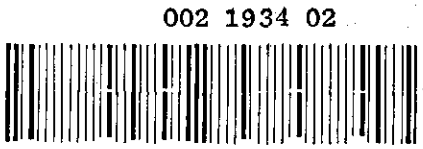

STUDIES RELATED TO THE WESTPHALEN REARRANGEMENT

A Thesis

Submitted by

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and supervised by Dr. Brian A.Marples, B.Sc., Ph.D.

in Partial Fulfilment of the

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The author would like to thank Dr. B.A.Marples for his valuable and stimulating suggestions, and to the staff of the Organic Chemistry Laboratories for some enthusiastic discussions.

I am also grateful to my wife, Josephine, for her encouragement.

Finally my thanks go to the Science Research Council for their financial support.

Summary.-

The reaction of four 3β-hydroxy-derivatives of Westphalen's diol with lead tetraacetate is described. The major products are the ethers 6β-acetoxy-3β,5-oxaethano-19-nor-5β-cholest-9(10)-ene (11[5]), 6β-acetoxy-9α,10-epoxy-3β,5-oxaethano-19-nor-5β,10α-cholestane, 6β-acetoxy-9β,10-epoxy-3β,5-oxaethano-19-nor-5β,9β-cholestane, and 6β-acetoxy-14-methyl-3β,5-oxaethano-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-ene in which the original 5β-methyl group has been functionalised. Oxidation of (11[5]) with chromic acid gave products of attack at the 9,10-double bond and/or the allylic position 11. The reduction of (11[5]) and subsequent oxidation and boron-trifluoride catalysed cleavage of the tetrahydrofuran ring is described.

The photolysis of two 3β-nitrite ester-derivatives of Westphalen's diol is described. The major products are 6β-acetoxy-9α,10-epoxy-5-syn-oximino-19-nor-5β,10α-cholestan-3β,ol, 6β-acetoxy-9α,10-epoxy-5-anti-oximino-19-nor-5β,10α-cholestan-3β-ol, and 6β-acetoxy-9β,10-epoxy-5-oximino-19-nor-5β,9β-cholestan-3β-ol. Deamination of the oximes to the respective hemiacetyl acetates is described.

Aprotic deamination of 3β,6β-diacetoxy-5α-aminocholestane gave a Westphalen rearrangement in which an increased ratio of Hofmann to Saytzeff product is obtained. Deamination of 6α-aminocholestan-3β,5β-diol gave

3β-hydroxy-A-homo-B-nor-5β-cholestan-4a-one. 6-Aminocholest-4,6-diene-3-one and 2-amino-5α-cholest-1-en-3-one are formed from 6α-azidocholest-4-en-3-one and 2β-azido-5α-cholestan-3-one respectively and spectroscopic data are reported for these enamines.

The 6β-acetoxy-,6-desoxy-, and 6-keto-derivatives of 3β-benzyloxy-5β-methyl-19-nor-cholestan-10-ol under dehydrating conditions rearrange to give the corresponding backbone rearranged products.

The 6α-acetoxy-,6β-acetoxy-, and 6-keto-derivatives of 3β-acetoxy-4,4-dimethyl-5α-cholestan-5-ol; 6α-acetoxy-, 6β-acetoxy-, and 6-keto-derivatives of 3β-acetoxy-4β-methyl-5α-cholestan-5-ol; and 3β,6β-diacetoxy-4α-methyl-5α-cholestan-5-ol undergo rearrangement, under Westphalen conditions, to give the corresponding 5β-methyl-$\Delta^{9(10)}$-compounds. The 6α-acetoxy- and 6-keto-derivative of 3β-acetoxy-4α-methyl-5α-cholestane-5-ol; and 6-desoxy-4,4-dimethyl-5α-cholestan-5-ol give elimination and/or acetylation. The 6β-acetoxy- and 6-keto-derivatives of 3β-methoxy-19-methyl-5α-cholestan-5-ol and 3β,6β-diacetoxy-10-ethenyl-5α-cholestan-5-ol rearrange, under Westphalen conditions, to give the 5β-ethyl-$\Delta^{9(10)}$-compounds and 5β-ethenyl-$\Delta^{9(10)}$-compound respectively. These results and rate data for some of the above reactions suggest that alkyl group migration is concerted with the heterolysis of the C(5)-O bond.

Deuteration studies in the rearrangement of the 10-ethenyl-5α-hydroxy-steroid suggest that a protonated cyclopropyl intermediate is involved.

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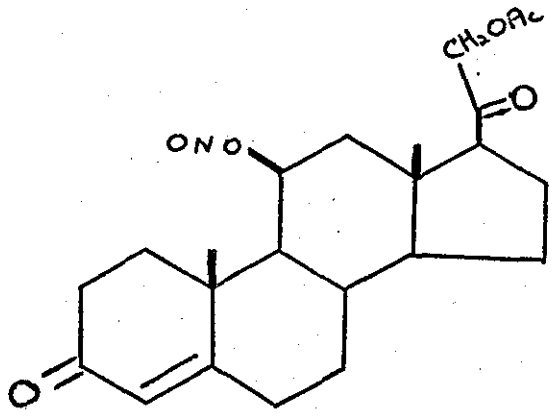
Introduction.-

Controlled introduction of substituents at the angular methyl groups in the steroid molecule was for years regarded as impracticable. The need for synthetic routes to naturally occurring hormones (e.g. aldosterone) catalysed research into methods of attacking the quaternary methyl group in steroids.

Realisation that hydrogen transfer can occur from an unactivated methyl group, given a suitable reactive species,[1] led to a search for alternative reactions of a similar nature. This resulted in the now accepted fact that an efficient hydrogen transfer reaction requires the generation of a free radical, or similarly reactive species, in close conformational proximity to an angular methyl which permits transfer through a six-membered transition state. This is well illustrated in the syntheses of aldosterone by the Barton reaction.[2] This involved the photolysis of the C-11β nitrite ester [1] forming the C-11β alkoxy radical [2] which in turn abstracts hydrogen from the C-18, via a six-membered transition state. The resulting methylene radical [3] after recombination with nitric oxide gives the nitroso monomer [4] which could be isolated as the corresponding nitroso dimer, or after isomerisation, as aldosterone acetate oxime [5]. Other common methods for generation of free radicals are by fragmentation of hypohalites and from alcohols by the action of lead tetraacetate.



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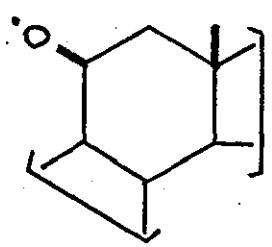

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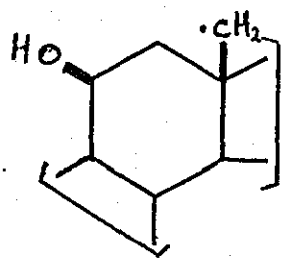

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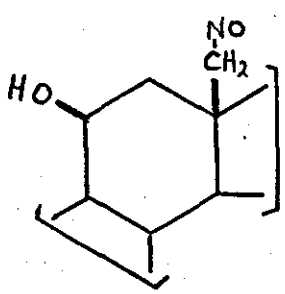

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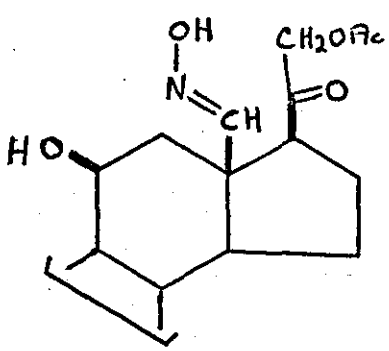
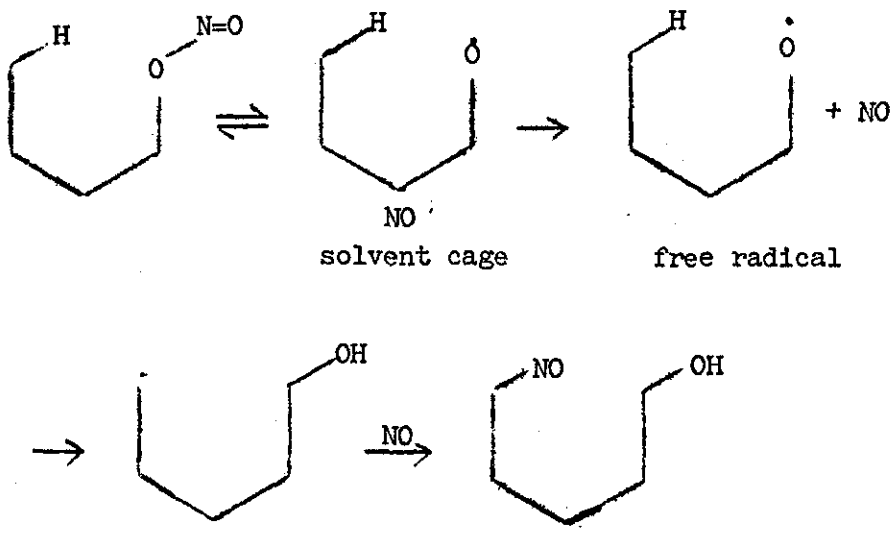


[5]

The Barton reaction was originally formulated to involve a four centred transitional species giving rise to a completely intramolecular radical induced group interchange. This mechanism was discarded by Akhtar[3] who suggested that the Barton reaction is best explained in terms of a 'non-cage free radical process' as indicated below.



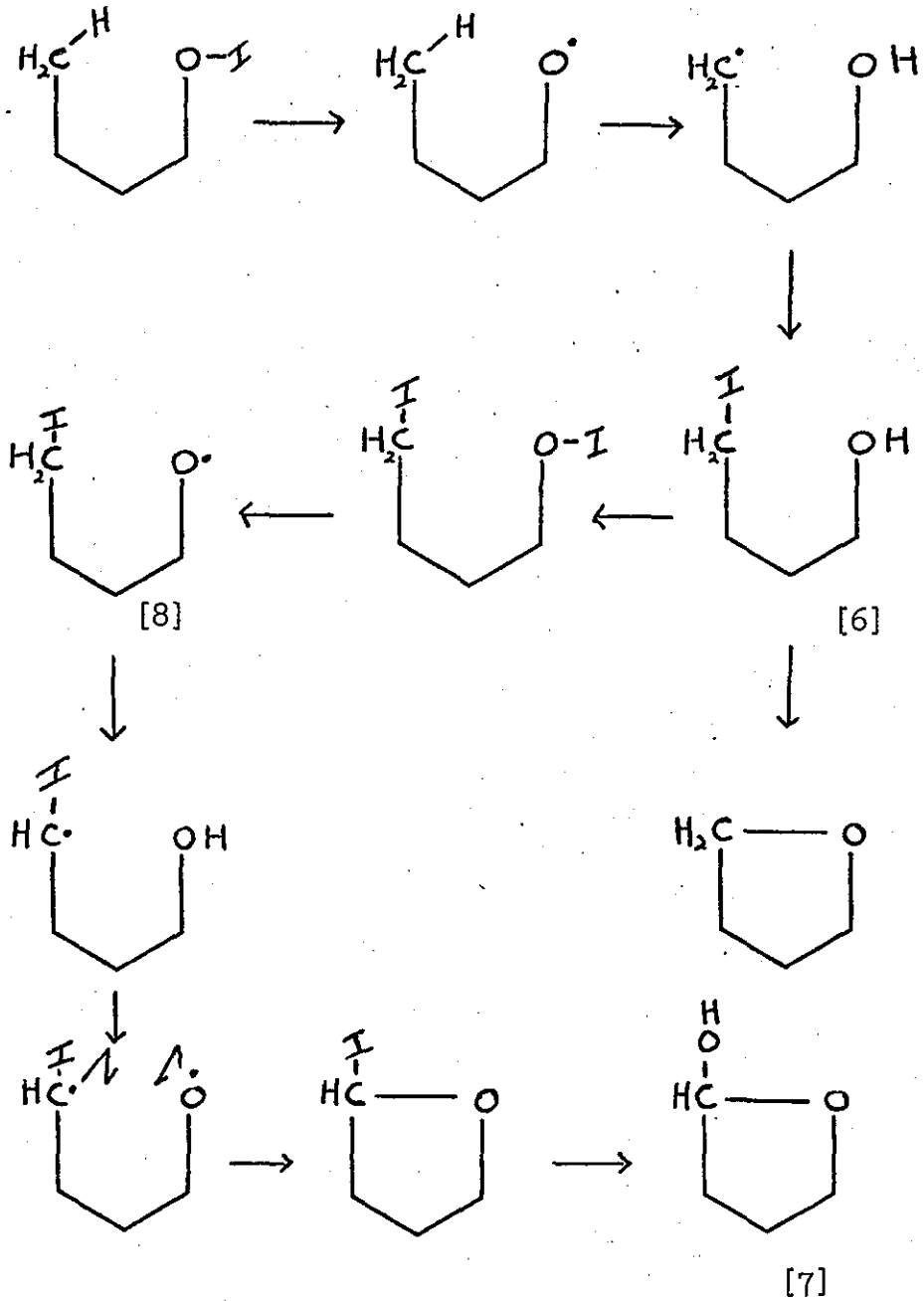
This was rationalised by irradiation of a mixture of cholestan-6β-ol and androstane-6β-ol nitrite esters containing isotopic nitrogen N^{15} and N^{14} respectively to half reaction. The recovered nitroso alcohols showed almost complete isotopic scrambling whilst the ~~exchanged~~ recovered nitrite esters showed no significant scrambling. Later work[4] has shown that photolysis of nitrite esters in the presence of suitable radical

sources (i.e. bromine) affords a product in which bromine is substituted at the δ-carbon atom rather than NO.

