact
formed.

Reaction of the $12\beta$-methyl-$11\alpha,12\alpha$-epoxide (102)
with boron trifluoride in benzene was shown by thin layer
chromatography to give two major products. Direct crystallisation of the reaction product gave an olefinic alcohol. It has not been possible to assign the structure of this compound without doubt, however it seems probable it is the 9α-hydroxy-Δ^{12,12'}-compound (110). The infrared spectrum showed the presence of hydroxyl at 3610cm⁻¹ and the presence of exocyclic methylene protons at 1640cm⁻¹. The tertiary character of the alcohol was demonstrated by the inability to effect acetylation with acetic anhydride-pyridine, or oxidation with chromic acid. The ultra violet spectrum showed absorption (\( E_{200} \) 2060) consistent with the double bond being only disubstituted. This compound did not colour tetranitromethane. The NMR spectrum showed the presence of an exocyclic methylene group with signals at \( \gamma \) 5.12 and \( \delta \) 4.94. Oxidation of this compound with osmic acid, followed by cleavage of the resulting diol with lead tetra-acetate gave an oil which showed absorption in the infrared spectrum at 1706cm⁻¹ due to a six-membered ring ketone. This demonstrates that the double bond of the parent olefin is exocyclic to a six-membered ring. The NMR spectrum of the hydroxy olefin shows the C₁₈- and C₁₉-methyl signals at \( \gamma \) 9.12 and \( \delta \) 8.97 respectively. The chemical shift of the C₁₈- and C₁₉-methyl groups due to the introduction of the 9α-hydroxy function is \( \Delta \gamma \), 0.01 and 0.13 respectively. (Zurcher quotes values \( \Delta \gamma \), 0.00 and 0.142 respectively.)
The only other product formed from this rearrangement was the 12β-methyl-11-ketone (110) isolated by chromatography of the mother liquors from the crystallisation of the 9α,12,12'-olefin (110). The presence of the six-membered ring ketone was demonstrated by the infrared absorption at 1712 cm⁻¹. The NMR spectrum showed the C₁₉-methyl group at 8 8.97 consistent with the deshielding to be expected for the 11-ketone. The 12-methyl group appeared as a doublet centred at 8 8.82 (J = 5 Hz). The compound was shown to exist as the most stable 12β-methyl isomer, as demonstrated by inability to epimerise the compound by adsorption onto alumina. This ketone is imagined to arise by a cis 1,2-hydride shift concerted with the rupture of the C₁₂-0 bond (112). The 12α-methyl-11-ketone (113) so formed would epimerise on the deactivated alumina used in the initial chromatography, to give the more stable 12β-methyl-11-ketone.

An analysis of the 11α,12α-epoxide-boron trifluoride reaction is complex since two conflicting tendencies need to be considered. C₁₂-0 cleavage would yield the more stable tertiary C₁₂-carbonium ion (compared with the secondary C₁₁-carbonium ion). However, in contrast the conformationally preferable 'axial cleavage' of an epoxide would occur via C₁₁-0 cleavage rather than C₁₂-0 cleavage. The minor product, the 11-keto-12-methyl compound (111) is formed via C₁₂-0 cleavage while the
9 α-hydroxy-Δ12,12'-olefin could only be formed via C11-O cleavage followed by electronic shifts similar to sequence (114).

**Perchloric acid catalysed rearrangement of the ring C epoxides**

The perchloric acid catalysed rearrangement of the 12β,12'-epoxide in acetone-methylene chloride gave two products. The hydrocarbon, as formed from the boron trifluoride catalysed rearrangement of the same epoxide, was formed as the major product. No aldehyde was formed. The other product is assigned the cyclic ether structure (115). The perchloric acid catalysed rearrangement of the 12α,12'-epoxide gave this same cyclic ether (115) as the major product. This compound shows no hydroxyl absorption in the infrared spectrum and no double bond absorption in the ultraviolet spectrum in the region 360-200 μm. The NMR spectrum shows the \( \text{CH}_2\text{O} \) moiety at \( τ=6.05 \) (\( J=3\alpha/\alpha \)). The absence of any absorption other than the 3α,16α and 26-hydrogen atoms in this region shows that the ether is linked to a tertiary carbon position. It is imagined that the cyclic ether arises by a mechanism involving two 1,2-hydride shifts (116).