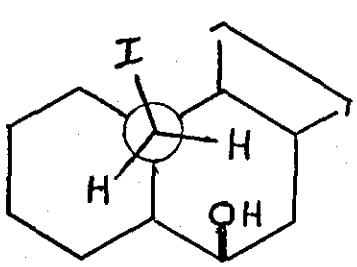
A large number of reactions resulting from the production of alkoxy radicals by the Barton reaction i.e. intramolecular radical capture, and the formation of ketones are reported in the literature and these are comprehensively covered in the review by A.L.Nussbaumn and C.H.Robinson.[5]

Homolysis of hypoiodites give rise to alkoxy radicals which can attack a non-activated C-H bond at a δ-C atom and lead to a tetrahydrofuranoid derivative. A large variety of reactions, by use of the hypoiodite method, leading to functionalisation of angular methyl groups at C-10, C-13, and C-14 have been studied by a number of workers.[6] The hypoiodites are generated in situ by means of lead tetraacetate and iodine and under the conditions employed for alkoxy radical generation two reaction pathways compete. The hypoiodite can form an alkoxy radical giving rise to a cyclic ether or if this is not an efficient reaction competition from an ionic reaction can occur giving a ketone as well as a cyclic ether.

The hypoiodite reactions, unlike the Barton reaction where only single intramolecular substitution can occur, often give rise to complex mixtures. These arise by further reaction of the monoiodinated alcohol [6], initially



[8] [6] [7]

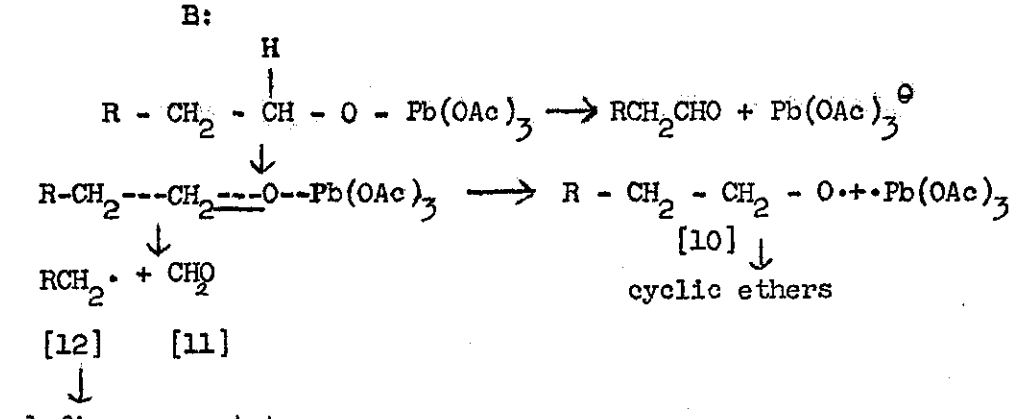


[9]

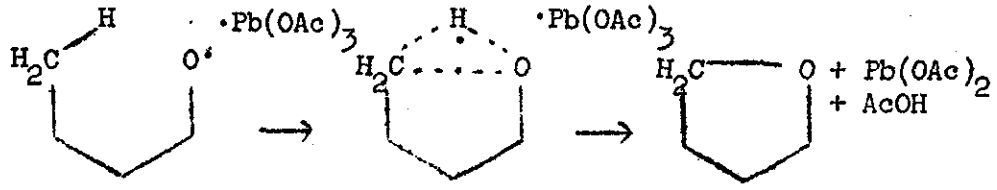
formed, resulting in radical attack at the 8-carbon atom as indicated in the scheme giving an iodoether which on hydrolysis gives the hemi-acetal [7].

The degree of bifunctional attack is dependent to a large extent upon the steric relationship of the monoiodinated alcohol intermediate. The cyclic ether formation requires the iodohydrin to be conformationally held [9] so that rear-side attack by the oxygen substituent can occur by way of a linear transition state ($O--CH_2--I$). This could involve an S_N2 process with attack by the C-6 oxygen lone pair upon the 19-iodomethyl group or an S_H2 reaction by formation of the alkoxy radical intermediate [8]. The latter is reported to be energetically favoured.(7)

Lead tetraacetate in boiling benzene converts steroid alcohols to the lead alkoxide(8) which can undergo heterolytic or homolytic cleavages. Polar cleavage of lead alkoxide tends to predominate in polar or basic solvents as indicated below. Homolytic cleavage can occur, giving rise to an alkoxy radical [10], or alternatively cleavage of the α,β carbon-carbon bond giving rise to a carbonyl compound [11] and an alkyl radical [12].



In the presence of a suitably placed δ-carbon atom (as in previous cases) a cyclic ether is formed via a transition state [13] by direct oxidation.(6b)



[13]

As the intermediate in the lead tetraacetate functionalisation reactions is not sterically demanding, unlike the iodo-alcohol intermediate in the hypoiodite reaction, this route can often be used to functionalise sterically crowded δ-carbon atoms.

The effects of neighbouring groups (i.e. C=O, C=C) and the presence of a tertiary C-H bond at the δ-carbon atom upon the course of the free radical reactions have been comprehensively reviewed by K.Heusler and J.Kalvoda.(6b) Other less common, photolytically induced hydrogen transfer reactions, not discussed, occur on irradiation of N-iodoamides (9) and cyanohydrins.(10)

The functionalisation of the 5β-methyl group in a Westphalen diol diacetate derivative, using lead tetra-acetate has recently been reported.[11] This briefly reported reaction is fully investigated and other related methods of functionalisation are briefly discussed. Some reactions of the resulting ether[11] have been investigated. Functionalisation and some reactions of other Westphalen's diol diacetate derivatives are described.

Discussion.-

The required 3β-hydroxy-6β-acetoxy-compound (1[4c]) was prepared by the method of Marples and Harrington.[11]

Benzyl cholesteryl ether (1[1a])[12] was oxidised with monoperphthalic acid to the mixed epoxides (1[2]) which were hydrolysed with periodic acid in acetone[13] to the diol (1[3b]). Acetylation of (1[3b]) gave the mono-acetate (1[3a]) which in sulphuric acid-acetic anhydride-acetic acid [14] rearranged to the Westphalen derivative (1[4a]). Hydrogenolysis of (1[4a]), with a palladium-charcoal catalyst gave (1[4c]) which was heated in boiling cyclohexane:benzene (1:1) with lead tetraacetate (4 molar excess) for 2 hr.. Column chromatography and preparative t.l.c. of the crude product gave some starting material, the ether (11[5])(34%), the Westphalen diol derivative (1[4d]) (7%), the ketone (11[3])(7%), the ether (11[6]) (1.7%), and impure polar fractions. Spectroscopic and analytical data gave a clear indication of the structure of the ether (11[5]). From the ^{1}H n.m.r. spectrum of (11[5]) the observed geminal coupling constant for the α-methylene group in the tetrahydrofuran ring (J_{AB} ca. 8.5 Hz.,) is in good agreement with those reported for similar systems.[19] The presence of a 9,10-double bond is confirmed by the intense end absorption in the u.v. spectrum (at 210 nm. ε 7760).[20] Although the ketone (11[3]) was not crystalline [21]

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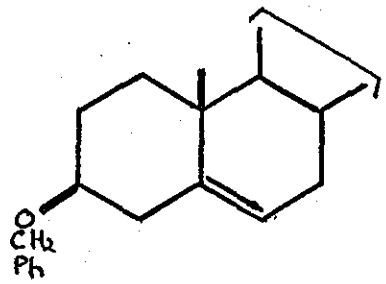

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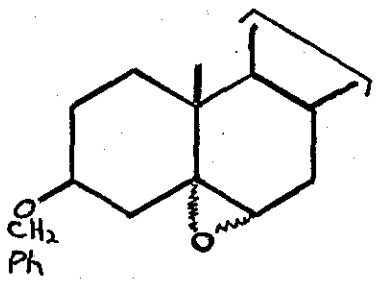

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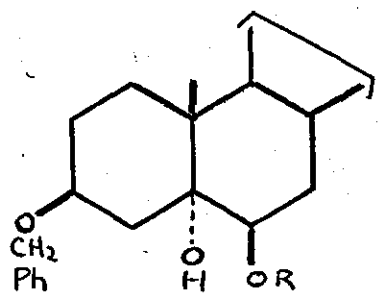

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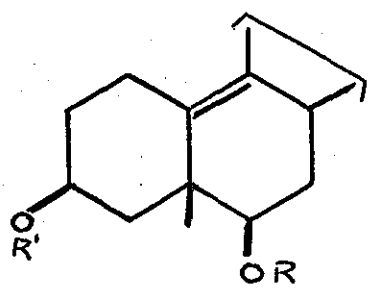

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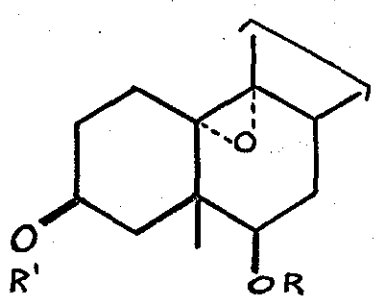

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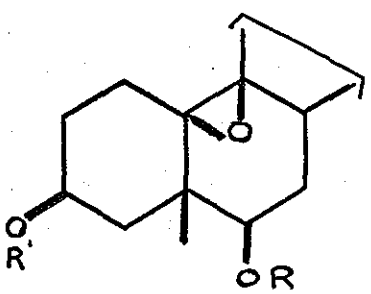
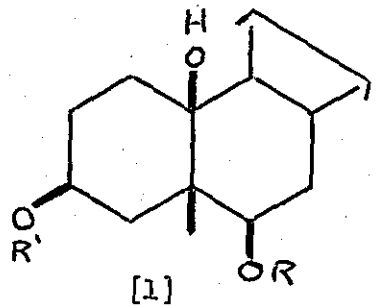


[6]

	R'	R
(a)	$PhCH_2$	Ac
(b)	$PhCH_2$	H
(c)	H	Ac
(d)	Ac	Ac
(e)	NO	Ac



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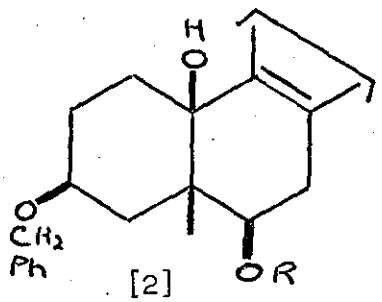
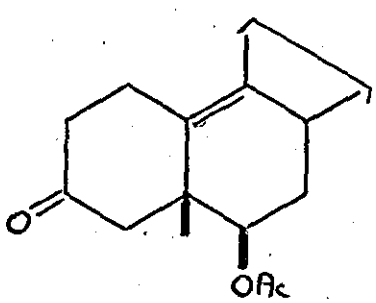


[2]

	R'	R
(a)	$PhCH_2$	H
(b)	$PhCH_2$	Ac
(c)	Ac	Ac
(d)	H	H



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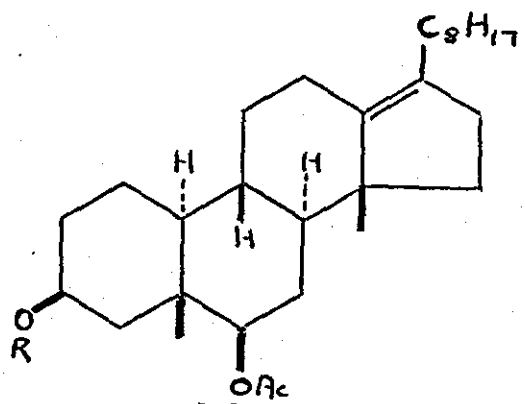
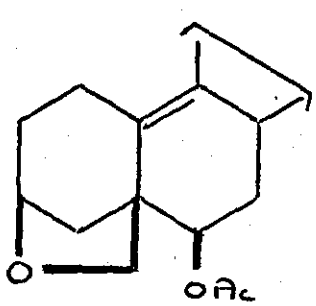


[4] (a) R = H

(b) R = $PhCH_2$



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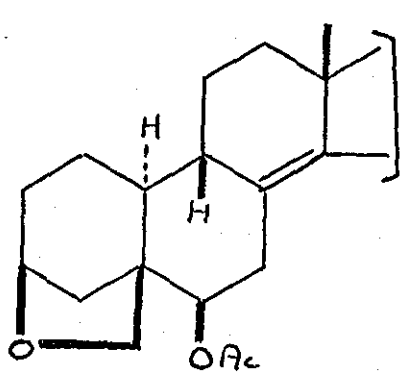
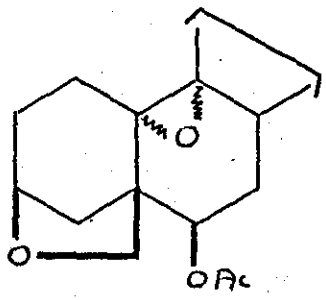


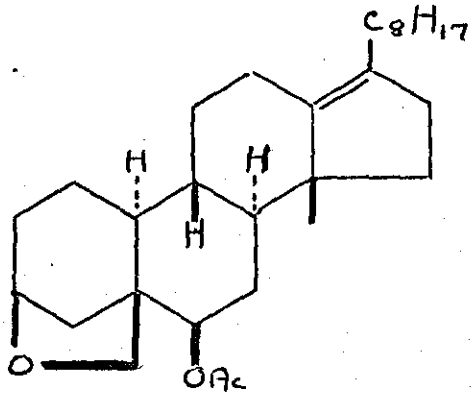
[6]

its identity was confirmed by its reduction, with sodium borohydride, to the alcohol (1[4c]). High intensity end absorption in the u.v. spectrum of (11[6]) (at 210 nm., ε 8350) suggests the double bond is in the 8,14- rather than the alternative 8,9-position;[20] This is confirmed by the downfield position of the C(18)-Me signal (τ 9.15) in the ^{1}H n.m.r. spectrum of (11[6]) relative to that in (11[5]).[22] The C-6 methine proton is in an axial conformation since it is spin-spin coupled to an axial (J, apparent ca. 12 Hz.) and an equatorial (J, apparent ca. 4.5 Hz.) proton at C-7. This is consistent with the assigned 9β,10α-configuration. Both the 9β,10β- and 9α,10β-isomers of (11[6]) would, from models, have an equatorial proton at C-6, and the 9α,10α-isomer would be expected to have a skew-boat B-ring conformation resulting in approximately equal coupling constants (ca. 7-9 Hz,) for spin-spin coupling between the C-6 proton and the α- and β-protons at C-7.

Acetylation of two polar fractions from the original chromatography and further t.l.c. gave the isomeric compounds (111[5b])(0.5%) and (111[6b])(0.5%). The ^{1}H n.m.r. spectra of (111[5b])and (111[6b])confirmed the absence of the angular methyl group at C-5 and, in the latter, a peak at τ 9.45 showed the presence of a cyclopropane ring. The mass spectra of (111[5b])and (111[6b])(Table) confirmed the assigned structures. It seems likely that



[1] (a) α-epoxide
(b) β-epoxide



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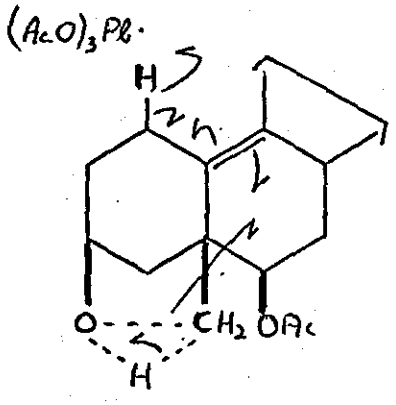

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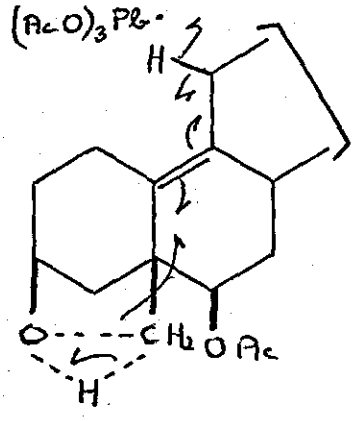

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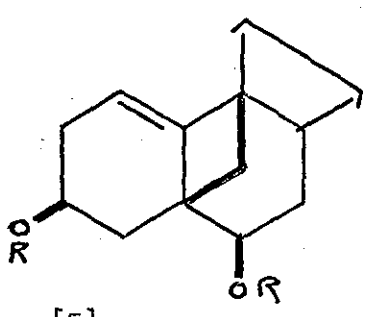

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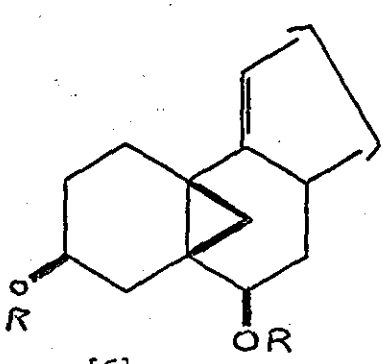
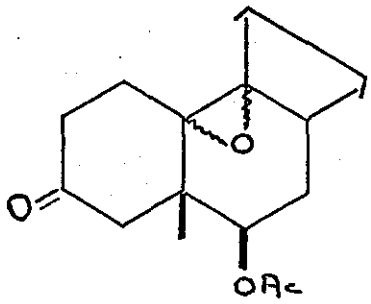


[6]

(a) R = H

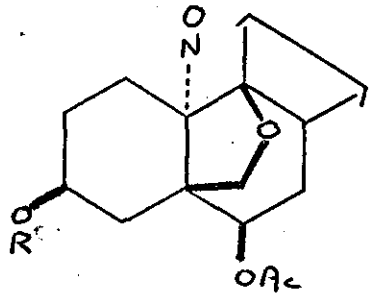
(b) R = Ac

(111[5a]) and (111[6a]) are formed by hydrogen abstraction from the allylic positions (1 and 11) and participation of the double bond as shown in (111[3]) and (111[4]). The reaction of the alcohol (1[4c]) with lead tetraacetate was also carried out at room temperature by irradiating the mixture with u.v.light,[6] the only identifiable product was the ether (11[5]). The reaction of (1[4c]) with lead tetraacetate in iodine,[6] both in the presence and the absence of light, gave a complex mixture in which only a small quantity of the ether (11[5]) was detected by t.l.c. No identifiable product was isolated after chromic acid oxidation.[6c] The lack of success with the hypoiodite reaction is probably due to the formation of bi-functional products, as the iodohydrin intermediate formed cannot be conformationally held in a position which could lead to a linear transition state with the C-3 oxygen substituent due to interaction with the steroid B ring (see introduction). Photolysis of the nitrite ester (1[4e]), prepared by treating (1[4a]) with nitrosyl chloride in pyridine, gave only small amounts of the ketone (11[3]) and some of the alcohol (1[4c]). These undoubtedly are formed by thermal decomposition of the nitrite ester, which is known to be catalysed by traces of water or acid impurities as follows.[23]



[1] α-epoxide

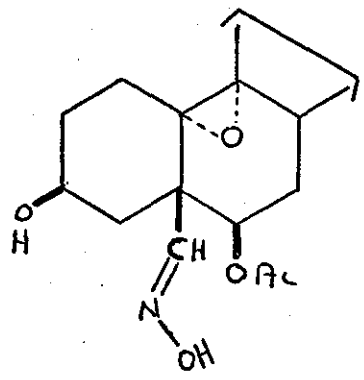
[1a] β-epoxide



[2]

(a) R = H

(b) R = Ac



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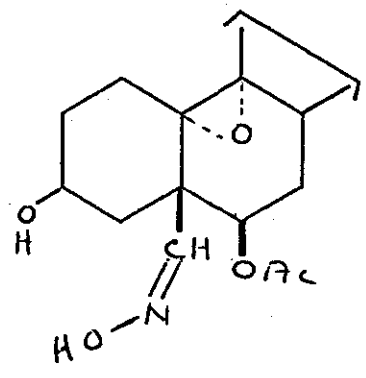
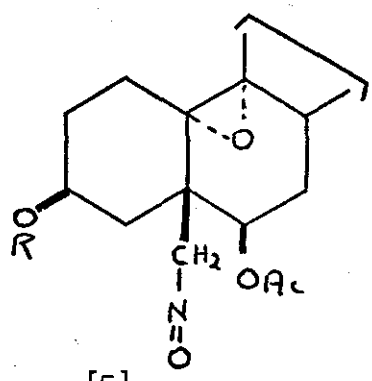


[4]

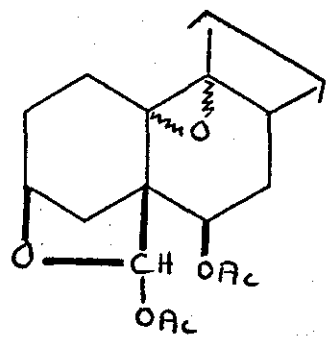
(a) 9(10)β-epoxide



[5]

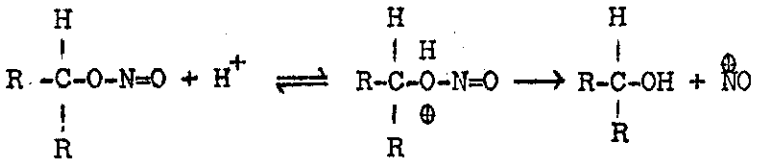
(a) R = H

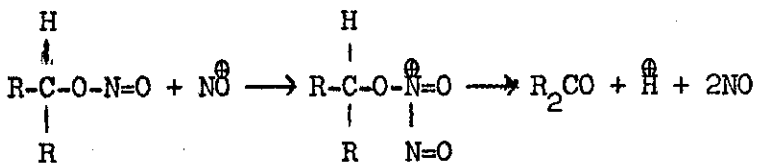
(b) R = Ac



[6] α-epoxide

[6a] β-epoxide





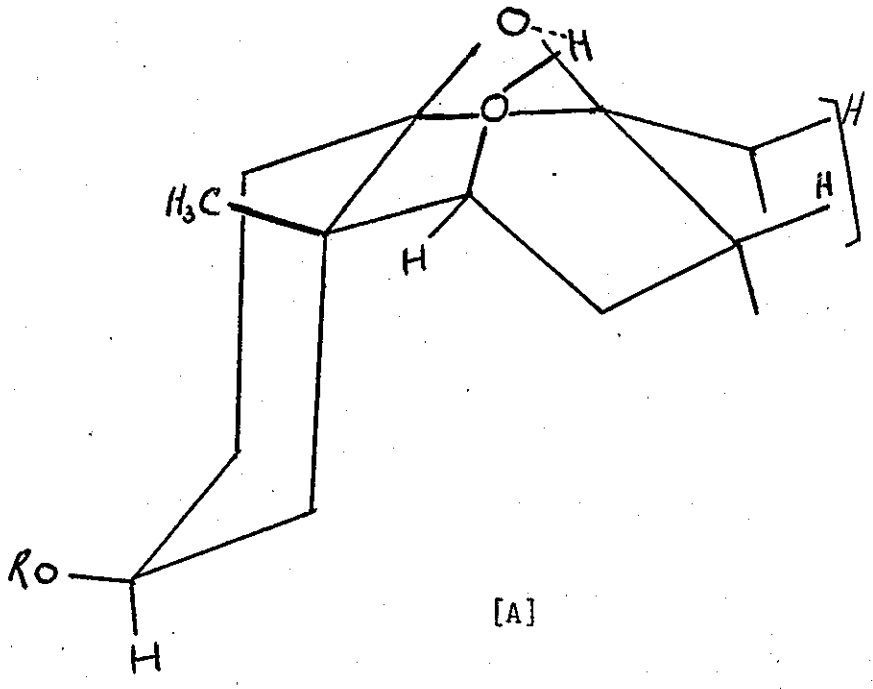
The nitrite ester (1[4e]), on standing, underwent atmospheric hydrolysis giving the alcohol (1[4c]). Purification was only possible by rapid preparative t.l.c. and even then the nitrite ester was contaminated with about 5% of the alcohol. As great care was taken to eliminate moisture from the photolysis reaction it would seem that 3-hydroxy-steroid (1[4c]) present in the starting material is sufficiently acidic to catalyse the formation of the ketone (11[3]). The failure of the Barton reaction with (1[4e]) may be due to the intermediacy of the homo-allylic 5-methylene radical which probably rearranges to give a complex product mixture. In the lead tetra-acetate reaction the radical intermediate is not formed and the intermediate (111[3/4]) is oxidised directly.(6b) Participation of the double bond could only occur in the specific way previously indicated. It was felt at this stage that removal of the 9,10-double bond by epoxidation would minimise the neighbouring group effects observed above and result in improved yield of functionalised product.

In addition the need for 9- and 10-hydroxy steroids prompted the attempted lithium aluminium hydride reduction of the 9,10-epoxides.