Also formed from the acid catalysed rearrangement of the 12α,12'-epoxide was a trace of an aromatic compound, which was not further studied, and a small amount (10%) of
12β-12'-aldehyde (104).

The 12β-methyl-11α,12α-epoxide (102) showed no reaction in twelve hours with perchloric acid.

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<th>Compound</th>
<th>C-19</th>
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<tbody>
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<td>0.15(J=3c/s)</td>
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<td>9.03</td>
<td>9.13</td>
<td>6.05(J=3c/s)</td>
</tr>
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EXPERIMENTAL

12-Methylene tigogenin acetate

An ethereal solution of butyl lithium (1.5N; 380ml) was added to a suspension of methyl tri-phenyl phosphonium bromide (178g) in dry ether (2.5l). The solution was stirred under a nitrogen atmosphere for 3 hr. Hecogenin acetate (22.5g) in dry ether (1.5l) was added, and the resulting solution stirred overnight. Ether was distilled off at the same time as tetrahydrofuran was added, until most of the ether had been replaced. The mixture was then refluxed for 6 hr, cooled, diluted with water and extracted with ether. After successive washings with hydrochloric acid (2N) and water the total reaction mixture was dissolved in pyridine (100ml) and acetic anhydride (40ml) and left at room temperature for 18 hr. After extraction of the steroidal material with ether, the product was adsorbed onto alumina (2kg). Elution with light petroleum and crystallisation from acetone gave 12-methylene tigogenin acetate (20.5g), m.p. 180-182°, $[\alpha]_D^{24} -18^0 (c 1,02)$, $\lambda_{max}$ 1742, 1242, 1650 and 885 cm$^{-1}$. (Lit. 39 m.p. 179.5-189.5°, $[\alpha]_D^{24} -24.1$).
Preparation of 12,12'-epoxides

To a solution of 12-methylene-tigogenin acetate (21.5g) in dry benzene (21) was added an ethereal solution of monoperphthalic acid (0.7M; 200ml). The solution was kept at room temperature overnight. The steroidal material was isolated by use of ether, and adsorbed onto alumina (1kg). Elution with light petroleum-benzene (3:7) and crystallisation from acetone gave 3β-acetoxy-12,12'-epoxy-5α,25D-spirostan as needles (6.2g), m.p. 172-173°C, $[\alpha]_D -62^o$ (e 1.17), $\lambda_{max}$ 1742 and 1242cm$^{-1}$. (Found: C, 74.6; H, 9.7. C$_{30}$H$_{46}$O$_5$ requires C, 74.0; H, 9.5%).

Elution with benzene, benzene-ether gave after crystallisation from methanol 3β-acetoxy-12α,12'-epoxy-5α,25D-spirostan as needles (10.8g), m.p. 242-243°C, $[\alpha]_D -10^o$ (e 0.93), $\lambda_{max}$ 1742 and 1242cm$^{-1}$. (Found: C, 74.3; H, 9.5. C$_{30}$H$_{46}$O$_5$ requires C, 74.0; H, 9.5%). (cf. Lit. 38 β-epoxide m.p. 240-242°C, $[\alpha]_D -24^o$ (e 1.2).

Reduction of 12β,12'-epoxide

To a solution of the 12β,12'-epoxide (500mg) in dry tetrahydrofuran (50ml) was added lithium aluminium hydride (500mg) and the resulting suspension heated under reflux for 4 hr. After careful addition of ethyl acetate the steroidal material was isolated by use of ether. Crystallisation from light petroleum-methanol gave
12β-hydroxy-12α-methyl-tigogenin as needles (350mg), m.p. 200–201°, [α]D -40° (c 1.05), Η max. 3610 cm⁻¹. (Found: C, 74.7; H, 10.4. C₂₆H₄₆O₄ requires C, 75.3; H, 10.4%).