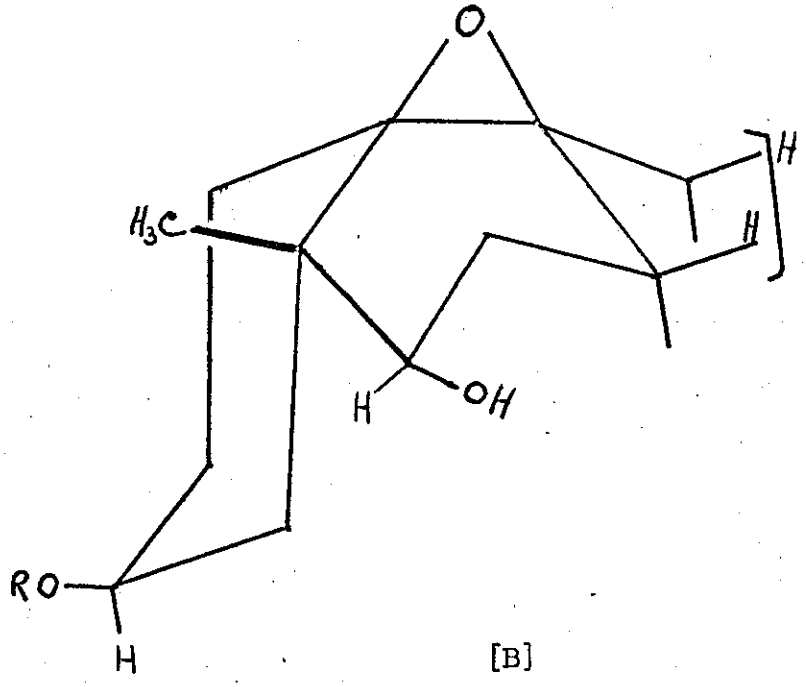
The Westphalen derivative (1[4a]) was oxidised with monoperphthalic acid and column chromatography of the crude product gave the α-epoxide (1[5a]) (53%) and the β-epoxide (1[6a]) (37%). The epoxide group in (1[5a]) is assigned the α-configuration as the hydrolysed product (1[5b]) shows no hydrogen bonding in its solution i.r. spectrum, whilst the hydrolysed product (1[6b]) shows considerable hydrogen bonding in its i.r. spectrum. Hence (1[6a]) is assigned the β-configuration. Mousseron-Canet[15] has reported such hydrogen bonding for 9β,10β-epoxides of 6β-hydroxy Westphalen derivatives. The above assignment was confirmed by the low field position of the 5-methyl resonance in the ^{1}H n.m.r. spectrum of (1[5a]) (τ 8.8). This deshielding is analogous to the deshielding influence of the 5α,6α-epoxides upon the 10-methyl resonance observed by Cross.[16]

The epoxide (1[5b]) on treatment with lithium aluminium hydride in anhydrous tetrahydrofuran gave only unchanged starting material. The epoxide (1[6b]) under similar conditions gave after preparative t.l.c. the diol (11[1a]) (60%), olefin (11[2a]) (13%), and the triol (11[1d]) (26%). Acetylation of (11[1a]), (11[2a]) and (11[1d]) with acetic anhydride in pyridine gave the hydroxy-acetates (11[1b]), (11[2b]), and the hydroxy-diacetate (11[1c]). The C-6 methine proton of (11[1b])

is in an equatorial conformation (^{1}H n.m.r. $W_{\frac{1}{2}}$ ca. 6 Hz.) indicating the 10β-configuration. The 9α-configuration is assumed since diaxial opening would be expected with lithium aluminium hydride. The normal diaxial opening of epoxides[17] may be achieved with attack by $H^{\ominus}$ at either C-9 or C-10 in the β-epoxide due to the possibility of half-chair [A] to half-chair [B] inversion of the B-ring. However attack at C-9 seems likely to be preferred since the epoxide will probably be held in the half-chair [A] by the hydrogen bonding between the 6β-OH and the epoxide. Also the transition state resulting from attack at C-9 seems sterically more favourable than the one resulting from attack at C-10, since, from models, the latter would be subject to an interaction with the 14α-H. In addition the steroid molecule would probably prefer to accommodate the A/B cis-ring junction resulting from C-9 attack rather than the B/C cis-ring junction resulting from C-10 attack. The α-epoxide (1[5b]) does not react probably because of steric hindrance to attack from the β-face. Elemental analysis showed (11[2a]) to be isomeric with starting material (1[6b]). Acetylation with acetic anhydride-pyridine gave the 6β-acetate (11[2b]). The i.r. spectrum of (11[2b]) showed the presence of a tertiary hydroxy-group. Lithium aluminium hydride has been reported by

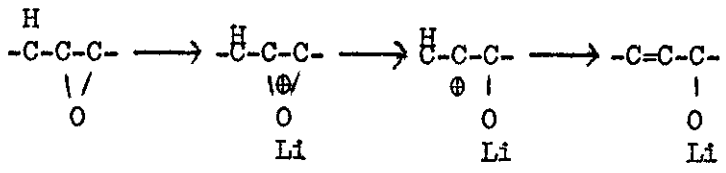


[A]



[B]

Y-Chretien-Bessiere and co-workers[18b] to rearrange epoxides to their corresponding allylic alcohols. It seems likely that (11[2a]) is formed from attack on the epoxide oxygen atom by $Li^{\oplus}$, acting as a Lewis acid,[18a] thus producing an electron deficient carbon centre at C-9. This is followed by loss of the C-8 proton giving the allylic alcohol (11[1a]) as indicated below.



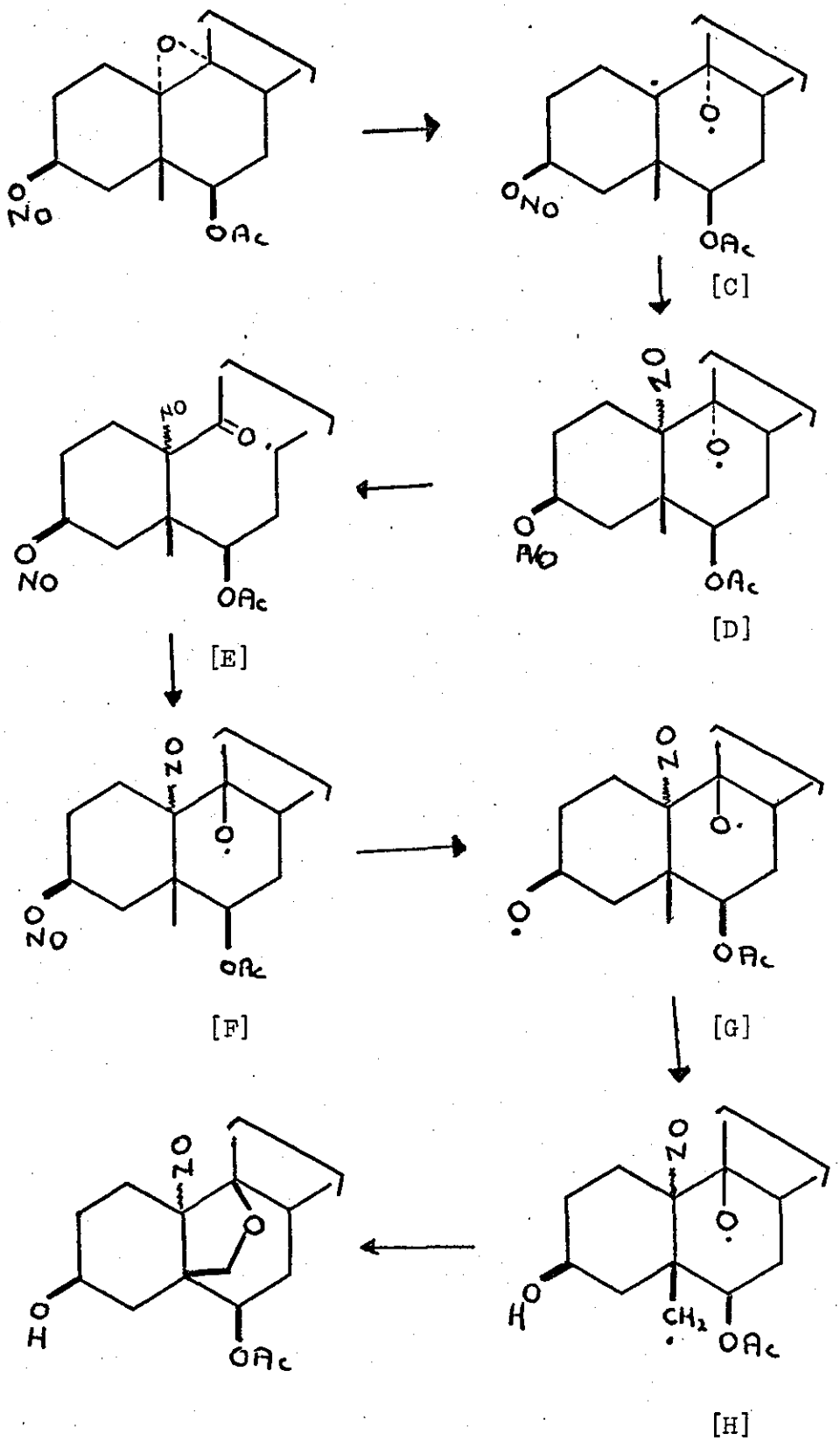
The presence of an 8,9-double bond is confirmed by the high field position of the 5- and C(18)-methyl signals in the ^1H n.m.r. spectrum of (11[2b]) relative to those in (11[1b]) (see experimental). The C-6 methine proton of (11[2b]) is in an equatorial conformation ($W_{\frac{1}{2}}$ ca. 12 Hz.) indicating the 10β-conformation. Spectroscopic and analytical data for (11[1d]) and its acetylated derivative (11[1c]) give a clear indication of their structure. The i.r. spectrum of (11[1c]) indicates the presence of a tertiary hydroxy-group and the absence of the benzyloxy-group. The ^1H n.m.r. spectrum of (11[1d]) confirms the absence of the benzyloxy-group. The ^1H n.m.r. spectrum of (11[1c]) indicates the presence of two acetate methine protons with the C-6 methine proton being in an equatorial conformation ($W_{\frac{1}{2}}$, ca. 5 Hz.) indicating the <u>cis</u>-configuration

of the A/B ring junction. It seems likely that (11[1d]) is formed by hydrogenolysis of the benzyloxy-group under the conditions employed.

Hydrogenolysis of (1[5a]) and (1[6a]), with palladium-charcoal, gave the hydroxy-acetates (1[5c]) and (1[6c]) respectively. Functionalisation of (1[5c]) and)1[6c]) with lead tetraacetate gave after preparative t.l.c. the ethers (111[1a]) (76%) and (111[1b]) (50%) respectively. Spectroscopic and analytical data (see experimental) give a clear indication of the structures of the respective ethers. The observed geminal coupling for the α-methylene group in the tetrahydrofuran ring of the ethers (111[1a]) and (111[1b]) is in good agreement with that observed for (11[5]) (^{1}H n.m.r. J ca. 8 Hz.). The nitrite esters (1[5e]) and(1[6e]) were prepared from the alcohols (1[5c]) and (1[6c]) on treatment with nitrosyl chloride in pyridine.

Photolysis of the nitrite ester (1[5e]) in benzene gave the ketone (IV[1]) (17%), ether (111[1a]) (2.2%), nitroso-acetate (IV[2]) (6.4%), alcohol (1[5c]) (15%) and a polar fraction (47%). Spectroscopic and analytical data gave a clear indication of the structure of the ketone (IV[1]) and the ether (111[1a]). The ether (111[1a]) had an R_F identical to that observed for an authentic sample. Attempts to crystallise failed but accurate mass measurement confirmed its structure as (111[1a]) (see Table). The i.r. spectrum of (IV[2a]) shows an intense

nitroso band (at 1640 cm.$^{-1}$) and a broad hydroxyl band (at 3650 cm.$^{-1}$). The ^{1}H n.m.r. spectrum shows peaks at τ 4.3-4.7 (low field portion of an AB quartet J ca. 12 Hz.), 4.9-5.6 (high field portion of an AB quartet and AcOCH), and 5.6-5.9 (m, OCH). Acetylation of (IV[2a]) with acetic anhydride in pyridine gave the diacetate (IV[2b]). From available data the two structures (IV[2a]) and (IV[5a]) can be tentatively suggested. Compound (IV[5a]) would be expected to exist as the nitroso-dimer but its failure to isomerise on refluxing in isopropanol[3] militates against this and suggests that the nitroso group is attached at a tertiary centre as in (IV[2a]). (IV[2a]) could arise by participation of the 9α,10α-epoxide as shown (scheme.) The opening of the α-epoxide is confirmed by the absence of any epoxide bands in the i.r. spectrum of (IV[2a]). The 9α,10α-epoxide upon irradiation could cleave to give an intermediate diradical [C]. The tertiary radical formed can combine with nitric oxide from solution to form a 10-nitroso intermediate [D]. The 9-alkoxy radical undergoes inversion[24] by initial rupture of the C(8)-C(9) bond to give the C(8)-radical [E] which combines to give a 9β-alkoxy radical [F]. Under the conditions employed the final step may involve cyclisation by combination of diradical [H] to give 5β,9β-tetrahydrofuranoid derivatives (IV[2a]).



Scheme

The polar fraction after further preparative t.l.c. gave the isomeric oximes (IV[3]) (4.3%) and (IV[4]) (11.0%). The structures of these products were deduced from spectroscopic and analytical data. Mass spectra (table) showed them to be isomeric ($C_{29}H_{47}O_5N$). (IV[3]) is assigned the syn-configuration as the oxime methine proton signal in the ^1H n.m.r. spectrum appears at lower field (τ 2.35) than does the corresponding signal in the ^1H n.m.r. spectrum of (IV[4]) (τ 2.8). This is due to the deshielding influence of the syn-hydroxy-group and is analogous to similar deshielding effects reported in the literature.[25]. Photolysis of (1[6e]), in benzene, gave, after preparative t.l.c., the ketone (IV[1a]) (10%), alcohol (1[6c]) (18%), and the oxime (IV[3a/4a]) (10%). The ketone (IV[1a]) was identified from its spectroscopic data (see experimental). The ^1H n.m.r. spectrum of (IV[3a/4a]) shows a singlet at τ 2.5 indicating the presence of an oxime. This was confirmed from its mass spectrum (Table), which showed it to be isomeric with (IV[3]). Available data does not permit one to assign a syn- or anti-configuration to the oxime (IV 3a/4a]). Treatment of (IV[3]) and (IV[3a]) with nitrous acid[26] in acetic acid gave the hemi-acetyl acetates (IV[6]) (32%) and (IV[6a]) (43%) respectively. These were characterised on the basis of their ^1H n.m.r. and mass spectra (see table). The ^1H n.m.r. spectra of (IV[6a])

and (IV[6]) respectively exhibited one proton singlets at τ 3.88 and τ 3.78 respectively assigned to the hemi-acetyl acetate methine. Attempted deoximation of the anti-oxime (IV[4]) with nitrous acid even under forcing conditions gave only unchanged starting material. No satisfactory explanation has yet been found to account for the inability of (IV[4]) to form the hemi-acetal.

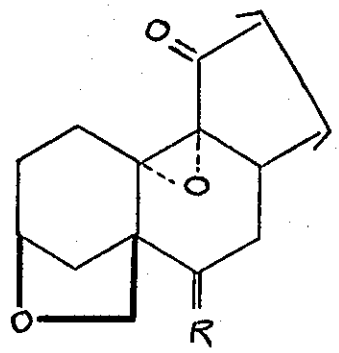
The above results endorse the previous suggestion that removal of the double bond would lead to higher yields of functionalised products. Though the low yields of oximes from the Barton reactions are disappointing, they nevertheless shown an improvement over the similar reactions with the 9,10-olefin (1[4e]).

The availability of the backbone acetate (11[4b]) [see Section 2 for preparation] prompted functionalisation of its hydrogenolysed derivative (11[4a]).

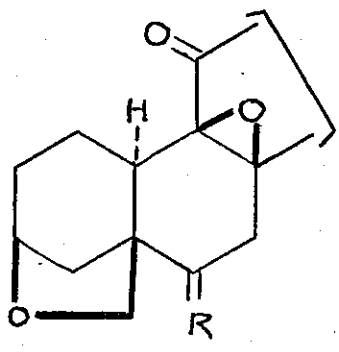
Functionalisation, using lead tetraacetate, gave after preparative t.l.c. the ether (111[2]) (50%) and starting material (11[4a]) (20%). Spectroscopic and analytical data give a clear indication as to its structure. In the ^{1}H n.m.r. spectrum of (111[2]) the α-methylene protons in the tetrahydrofuran ring, unlike the previous ethers, appear as a triplet (at τ 6.3) indicating the similar chemical shifts of the two protons.

Oxidation of the ether (11[5]) with chromic acid at 100° under conditions employed for the oxidation of 6,19-oxides,[27]

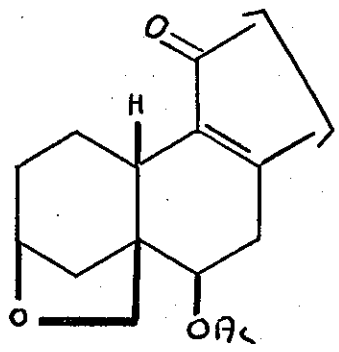
gave a complex mixture from which no products were identified. Room temperature oxidation gave the epoxy-ketones (V[1a]) (39%) and (V[2a]) (11%), the α,β-unsaturated ketone (V[3a]) (9%) and an impure fraction, which were separated by preparative t.l.c. from a complex polar fraction. The structures of these products were deduced from spectroscopic and analytical data. The i.r. spectra of (V[1a]) and (V[2a]) showed intense carbonyl bands (at 1710 and 1720 $cm.^{-1}$) and the mass spectra showed they were isomeric ($C_{29}H_{44}O_5$)(table). The ^1H n.m.r. spectra confirmed the presence of two methine protons (3-H and 6-H), an acetyl group and the $-OCH_2-$ group. In the spectrum of (V[1a]) the 12β-proton signal is clearly seen at τ 7.15 (d, J ca. 12 Hz.) thus confirming that the carbonyl group is at C-11. The α-configuration is assigned to the epoxide group in (V[1a]) because a solution i.r. spectrum of the hydrolysed product (V[1b]) shows no hydrogen bonding.[15] The epoxide group in (V[1a]) is assigned to the 9,10- rather than 8,9-position because of the downfield position of the signal, in the ^1H n.m.r. spectrum, due to the α-methylene of the tetrahydrofuran ring relative to that in the ether (11[5]).[22] Inspection of models shows that the oxygen atom of an 8β,9β-epoxide is close to the C(18)-methyl group, and the observed low field position (τ 9.02) of the C(18)-methyl group signal in the ^1H n.m.r. spectrum of (V[2a])



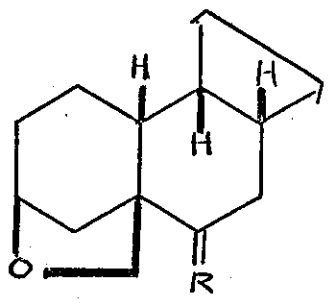
[1]



[2]



[3]



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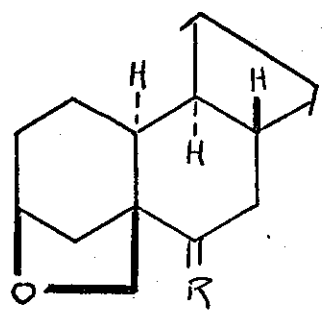

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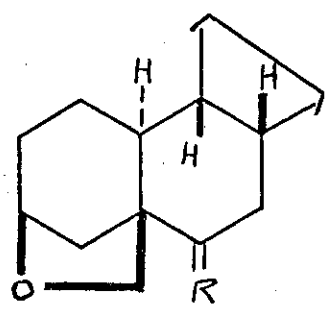


[6]

R

(a) α-H, β-OAc

(b) α-H, β-OH

(c) O

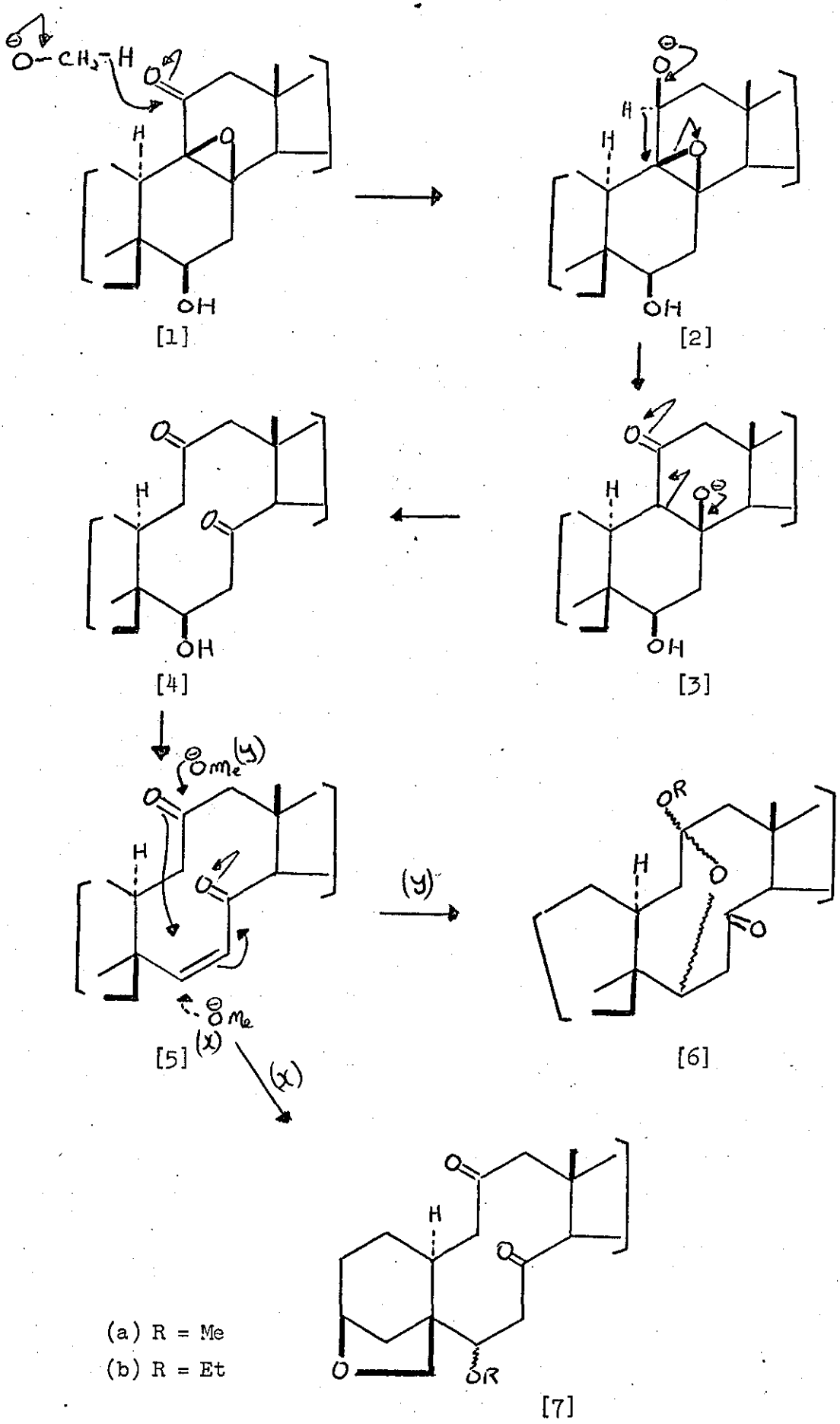
is consistent with this. The C-6 methine proton is in the axial conformation ($W_{\frac{1}{2}}$ ca. 15 Hz.) and this confirms the 10α-configuration (assuming the B-ring adopts the half-chair conformation). The u.v.spectrum of (V[3a]) in methanol, $\lambda_{max.}$ 252 nm. (ξ 8250), confirms the presence of an α,β-unsaturated ketone and also that the double bond is in the 8,9-position.[20] The C-6 methine proton is in an equatorial conformation (^{1}H n.m.r. $W_{\frac{1}{2}}$ ca. 9 Hz), showing the 10β-configuration. Hydrolysis of the impure fraction with 1% methanolic potassium hydroxide and further preparative t.l.c. gave pure (VII[7]) (2.5%). Elemental analysis and mass spectrum of (VII[7]) show the molecular formula to be $C_{27}H_{46}O_4$ and this indicates that hydroxylation of the 9,10- double bond has occurred. The structure of (VII[7]) is assigned on the basis of its ^{1}H n.m.r. spectrum which exhibited a methine multiplet equivalent to only two protons (τ 5.6-6.0), confirming that two of the hydroxyl groups are attached to tertiary centres. The spectrum also points to the presence of a 9β-hydroxy-group due to the down field position of the α-methylene signal of the tetrahydrofuran ring. The structure is assigned a 10α-hydroxy-group by assuming diaxial opening of a 9,10-epoxide precursor normally formed under the conditions employed. Under the acidic conditions one cannot preclude isomerisation of the olefin to 8,9-position resulting in a 8α,9β-dihydroxy- steroid and available

data does not allow one to distinguish between these two possibilities.