A solution of 12β-hydroxy-12α-methyl-tigogenin (280mg) pyridine (6ml) and acetic anhydride (1.2ml) was kept at room temperature overnight. Isolation by use of ether and crystallisation from light petroleum gave 3β-acetoxy-12β-hydroxy-12α-methyl-tigogenin as flakes (241mg), m.p. 226–227°, [α]D -50° (c 1.20), Η max. 3610, 1742 and 1242 cm⁻¹. (Found: C, 74.2; H, 10.2; C₂₆H₄₆O₅ requires C, 73.7; H, 9.9%).

**Dehydration of 3β-acetoxy-12β-hydroxy-12α-methyl-tigogenin**

A solution of the 12β-alcohol (190mg) in pyridine (6ml) and thionyl chloride (0.09ml) was kept at -20° for 30 min. Isolation by use of pentane, and crystallisation from acetone gave 12-methylene-tigogenin acetate (116mg), m.p. and m.m.p. with authentic sample 178–180°.

**Reduction of 12α,12'-epoxide**

To a solution of 12α,12-epoxide (750mg) in dry tetrahydrofuran (100ml) was added lithium aluminium hydride (750mg) and the resulting suspension heated under reflux for 4 hr. After careful addition of ethyl acetate the steroidal material was isolated by use of ether.
Crystallisation from light petroleum gave 12α-hydroxy-12β-methyl-tigogenin as fine needles (660mg), m.p. 210° (soften 115-126°), [α]D -33° (c 0.91), ν max. 3610 cm⁻¹. (Found: C, 74.7; H, 10.6. C_{28}H_{46}O_{4} requires C, 75.3; H, 10.4%).

A solution of the 12α-hydroxy-12β-methyl-tigogenin (550mg) in pyridine (10ml) and acetic anhydride (2.0ml) was kept at room temperature overnight. Isolation by use of ether and crystallisation from light petroleum gave 3β-acetoxy-12α-hydroxy-12β-methyl-5α,25D-spirostan as flakes (500mg), m.p. 222-223°, [α]D -35° (c 1.06), ν max. 3610, 1742 and 1242 cm⁻¹. (Found: C, 73.6; H, 10.0. C_{30}H_{48}O_{3} requires C, 73.7; H, 9.9%).

Dehydration of 3β-acetoxy-12α-hydroxy-12β-methyl-5α,25D-spirostan

A solution of the alcohol (400mg) in pyridine (6.0ml) and thionyl chloride (0.18ml) was kept at 20° for 30 min. Isolation by use of pentane and crystallisation from methanol gave 12-methyl-Δ^{11}-tigogenin acetate as fine needles (340mg), m.p. 156°, [α]D -47° (c 0.85), ν max. 1742, 1242 cm⁻¹. (Found: C, 76.5; H, 10.0. C_{30}H_{46}O_{4} requires C, 76.5; H, 9.9%). (Lit. 35 m.p. 162.5-164.5°, [α]D -45°).
Grignard on hecogenin acetate

A solution of hecogenin acetate (4.0g) in dry benzene (40ml) was added over 30 min. with stirring to ethereal methyl magnesium bromide (1.5M; 26ml). After stirring for 3 hr. a solution of ethyl acetate (0.5ml) in benzene (5ml) was added followed by aqueous ammonium chloride (10%; 30ml). Extraction of the steroidal material in the usual manner gave a solid shown by thin layer chromatography to be a mixture of diol and mono-hydroxy-mono-acetate. Acetylation of this mixture by reaction with acetic anhydride-pyridine (1:10) at 100° for 45 min. gave 3-aceotoxy-12-hydroxy-12-methyl-5α,25D-spirostane, crystallised from light petroleum as flakes (3.3g), m.p. and m.m.p. with an authentic sample 222-223°, $[\alpha]_D^2 = -35^\circ$ (g 1.03). The mother liquors (520mg) were shown by thin layer chromatography to contain only a trace of the less polar 12β-hydroxy isomer.