Attempted hydrolysis of (V[2a]) with methanolic potassium hydroxide solution (1%), did not give the 6β-hydroxy-compound (V[2b]) but gave, surprisingly, the 8,9-seco-methoxy-diketone (VI[7a]) (89%). The structure of (VI[7a]) is based largely on mass and other spectral and analytical data. The mass spectrum (Table) shows the molecular formula is $C_{28}H_{46}O_4$ and the base peak arises from loss of methanol (see table). The ^1H n.m.r. spectrum shows important peaks at τ 5.27-5.5 (m, 20CH), 6.63 (q, J_{AB} ca. 7.6 Hz., OCH_2), 6.06 (s, OMe) and 9.31 (s, 18-Me). The i.r. spectrum confirms the presence of the methoxy-group (2820 cm.$^{-1}$) and the carbonyl group (1720 cm.$^{-1}$) and the absence of a hydroxy-group. It seems likely that (VI[7a]) is formed by the route shown (VI). The initial steps are hydrolysis of the 6β-acetoxy-group and hydride reduction of the 11-keto-group. Although hydride reduction of carbonyl groups with potassium alkoxide[28] is not unusual, such an efficient reduction, as is apparent here, would not be expected particularly under the conditions employed. Alternatively hydride reduction of the epoxy-group may take place directly. Step (VI[3]) to (VI[4]) is a retro-aldol reaction which is followed by dehydration giving α,β-unsaturated ketone (VI[5]). The final step (VI[5]) to (VI[7a])(path x) involves Michael addition of methoxide to the

Δ^{6}-7-ketone. It is possible that a transannular Michael addition following attack of methoxide ion at C-11 (path(y)) could give the acetate (VI[6]). Since however the product is stable in aqueous methanolic sulphuric acid, the structure (VI[7]) is preferred. In addition the loss of methanol from the molecular ion in the mass spectrum is more reasonable for (VI[7a]) than for (VI[6]).[29] The formation of the medium-ring compound (VI[7a]) by retro-aldolisation is unusual. Previous work[30] suggests a tetracyclic structure would be preferred. Apart from the initial hydrolysis, all the steps outlined would be reversible. Compound (VI[7a]) was treated with EtOD-NaOD (72 hr. at 60°) in the expectation that the methoxy-group would be replaced by an ethoxy-group and that up to a maximum of 7 hydrogen atoms (positions 7, 9, 11 and 14) would be replaced by deuterium atoms. Mass spectral analysis of the product showed ions at m/e 460, 461, 462, 464 and 465 corresponding to the d_0(7%), d_1(25%), d_2(10%), d_4(9%) and d_5(50%) species of VI[7b]). The absence of any appreciable quantity of d_6 and d_7 species indicates that two of the hydrogen atoms of (VI[7b]) are only exchanged with difficulty.

Hydrogenation of the ether (11[5]) with platinum catalyst in acetic acid and a trace of perchloric acid gave the saturated ethers (V[4a]), (V[5a]), and (V[6a]). The ether (V[4a]), the major product (36%), was separated from

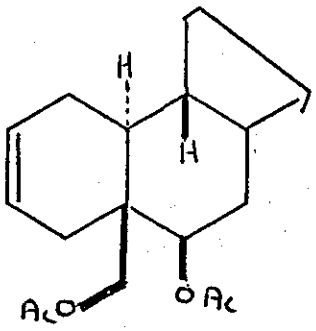


(a) R = Me
(b) R = Et

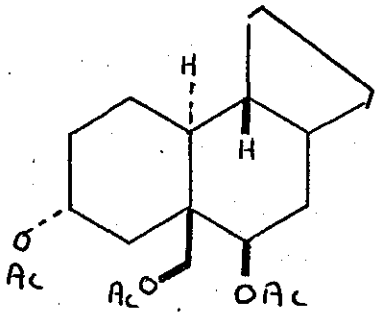
a mixture (43%) approximately (1:1) of (V[5a]) and (V[6a]) by preparative t.l.c. The latter mixture after hydrolysis and further t.l.c., gave (V[5b]) and (V[6b]). The C-6 methine proton of (V[4a]) is in an equatorial conformation (^{1}H n.m.r. $W_{\frac{1}{2}}$ ca. 5 Hz.) indicating the 10β-configuration. The 9β-configuration is assumed since cis-hydrogenation would be expected to provide the major product. Hydrogenation of Westphalen's diol derivatives similarly gives largely the 9β,10β-product.[31] In the ^{1}H n.m.r. spectra of the ethers (V[5b]) and (V[6b]), the C-6 methine proton signal is superimposed on that of the α-methylene group of the tetrahydrofuran ring, but it is clear that the $W_{\frac{1}{2}}$ in each of these is ca. 18 Hz., confirming the 10α -configuration. Reaction of (V[5b]) with trichloroacetyl isocyanate, in deuteriochloroform in the n.m.r. tube,[32] caused a shift of the C-6 methine proton signal downfield where it was clearly seen as a triplet. This confirms the 9α-configuration ($W_{\frac{1}{2}}$ ca. 18 Hz., J, apparent ca. 7-9Hz., cf. (11[6]) above). The ether (V[6b]) has therefore the 9β,10α-configuration.

Under the reaction conditions employed for hydrogenation isomerisation of the 9,10-double bond along the backbone could occur. The failure to isolate any isomeric olefins when hydrogenation was only allowed to proceed to half reaction militates against this possibility.

Reaction of (V[6b]) with boron trifluoride-ether in acetic anhydride[27] gave the diacetate (VII[1]) and the



[1]



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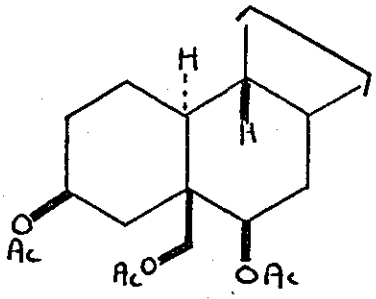
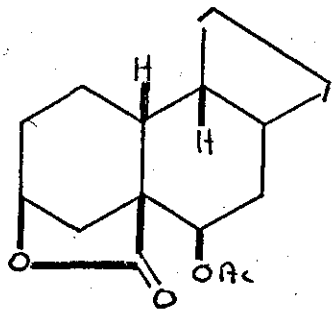
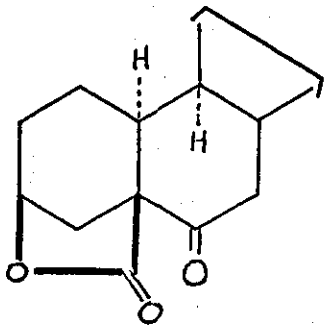


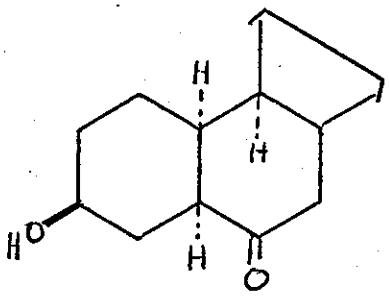
[3]



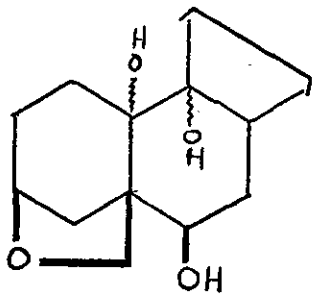
[4]



[5]



[6]



[7]

triacetates (VII[2]) and (VII[3]). The olefinic protons signals in the ^{1}H n.m.r. spectrum of (VII[1])appear as a broadened singlet, and this seems consistent with a 2,3- rather than a 3,4-double bond. The C(3)-O bond in (V[6b]) is probably cleaved in preference to the O-CH_2 bond. The attack of acetate ion may occur simultaneously at a C-3 carbonium ion. Such a carbonium-ion intermediate could account for the production of (VII[3]) but so could the alternative -O-CH_2 cleavage.

The ethers (V[4b]), (V[5b]) and (V[6b]) were oxidised with Jones reagent[33] to the ketones (V[4c]), (V[5c]) and (V[6c]) respectively. Oxidation of (V[4a]), with chromic acid in acetic acid at 100°,[27] gave the lactone (VII[4]); oxidation of the ketone (V[5c]) similarly gave the keto-lactone (VII[5]) and the ketol (VII[6]) (slightly impure). The latter arises from base-catalysed hydrolysis of (VII[5]) and decarboxylation of the resultant β-keto acid during work-up of the reaction mixture. This involved washing the ethereal solution of products with sodium hydroxide solution. The hydrolysis probably takes place by way of acyl-oxygen bond fission[34] with the consequence that the 3-hydroxy-group has the original β-configuration. The ^{1}H n.m.r. spectrum of (VII[6]) shows that the C-3 methine proton is in an axial conformation. In the A/B-trans-isomer this would be feasible if the A-ring adopted a skew-boat conformation. Such an energetically unfavourable

conformation seems unreasonable and consequently the A/B-cis configuration is assigned.

Mass Spectra.- The compounds examined are shown in the Table. The absence of a molecular ion in the spectrum of (III[5b]) could be due to allylic activation of the hydrogens at C-2, thus facilitating elimination of acetic acid. The spectrum of (IV[2b]), also, does not exhibit a molecular ion and the peak at m/e 517 corresponds to M-N. This is unusual as no evidence exists for loss of nitrogen from nitroso compounds.[35a] (IV[2b]) fragments further with loss of two molecules of acetic acid and formaldehyde. The loss of formaldehyde is also found in the fragmentation of (III[1a]) and (V[3]) and is probably lost from the tetrahydrofuran ring. The mass spectra of the oximes (IV[3]), (IV[4]) and (IV[3a]) show similar fragmentation patterns with initial breakdown giving M-OH peak (at m/e 472). The presence of the CH_2OAc group at C-5 in (VII[1]); (VII[2]) and (VII[3]) is confirmed by the loss of a fragment of mass 73 from the ion m/e 426, and also, in (VII[2]) and (VII[3]), from the ion m/e 486. A similar fragmentation has been reported for steroid 19-acetates.[36] The loss of carbon dioxide from (VII[5]) and the ion m/e 398 formed from (VII[4]) would be expected for a γ-lactone.[35b] The loss of a fragment of mass 59 (CH_3CO_2) in (V[2a]), and (IV[6]), in the ion m/e 456 formed from (IV[6a]) and to a smaller extent in (V[1a]) is unusual and the expected

elimination of acetic acid, apart from in the latter, is suppressed almost completely. Clearly 1,2-elimination, reported for cyclohexyl- and some steroid acetates[35c], is not important. Some of the above work has recently been reported, by us, in the literature.[38]

EXPERIMENTAL:-

Solutions were dried over anhydrous sodium sulphate. Column chromatography was carried out with deactivated (grade III) Camag or Woelm neutral alumina. Merck Kieselgel PF254 silica gel was used for preparative t.l.c.

I.r. spectra were determined (solutions in carbon tetrachloride unless otherwise specified) with Perkin-Elmer 237 and 257 spectrophotometers. U.v. spectra were determined (for solutions in hexane unless otherwise specified) with Unicam SP800 and Hilger and Watts Uvispek spectrometer. Mass spectra were determined with A.E.I. MS12 and MS902 mass spectrometers. Rotations were measured at room temperature with a Bendix polarimeter 143C for solutions in chloroform.

3β-Benzyloxycholest-5-ene (I[1]). - A mixture of 3β-hydroxycholest-5-ene (20g.), benzyl chloride (25ml.), powdered potassium hydroxide (120g.), and dry toluene (350 ml.) was heated under reflux and stirred for 4 hr. and then cooled. Water was added cautiously and the mixture was shaken. The organic layer was extracted with ether, the ethereal solution, dried, evaporated to give the benzyl ether (I[1]). m.p. acetone/pet. ether 117-8° (lit. 118.5°)[12]

3β-Benzyloxy-5ξ,6ξ-epoxycholestane (I[2]). - An ethereal solution of the olefin (10g. in 150ml.) an excess of monoperphthalic acid (18g. in 300 ml. of ether) was set aside at room temperature overnight. The solution was washed with sodium hydrogen carbonate solution until neutral

and was then dried. Removal of the solvent gave the epoxide mixture which was used without further purification.

3β-Benzyloxy-5α-cholestane-5,6β-diol (I[3b]).- A solution of the epoxide (10g.) (α- and β-) and periodic acid dihydrate (0.5g. per g. of steroid) in aqueous acetone[13] was heated under reflux for 30 min.. Water was added to precipitate the product. Filtration gave the diol (I[3b]) (9.7g.), m.p. 185-186°, $[\alpha]_D$ -4°(C,0.6), $\nu_{max.}$ (mull) 685 and 720 phenyl, and 3480 (OH) cm.$^{-1}$ (Found: C, 80.0; H, 10.6. $C_{34}H_{54}O_3$ requires C, 79.95; H, 10.65%).

6β-Acetoxy-3β-benzyloxy-5α-cholestan-5-ol (I,[3a]).- A solution of diol (8g.) (I[3b]) in pyridine (75 ml.) and an excess of acetic anhydride (8 ml.) was set aside at room temperature overnight. Reaction was completed by heating the mixture on a boiling water-bath for 1 hr., the mixture was then poured onto crushed ice. Filtration gave the hydroxy-acetate (I[3a]) (7.4g.) m.p.133-135° (from aqueous acetone), $[\alpha]_D$ - 37° (C, 0.7), $\nu_{max.}$ (mull) 685 and 725 (phenyl), 1720 (C=O), and 3500 (OH) cm.$^{-1}$ (Found: C, 78.05; H, 10.1. $C_{36}H_{56}O_4$ requires C, 78.2; H, 10.2%).