Epoxidation of 3β-acetoxy-12-methyl-5α,25D-spirost-11,12-ene

To a solution of 3β-acetoxy-12-methyl-5α,25D-spirost-11,12-ene (24g) in chloroform (800ml) was added an ethereal solution of monoperphthalic acid (450ml; 0.65N) and the solution kept at room temperature for 1 hr. Isolation of the steroidal material by use of ether and crystallisation from methanol gave 3β-acetoxy-12β-methyl-11α,12α-epoxy-5α,25D-spirostane (17g) m.p. 204-205°,
$[\alpha]_D^{20} = -52^\circ$ (c 1.10), $\nu_{\max}$ 1742 and 1242 cm$^{-1}$. (Found: C, 73.6; H, 9.5. C$_{30}$H$_{46}$O$_5$ requires C, 74.0; H, 16.4%).

The mother liquors on examination by thin layer chromatography showed only a faint trace of a less polar compound which could be the 11$\beta$,12$\beta$-epoxy isomer.

Reduction of the 11$\alpha$,12$\alpha$-epoxide

To a solution of the 11$\alpha$,12$\alpha$-epoxide (1g) in dry ether (100ml) was added lithium aluminium hydride (1.0g) and the mixture heated under reflux for 10 hr. After careful addition of ethyl acetate the steroidal material was isolated by use of ether. The resulting product was adsorbed onto deactivated alumina (25g). Elution with benzene gave after crystallisation from methanol 3$\beta$-hydroxy-11$\alpha$,12$\alpha$-epoxy-12$\beta$-methyl-5$\alpha$,25D-spirostan (306mg), m.p. 234-236$^\circ$; $[\alpha]_D^{20} = -49^\circ$ (c 0.97). (The acetate, m.p. and m.m.p. with an authentic sample 203-205$^\circ$.)

Elution with ether and crystallisation from light petroleum gave 12$\alpha$-hydroxy-12$\beta$-methyl tigogenin as fine needles (670mg) m.p. and m.m.p. with an authentic sample 210-211$^\circ$ (The acetate, m.p. and m.m.p. with an authentic sample 222$^\circ$). These compounds were shown by thin layer chromatography to be pure and to differ from the less polar 12$\beta$-hydroxy isomer.
Reaction of 3β-acetoxy-12β,12′-epoxy-5α,25D-spirostan-24C with boron trifluoride in benzene

The 12β,12′-epoxide (1.8g) in anhydrous benzene (180ml) was treated with boron trifluoride-etherate (1.8ml) for 1 min., then ether added and the solution washed with aqueous sodium bicarbonate and water. The solvents were removed and the product adsorbed onto deactivated alumina (100g). Elution with light petroleum-benzene (10:1) gave a hydrocarbon (524mg) which crystallised from ethanol as cubes, m.p. 140-141°C, [α]D -49° (c 1.235), UV: λ 220 4550, ɛ 245 8450, ɛ 210 12,000, ɛ 205 15,200, 200 17,600, ʋ max. 1742 and 1242cm⁻¹. (Found: C, 76.5; H, 9.8. C₃₀H₄₆O₄ requires C, 76.9; H, 9.5%).

Elution with light petroleum-benzene (1:1) gave 3β-acetoxy-5α,25D-spirostan-12β-aldehyde (735mg) which crystallised as needles from light petroleum, m.p. 178-179°C, [α]D -106° (c 1.14), ʋ max. 2717cm⁻¹. (C=O), 1739 and 1242cm⁻¹. (Found: C, 73.9; H, 9.6. C₃₀H₄₆O₅ requires C, 74.0; H, 9.5%).