6β-Acetoxy-3β-benzyloxy-5-methyl-19-nor-5β-cholest-9(10)-ene (I[4a]).- A solution of sulphuric acid in acetic acid (15ml., 0.25M) was added to a solution of the hydroxy-acetate (I[3a]) (1.5g.) in 10% acetic anhydride-acetic acid (80ml.) at 30°. The mixture was maintained at 35°-40° for 10 min. and was then poured into brine. The resultant mixture was extracted

with ether (x 2) and the combined extracts were washed free of acid with sodium hydrogen carbonate solution. After further washing with water, the solvent was removed and the crude product was purified by column chromatography. Elution with light petroleum ether (b.p. 60-80°), gave the acetate (I[4a]) (0.8g.) m.p. 60-61° (from methanol-acetone-water), $[\alpha]_D$ + 71° (C, 1.7), $\nu_{max.}$ (film) 695 and 730 phenyl and 1740 (C = O) cm.$^{-1}$, τ 2.76 (s, phenyl), 5.1 - 5.4 (m, AcOCH), 5.54 (s, OCH_2), 6.2 - 6.5 (m, OCH), 8.02 (s, AcO), 8.76 (s, 19Me), and 9.22 (s, 18Me) (Found:- C, 80.7; H, 10.05. $C_{36}H_{54}O_3$ requires C, 80.85; H, 10.2%).

6β-Acetoxy-3β-benzyloxy-9α,10-epoxy-5-methyl-19-nor-5β,10α-cholestane (I[5a]), and 6β-Acetoxy-3β-benzyloxy-9β,10-epoxy-5-methyl-19-nor-5β,9β-cholestane (I[6a]).- An ethereal solution of the olefin (I[4a]) (300mg.) and an excess of monoperphalic acid (70ml.)(60g.monoperphalic acid per 1000ml. ether) was set aside at room temperature.overnight. The solution was washed with sodium hydrogen carbonate solution until neutral and was then dried. Removal of solvent gave the epoxide mixture. Separation was effected by column chromatography, elution with 5% ether/light petroleum (b.p. 60-80°), gave the α-epoxide (I[5a]) (160mg.), m.p. 88-90° (from methanol-water), $[\alpha]_D$ + 13.3° (C, 0.4), $\nu_{max.}$ 695 and 730 (phenyl), and 1745 (C = O) cm.$^{-1}$, τ 2.72 (s, phenyl), 4.9 - 5.3 (m, AcOCH), 5.52 (s, OCH_5), 6.05 - 6.4 (m, OCH, $W_{\frac{1}{2}}$ ca. 10 Hz.),

8.05 (s,AcO), 8.8 (s, 5-Me), and 9.25 (s, 18-Me) (Found: C, 78.27; H, 9.936. $C_{36}H_{54}O_4$ requires C, 78.50; H, 9.88%) and the β-epoxide (I[6a]) (110mg.) (oil), $[\alpha]_D$ + 43° (C, 0.5), $\nu_{max.}$ 695 and 735 (phenyl), and 1740 (C = O) cm.$^{-1}$, τ 2.72 (s, phenyl), 5.0 - 5.45 (q, J (apparent) ca. 6 and 14Hz. AcOCH-), 6.5 (s, $-OCH_2-$), 6.2 - 6.5 (m, $W_{\frac{1}{2}}$ ca. 18 Hz., -OCH-), 8.0 (s, AcO), 8.9 (s, 5-Me), and 9.25 (s, 18-Me) (Found: C, 78.50; H, 10.2. $C_{36}H_{54}O_4$ requires C, 78.50; H, 9.88%).

3β-Benzyloxy-9α,10-epoxy-5-methyl-19-nor-5β,10α-cholestan-6β-ol (I[5b]), and 3β-Benzyloxy-9β,10-epoxy-5-methyl-19-nor-5β,9β-cholestan-6β-ol (I[6b]).- A 1% aqueous methanolic potassium hydroxide (10ml.) solution of steroid epoxide was heated under reflux for 15 min. and was then poured into water. Extraction with ether gave the epoxy-alcohol. The epoxy-acetate (I [5a]) (60mg.) gave the alcohol (I[5b]) (49mg.) m.p. 126-7° (methanol) $[\alpha]_D$ +25° (C, 1.0), $\nu_{max.}$ 3620 (sharp, -OH) cm.$^{-1}$, τ 2.68 (s, phenyl), 5.45 (s, $-OCH_2$), 6.1 - 6.5 (m, 2, OCH protons), 8.95 (s, 5-Me), and 9.26 (s, 18-Me). (Found: C, 80.26, H, 10.2. $C_{34}H_{52}O_3$ requires C, 80.26; H, 9.88%). The epoxy-acetate (I[6a]) (60mg.) gave the alcohol (I [6b]) (43.5 mg.) (oil), $[\alpha]_D$ + 38.5 (C, 0.9), $\nu_{max.}$ 3600-3300 (broad,-OH) cm.$^{-1}$, τ 2.6 (s, phenyl), 5.4 (s, $-OCH_3$), 6.1 - 6.4 (m, OCH), 6.5 - 6.8 (m, OCH), 8.7 (s, 5-Me), and 9.19 (s, 18-Me). (Found: C, 79.97; H, 10.51. $C_{34}H_{52}O_3$ requires C, 80.26; H, 9.88%).

Lithium aluminium hydride reduction of 3β-Benzyloxy-9β,10-epoxy-5-methyl-19-nor-5β,9β-cholestan-6β-ol (I[6b]). - A solution of epoxy-alcohol (I[6b]) (250 mg.) in dry tetrahydrofuran (25 ml.) was treated with lithium aluminium hydride (250mg.) and the mixture refluxed for 6 hr. The excess reducing agent was decomposed with methanol and the mixture extracted with ether. The ethereal layer was washed with water, dried and removal of the solvent gave a crude product. Preparative t.l.c. [elution (x1) with ethylacetate-benzene (10:1)], gave 3β-benzyloxy-5-methyl-19-nor-5β-cholestan-6β,10-diol (II [1a]) (150mg.), an oil, $[\alpha]_D$ + 12°(C, 2.2) $\nu_{max.}$ (KBr) 700 and 735 (phenyl) and 3400 (broad, OH) cm.$^{-1}$, τ 2.68 (s, phenyl), 5.57 (s, -OCH_2-), 6.3 - 6.5 ($W\frac{1}{2}$ ca. 8Hz., m, -OCH), 6.6 - 6.9 (m, $W\frac{1}{2}$ ca. 9Hz., OCH), 8.6 (s, 5-Me), and 9.28 (s, 18-Me) (Found: C, 80.2; H, 10.4. $C_{34}H_{54}O_3$ requires C, 79.95; H, 10.66%), 3β-benzyloxy-5-methyl-19-nor-5β-cholest-8(9)-en-6β,10-diol (II [2a])(32 mg.) m.p. 152-3°(methanol), $[\alpha]_D$ + 25° (C, 1.3), $\nu_{max.}$ (KBr) 700 and 740 (phenyl), and 3400 (broad, -OH) cm.$^{-1}$, τ 2.55 (s, phenyl), 5.38 (s, -O-CH_2), 5.9 - 6.5 (m, 2 O-CH), 9.01 (s, 5Me), and 9.3 (s, 18Me) (Found: C, 79.84; H, 10.34. $C_{34}H_{52}O_3$ requires C, 80.26; H, 10.3 %), and 3β,6β,10β-trihydroxy-5-methyl-19-nor-5β, 10β-cholestane (II[1d]) (64mg.) m.p. 245-8° (methanol), $[\alpha]_D$ 0, $\nu_{max.}$ (KBr) 3400 (broad, -OH) cm.$^{-1}$, τ (very weak spectrum) 8.52 (s, 5-Me), and 9.3 (s, 18-Me) (Found: C, 79.95; H, 11.37. $C_{27}H_{48}O_3$ requires C, 77.09; 11.50%).

The above fractions were acetylated with acetic anhydride in pyridine. The diol (II [1a]) (100 mg.) gave the acetate (II [1b]) (80 mg.) m.p. 135-6 (methanol), $[\alpha]_D$ - 3° (C, 1.7), $\nu_{max.}$ (mull) 695 and 720 (phenyl), 1745 (OAc), and 3600 (sharp, -OH) cm.$^{-1}$, τ 2.7 (s, phenyl), 5.2 - 5.4 (m, $W\frac{1}{2}$ ca. 6Hz., AcOCH), 5.5 (s, CH_2-O), 6.2 - 6.5 (m, $W\frac{1}{2}$ ca. 9Hz., -OCH), 7.92 (s, AcO), 8.78 (s, 5-Me), and 9.29 (s, 18-Me) (Found:C,78.20;H,10.42 $C_{36}H_{56}O_4$ requires C,78.21;H,10.21%)

A crude sample of diol (II[2a]) (300 mg.) gave the acetate (II[2b]) (225mg.), oil, $[\alpha]_D$ + 4°(C, 4.5), $\nu_{max.}$ 700 and 720 (phenyl), 1745 (AcO), and 3640 (sharp OH) cm.$^{-1}$, τ 2.8 (s, phenyl), 4.8 - 5.1 (m, $W\frac{1}{2}$ ca. 14Hz., AcOCH), 5.6 (s,CH_2-O), 6.3 - 6.7 (m, OCH), 8.05 (s, AcO), 9.1 (s, 5-Me), and 9.35 (s, 18-Me). Triol (II[1d]) (150mg.) gave the <u>diacetate</u> (II[1c]) (101mg.), m.p. 124 - 5° (methanol) $[\alpha]_D$ - 7° (C, 1.5), $\nu_{max.}$ 1750 (AcO-), 3635 (sharp, OH), τ 4.98 - 5.15 (m, $W\frac{1}{2}$ ca. 8Hz, AcOCH), 5.2 - 5.45 (m, $W\frac{1}{2}$ ca. 5Hz., AcOCH), 8.02 (s, AcO), 8.9 (s, 5-Me) and 9.3 (s, 18-Me). (Found: C, 73.80; H, 10.11. $C_{31}H_{52}O_5$ requires C, 73·76; 10.38%).

<u>6β-Acetoxy-3β-benzyloxy-5,14-dimethyl-18,19-bisnor-5β,10α, 9β,8α,14β-cholest-13(17)-ene</u>.(II[4b]). - prepared as described in the following chapter.

<u>6β-Acetoxy-5-methyl-19-nor-5β-cholest-9(10)-en-3β-ol</u> (I[4c]), <u>6β-acetoxy-9α 10-epoxy-5-methyl-19-nor-5β,9α, 10α-cholestan-3β-ol (I[5c])</u> <u>6β-acetoxy-9,10β-epoxy-5-methyl-19-nor-5β,9β, -cholestan-3β-ol</u> (I[6c]), and <u>6β-acetoxy-5,14-dimethyl-18,19-bisnor -5β,10α,9β,8α,14β-cholest-13(17)-en-3β-ol(II[4a])</u>.-

An ethyl acetate solution of the steroid was shaken with 10% palladium on charcoal catalyst, in an atmosphere of hydrogen at room temperature until the uptake of hydrogen ceased. The solution was filtered and evaporated. Acetate (I[4a]) (~~4.75~~ 4.75mg.) gave the alcohol (I[4c]) (380mg.), m.p. 141-142° (from aqueous acetone) (lit.,[21] m.p. 142-144).

Acetate-α-epoxide (I[5a])(200mg.) gave the alcohol (I[5c])(150mg.), m.p. 128-30° (from methanol) $[\alpha]_D$ 0 $\nu_{max.}$ (KBr) 1740 (AcO), 3500 (OH). τ 4.9 - 5.3 (m, $W\frac{1}{2}$ ca. 18 Hz., AcOCH), 5.7 - 5.9 (m, $W\frac{1}{2}$ ca. 9Hz., - OCH), 8.05 (s, AcO), 8.75 (s, 5-Me), and 9.25 (s, 18-Me) (Found: C, 75.67; H, 10.57. $C_{29}H_{48}O_4$ requires C, 75.6; H, 10.5%).

Acetate-β-epoxide (I[6a]) (200mg.) gave the alcohol (I[6c])(200mg.), m.p. 62-3° (methanol), $[\alpha]_D$ + 81°(C, 0.6), τ 5.1 - 5.44 (m, W% ca. 18 Hz., AcOCH-), 5.8 - 6.2 (m, $W\frac{1}{2}$ ca. 14Hz., -OCH-), 8.03 (s, AcO), 8.92 (s, 5-Me), and 9.2 (s, 18-Me) (Found: C, 75.0; H, 10.3. $C_{29}H_{48}O_4$ requires C, 75.6; H, 10.5%).