Elution with ether gave an unsaturated alcohol (350mg) crystallised as needles from methanol, m.p. 219-222°C, [α]D -47° (c 0.74), UV: λ 220 840, ɛ 245 1,170, ɛ 210 2,080, ɛ 205 4,170, ɛ 200 7,800, ʋ max. 3571, 1742, 1242, and 1639cm⁻¹. This compound did not acetylate with acetic anhydride-pyridine at room temperature. It could not be oxidised with 2,3-dichloro-5,6-dicyano-benzoquinone, or with chromic acid.
Oxidation of hydrocarbon

A solution of hydrocarbon (250mg), osmium tetroxide (500mg), pyridine (3ml) and benzene (10ml) was kept at room temperature for 3 weeks. Hydrogen sulphide was passed through the solution, and the precipitated osmium sulphide filtered. Evaporation of solvents gave a solid which with potassium hydroxide (250mg) in aqueous ethanol (90%; 25ml) was heated under reflux for 2 hr. The product isolated by use of ether was stirred with lead tetra-acetate (2g) in tert-butanol (30ml), acetic acid (30ml), for 18 hr at room temperature. After addition of ethylene glycol (10ml) the steroidal material, extracted by use of ether, gave on crystallisation from light petroleum carbonyl compound (130mg), m.p. 164-165°,[α]D -26.4 (c 1.33), λ max. 3597 cm⁻¹ (OH), 1742 cm⁻¹ (5-membered ring ketone), 1718 and 1354 cm⁻¹. (COCH₃), (Found: C, 71.5; H, 9.4%).

Reaction of 3β-acetoxy-12β,12'-epoxy-5α,25D-spirostan with boron trifluoride in ether

The 12β,12'-epoxide (1.6g) and boron trifluoride-etherate (1.6ml) were allowed to react in anhydrous ether (160ml) for 3 min. After the solution was washed with aqueous sodium bicarbonate and water, the solvents were removed and the product adsorbed onto deactivated alumina (100g). Elution with light petroleum-benzene (3:1) gave
hydrocarbon (50µmg) m.p. and m.m.p. with previous sample 140-141°. Elution with light petroleum-benzene (1:1) gave $3\beta$-acetoxy-5α,25D-spirostane 12$\beta$-aldehyde (706mg), m.p. and m.m.p. with previous sample 178-179°. Elution with ether gave diol. Crystallised from light petroleum as needles (175mg), 165-166°, $[\alpha]_D^{20} -46°$ (c 0.97), $\nu_{\text{max.}}$ 3610, 3496, 1745 and 1242 cm$^{-1}$ (Found: C, 71.1; H, 9.5.

C$_{30}$H$_{48}$O$_6$ requires C, 71.4; H, 9.6%)

Acetylation of diol (10mg) with acetic anhydride-pyridine for 1 hr at 100° gave an oil, $\nu_{\text{max.}}$ 3610, 1742 and 1242 cm$^{-1}$.

Rearrangement of $3\beta$-acetoxy-12$\beta$,12'-epoxy-5α,25D-
spirostane with perchloric acid

A solution of 12$\beta$,12'-epoxide (1g) in methylene chloride (30ml) and acetone (60ml) was treated with aqueous perchloric acid (1.5M; 1.0ml). After 15 min at 20° the solution was diluted with water and the organic phase washed neutral. The solvents were removed and the product adsorbed onto alumina (80g). Elution with light petroleum-benzene (9:1) gave hydrocarbon (809mg) m.p. and m.m.p. with previous sample 140-141°. Elution with benzene gave cyclic ether (180mg), m.p. 210-211°$[\alpha]_D^{20} -35°$ (c 0.90), UV:

$\epsilon_{200}$ 640, $\epsilon_{205}$ 430, $\epsilon_{210}$ 270, $\epsilon_{215}$ 230, $\epsilon_{220}$ 210,

$\nu_{\text{max.}}$ 1742 and 1242 cm$^{-1}$, (Found: C, 72.7; H, 9.4; F, 0.0.

C$_{30}$H$_{46}$O$_5$ requires C, 74.0; H, 9.5%).
Reaction of 3β-acetoxy-12α,12'-epoxy-5α,25D-spirostan-12α-aldehyde with boron-trifluoride in benzene

The 12α,12'-epoxide (1.6g) in anhydrous benzene (160ml) was treated with boron trifluoride-etherate (1.6ml) for 5 min. Ether was added and the solution washed with aqueous sodium bicarbonate and water. After removal of solvents crystallisation from methanol gave 3β-acetoxy-5α,25D-spirostan-12α-aldehyde (290mg) as needles, m.p. 190-193°, [α]D -30° (c 0.94), λmax 2725cm⁻¹ (e 310), 1742 and 1242cm⁻¹. (Found: C, 73.7; H, 9.6. C30H46O5 requires C, 74.0; H, 9.5%). After removal of solvents from the mother liquor the residue was adsorbed onto deactivated alumina (80g). Elution with light petroleum-benzene gave hydrocarbon (300mg) which was not further examined.

Elution with benzene and crystallisation from light petroleum gave 3β-acetoxy-5α,25D-spirostan-12β-aldehyde (500mg), m.p. and m.m.p. 178-179°, [α]D-106° (c 0.95). Elution with ether gave an oil (195mg) which was not further examined.

Epimerisation of 3β-acetoxy-5α,25D-spirostan-12α-aldehyde

The 12α-aldehyde (180mg) and potassium hydroxide (200mg) were dissolved in aqueous ethanol (90%; 20ml) and kept at room temperature for 18 hr. The isolated product, λmax 3610, 2725 and 1742cm⁻¹ in pyridine-acetic anhydride was kept at room temperature for 18 hr. Isolation in the
usual manner and crystallisation from light petroleum gave
3\( \beta \)-acetoxy-5\( \alpha \),25D-spirostane 12\( \beta \) - aldehyde (180mg),
m.p. and m.m.p. 178-179°.

**Reaction of 3\( \beta \)-acetoxy-12\( \alpha \),12\( \beta \)'-epoxy-5\( \alpha \),25D-spirostane**

with boron trifluoride in ether

The 12\( \alpha \),12\( \beta \)-epoxide (1.65g) in anhydrous ether
(165ml) was treated with boron trifluoride-etherate (1.6ml)
for 35 min. Isolation of steroidal material in the usual
manner and crystallisation from methanol gave 3\( \beta \)-acetoxy-
5\( \alpha \),25D-spirostane 12\( \alpha \) - aldehyde (450mg), m.p. and m.m.p.
190-193°, \([\alpha]_D^{25}-30° (c 0.96)\). The solvents were removed
from the mother liquors and the residue adsorbed onto
deactivated alumina (100g). Elution with light petroleum-
benzene (10:1) gave hydrocarbon (327mg) m.p. 139-140°,
identical in all respects with previous sample. Elution
with benzene and crystallisation from light petroleum gave
3\( \beta \)-acetoxy-5\( \alpha \),25D-spirostane 12\( \beta \)-aldehyde (311mg), m.p.
and m.m.p. 178-179°. Elution with ether gave an oil (150mg)
which was not further examined.

**Rearrangement of 3\( \beta \)-acetoxy-12\( \alpha \),12\( \beta \)'-epoxy-5\( \alpha \),25D-
spirostane with perchloric acid**

A solution of the 12\( \alpha \),12\( \beta \)-epoxide (1g) in methylene
chloride (10ml) and acetone (50ml) was treated with
perchloric acid (1.5M; 4.0ml). After 18 hr at room
temperature the solution was diluted with water and the organic phase washed neutral, and the solvents removed. Crystallisation from methanol gave cyclic ether (370mg), m.p. 220-222°, \([\alpha]_D^{25} -35^0 (c 1.15)\), identical in all respects with previous sample. The solvent was removed from the mother liquors and the residue adsorbed onto deactivated alumina (60g). Elution with light petroleum and crystallisation from pentane gave aromatic compound as needles (190mg), m.p. 196-198°, \([\alpha]_D^{25} -69^0 (c 0.96)\) \(\lambda_{max.} 261.2, 254.8 (\epsilon 980), 249.1, 243.4, 238.2, 233.2m\mu\), \(\upsilon_{max.} 1742\) and 1242cm\(^{-1}\), (Found: C, 75.8; H, 10.2%). Elution with light petroleum-benzene (2:1) gave 3\(\beta\)-acetoxy-5\(\alpha\),25D-spirostan 12\(\beta\)-aldehyde (100mg) m.p. and m.m.p. 176-177°. Elution with benzene gave further cyclic ether m.p. and m.m.p. 220-222°.

Reaction of 3\(\beta\)-acetoxy-11\(\alpha\),12\(\alpha\)-epoxy-12\(\beta\)-methyl-5\(\alpha\), 25D-spirostan with boron trifluoride in benzene

The 11\(\alpha\),12\(\alpha\)-epoxy-12\(\beta\)-methyl compound (2.7g) in anhydrous benzene (270ml) was treated with boron trifluoride-etherate (2.7ml) for 1 hr. Isolation of the steroidal material in the usual manner and crystallisation from light petroleum gave 3\(\beta\)-acetoxy-9\(\alpha\)-hydroxy-12-methylene-5\(\alpha\),25D-spirostan (1.3g), m.p. 223-224°, \([\alpha]_D^{25} -54^0 (c 1.06)\), UV: \(\epsilon 210 0, \epsilon 205 820, \epsilon 200 2960, \upsilon_{max.} 3610, 1742, 1640,\) and 1242cm\(^{-1}\), (Found: C, 73.8; H, 9.5, \(\% 3046\)).
C, 74.0; H, 9.5%). This alcohol could not be acetylated by reaction with acetic anhydride-pyridine or oxidised with chromic acid.

After removal of solvents, from the mother liquors from the above crystallisation of hydroxy olefin, the residue was adsorbed onto deactivated alumina (150g). Elution with light petroleum-benzene (1:1) and crystallisation from methanol gave \( \beta\beta\text{-acetoxy-12}\beta\text{-methyl-5}\alpha,25\text{D-spirostan-11-one} \) (410mg) as needles, m.p. 194-195°, \( [\alpha]_D -49^0 \) (c 0.88), \( \epsilon_{\text{max}} \) 1742 and 1242 cm\(^{-1}\) (-\( \alpha \)Ac), 1712 cm\(^{-1}\) (six-membered ring ketone). (Found: C, 74.0; H, 9.7. \( C_{30}H_{46}O_5 \) requires C, 74.0; H, 16.4%). Elution with benzene, benzene-ether gave further hydroxy olefin (210mg), m.p. and m.m.p. 223-224°.

\( \beta\beta\text{-Acetoxy-12}\beta\text{-methyl-5}\alpha,25\text{D-spirostan-11-one} \) was adsorbed onto alumina for 24 hr. Elution with ether and crystallisation from methanol gave back unchanged starting material, m.p. and m.m.p. 194-195°.

**Oxidation of \( \beta\beta\text{-acetoxy-9}\alpha\text{-hydroxy-12-methylene-5}\alpha,25\text{D-spirostane} \)**

A solution of \( \beta\beta\text{-acetoxy-9}\alpha\text{-hydroxy-12-methylene-5}\alpha,25\text{D-spirostane} \) (100mg) and potassium hydroxide (100mg) in aqueous ethanol (10ml; 90%) was kept at room temperature overnight. Isolation of the steroidal material in the usual manner gave a solid which with osmic acid (100mg) in
pyridine (10ml) was kept at room temperature for 2 weeks. Hydrogen sulphide was passed through the solution, and the precipitated osmium sulphide filtered. Evaporation of solvents gave an oil (60mg). The oil with lead tetra-acetate (100mg) in acetic acid-tert-butanol (20ml, 1:1) was stirred for 24 hr. After addition of ethylene glycol (5ml) the steroidal material was extracted by use of ether to give after removal of solvents an oil (42mg), \( \text{max. 1701 cm}^{-1} \).
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