Acetate-13(17)-olefin (II[4b])(450 mg.) gave the alcohol II[4a])(400mg.), as a gum, $[\alpha]_D$ + 17°(C, 2.3), $\nu_{max.}$ 1740 (AcO-), and 3640 (sharp;OH) τ 5.2 - 5.8 (m, AcOCH), 5.8 - 6.1 (m, O-CH), 8.04 (s, AcO), 8.9 (s, 5-Me), 9.00 and 9.1 (d, J 6Hz., 21-Me), and 9.12 (s, 14-Me) (see Discussion for mass spectrum).

Thermal Functionalisation of the alcohols (I[4c]), (I[5c]), (I[6c]) and (II[4a]).- Solutions of steroid in dry benzene-cyclohexane (1:1) and lead tetraacetate (4 molar excess) were heated under reflux, in an atmosphere of nitrogen, for the periods specified below; the reaction mixture was filtered, poured into water and the organic layer was separated and dried. Removal of the solvent gave the crude product which was purified by column chromatography and/or preparative t.l.c..

The alcohol (I[4c])(7g.) in 2 hr. gave an oil which was separated into two fractions by column chromatography. The less-polar fraction was separated into the following components by t.l.c. [elution (x3) with benzene-ethylacetate (30:1)]: the diacetate (I[4d])(400mg.), m.p. 124-125°, $[\alpha]_D$ + 84° (C, 0.9) (lit.,[37] m.p. 127-128° $[\alpha]_D$+ 84°). 6β-Acetoxy-5-methyl-19-nor-5β-cholest-9(10)-en-3-one (II[3]) (400mg.) , oil, $[\alpha]_D$ + 40°(C, 1.0) (Lit.,[21] $[\alpha]_D$+44°), reduction with sodium borohydride in ethanol gave the alcohol (I[4c]) m.p. 140°, 6β-acetoxy-3β,5-oxaethano-19-nor-5β-cholest-9(10)-ene (II [5])(2g.), m.p.112-114° (from aqueous methanol), $[\alpha]_D$ -25° (C, 1.0), $\nu_{max.}$(KBr) 1740 (C = 0) cm.$^{-1}$, τ 5.0 - 5.2 (q, J (apparent) ca. 12 and 5 Hz., AcOCH), 5.5 - 5.8 (m, ca. $W\frac{1}{2}$ 12 Hz., OCH), 6.4 (q, J_{AB} ca. 8.5 Hz., -OCH_2-), 8.5 (s, AcO), and 9.2 (s, 18-Me), (see Discussion for u.v. result). (Found: C, 78.7; H, 10.45. $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.45%), 6β-acetoxy-3β,5-oxaethano-19-nor-5β,9β,10α-cholest-8(14)-ene (II [6])(100mg.) m.p. 83-84° (from aqueous

methanol), $[\alpha]_D$ + 32° (C, 0.4), $\nu_{max.}$ (mull) 1745 (C = O) cm.$^{-1}$, τ 5.42 (q, J (apparent) ca. 12 and 4.5 Hz., AcOCH-), 5.7 - 6.0 (m, OCH), 6.16 (q, J_{AB} ca. 8 Hz., OCH_2), 7.98 (s, AcO), 9.12 (d, J ca. 6 Hz., side-chain), and 9.15 (s, 18-Me) (see Discussion for u.v. results) (Found: C, 78.7; H, 10.4: $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.45%), and starting material (I[4c])(1.1g.). The polar fraction after t.l.c. [elution (x 4) with benzene-ethylacetate (3:1)] gave two major fractions which were acetylated with acetic anhydride in pyridine. Further t.l.c. [elution with benzene-ethylacetate (10:1)], gave 3β,6β-diacetoxy-5,9-methano-19-nor-5β,9β-cholest-1(10)-ene (III[5])(38mg.) as a gum, $[\alpha]_D$ + 15° (C, 0.8), $\nu_{max.}$ (film) 1745 (C = O)cm.$^{-1}$, τ 4.6 - 5.0 (m, = CH and AcOCH), 5.0 - 5.4 (m, AcOCH), 7.98 and 8.04 (s, AcO), 9.13 (d, side-chain), and 9.35 (s, 18-Me) (see Discussion for mass spectrum), and 3β,6β-diacetoxy-5,10β-methano-19-nor-5β-cholest-9(11)-ene (III [6]) (36 mg.) as a gum, $[\alpha]_D$ + 23° (C, 0.8), $\nu_{max.}$ (film) 1745 (C = O), and 1650 (C = C) cm.$^{-1}$, τ 4.4 - 4.7 (m, = CH), 4.9 - 5.1 (m, AcOCH), 5.3 - 5.6 (m, AcOCH), 7.95 (s, AcO), 8.05 (s, AcO), 9.08 (d, side chain), 9.34 (s, 18-Me), and 9.45 (m, cyclopropane) (see Discussion for mass spectrum).

The α-epoxy-alcohol (I[5c])(180mg.) in 2 hrs. gave an oil which after t.l.c. [elution with benzene-ethyl acetate (3:1)] gave 6β-acetoxy-9α,10-epoxy-3β,5-oxaethano-19-nor-5β,10α-cholestane (III[1a]) (138mg.) m.p. 115-6° (from methanol),

$[\alpha]_D$ - 12° (C, 0.5), $\nu_{max.}$ (KCl) 1740 (C = O) cm.$^{-1}$, τ 5.18 - 5.34 (m., $W_{\frac{1}{2}}$ ca. 8Hz., AcOCH), 5.48 - 5.73 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., OCH-), 6.35 (q, J_{AB} ca. 8Hz., -OCH_2-), 8.05 (s, AcO), and 9.23 (s, 18-Me). (Found: C, 75.75; H, 10.3 $C_{29}H_{46}O_4$ requires C, 75.94; H, 10.11%).

The β-epoxy-alcohol (I[6c]) (100 mg.) in 4 hrs. gave an oil which after t.l.c. [elution with benzene-ethyl acetate(3:1)] gave 6β-acetoxy-9β,10-epoxy-3β,5-oxaethano-19-nor-5β-cholestane (III[1b])(50mg.), oil, $[\alpha]_D$0°, $\nu_{max.}$ 1745 (C = O)cm.$^{-1}$, τ 4.98 - 5.83 (q, J(apparent) ca. 5 and 10 Hz AcOCH), 5.65 - 5.00 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., OCH), 6.23 (q, J_{AB} ca. -OCH_2), 8.02 (s, OAc), and 9.2 (s, 18-Me) (Found: C, 75.97; H, 10.12 $C_{29}H_{46}O_4$ requires C, 75.94; H, 10.11%).

The alcohol (II[4a])(150mg.) in 2½ hr. gave an oil which after t.l.c. [elution (x2) with benzene-ethyl acetate (3:1)], gave 6β-acetoxy-14-methyl-3β,5-oxaethano-18,19-bis-nor-5β,10α,9β,8α,14β-cholest-13(17)-ene (III[2])(67mg.) a gum, $[\alpha]_D$ - 15 (C, 1.3), $\nu_{max.}$ 1745 (C = O) cm.$^{-1}$, τ 5.05 - 5.4 (m, AcOCH), 5.7 - 6.00 (m, OCH), 6.3 (s, OCH_2-), 8.0 (s, AcO), 9.00 and 9.10 (d, J ca. 6Hz., 21-Me), and 9.15 (s, 14-Me) (Found: C, 78.69; H, 10.43 $C_{29}H_{46}O_3$ requires C, 78.68; H, 10.47), and starting material (II[40])(30mg.).

Treatment of (I[4c]) and (I[5c]) with nitrosyl chloride:- Nitrosyl chloride gas was bubbled into a solution of steroid in pyridine (100ml. per g.) for 4 min. at -20°C. The mixture was then poured into ice and extracted with ether. The

ethereal layer was then dried and the solvent evaporated.

The hydroxy-acetate (I[4c])(200mg.) gave a yellow oil which, after t.l.c. [elution with benzene-ethyl acetate (3:1)], gave 6β-acetoxy-5-methyl-19-nor-5β-cholest-9(10)-en-3β-ol nitrite (I[4e])(150mg.) as a gum (attempts to crystallise gave only starting material). $\nu_{max.}$ 1600 and 1640 (-O-N=O), and 1740 (C = O) cm.$^{-1}$ τ 4.1 - 4.5 (m, ONOCH), 5.1 - 5.5 (m, AcOCH), 8.02 (s, AcO), 8.90 (s, 5-Me), and 9.2 (s, 18-Me).

The hydroxy-α-epoxide (I[5c])(190) gave an oil which, after t.l.c. [elution with benzene-ethyl acetate (3:1)], gave 6β-acetoxy-9α,10-epoxy-5-methyl-19-nor-5β,10α-cholestan-3β-ol nitrite (I[5e])(150mg.) as a gum, $\nu_{max.}$ 1650 (-O-N=O), and 1745(C = O) cm.$^{-1}$ τ 4.1 - 4.35 (m, ONOCH), 4.9 - 5.3 (m,AcOCH), 8.05 (s, OAc), 8.9 (s, 5-Me), and 9.22 (s, 18-Me).

Photolysis of nitrite esters (I[4e]) and (I[5e]).- Solutions of steroid in dry benzene were irradiated, in an atmosphere of nitrogen, for the period specified below, with a 200 watt mercury vapour lamp. The solutions were then concentrated.

The nitrite ester (I[4e])(350mg.) in 2 hrs. at 0°C gave an oil which after t.l.c. [elution with benzene-ethyl acetate (3:1)], gave the keto-acetate (II[3]) (30mg.), hydroxy-acetate (I[4c]) (70mg.) and another three fractions containing numerous unidentifiable products.

The α-epoxy-nitrite ester (1[5e])(1.0g.) in 2 hrs. at 16°C gave an oil which after t.l.c. [elution with benzene-ethyl acetate(3:1)], gave 6β-acetoxy-9α,10-epoxy-5-methyl-19-nor-

5β,10α-cholestan-3-one (IV[1])(180mg.), m.p. 122-3° (from methanol) $[\alpha]_D$ + 5.3° (C, 0.9), $\nu_{max.}$ 1720 and 1740 (C = O) cm.$^{-1}$, τ 4.8 - 5.2 (m, AcOCH), 8.05 (s, AcO), 9.0 (s, 5-Me), and 9.25 (s, 18-Me) (Found: C, 75.91; H, 10.05; $C_{29}H_{46}O_4$ requires C, 75.9; H, 10.1%), mixture (338mg.) which, after further t.l.c. [elution with benzene-ethyl acetate (10:1)], gave (III[1a])(22mg.) as a gum, $\nu_{max.}$ 1750 (C = O) cm.$^{-1}$ τ 5.1 - 5.4 (m, $W_{\frac{1}{2}}$ 9Hz., AcOCH), 5.4 - 5.7 (m, $W_{\frac{1}{2}}$ 8Hz., OCH), 6.4 (q, J_{AB} ca. 9 Hz., $-OCH_2$), 8.05 (s, AcO), and 9.22 (s, 18-Me) (see Discussion for mass spectrum), (IV[2a])(64mg.) $\nu_{max.}$ 1640 (-N=O), 1750 (C = O), and 3650 (broad, OH), cm.$^{-1}$, τ 4.95 (q., J_{AB} ca. 12 Hz.,OCH_2), 4.9 - 5.2 (m, $W_{\frac{1}{2}}$ ca. 20 Hz., AcOCH), 5.6 - 5.9 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., OCH), 8.02 (s, AcO), and 9.20 (s, 18-Me), hydroxy-acetate (I[5c])(153mg.), and mixture (470 mg.) which, after further t.l.c. [elution with ethyl acetate], gave 6β-acetoxy-9α,10-epoxy-5-syn-oximino-19-nor-5β,10α-cholestan-3β-ol (IV [3]) (43mg.) m.p. 198-199° (from chloroform-hexane), $[\alpha]_D$ + 44 (C, 1.4), $\nu_{max.}$ 1740 (C = O), and 3600-3100 (broad, -OH)cm.$^{-1}$, τ ($CDCl_3$) 2.35 (s, syn- $\overset{H}{C} = \overset{O}{N}$), 4.8 - 5.1 (m, AcOCH), 5.7 - 6.0 (m, OCH), 8.02 (s, AcO), and 9.22 (s, 18-Me) (see Discussion for mass spectrum) (Found: C, 71.16; H, 9.61 $C_{29}H_{47}O_5N$ requires C, 71.13; H, 9.68), and 6β-acetoxy-9α,10-epoxy-5-anti-oximino-19-nor-5β,10α-cholestan-3β-ol (IV[4]) (110mg.) m.p. 100° (amorphous solid), $[\alpha]_D$ 36.6° (C, 1.9), $\nu_{max.}$ 1750 (C = O), 3600-3300 and 3650 (OH) cm.$^{-1}$, τ 2.8

(s, $\overset{H}{\underset{|}{C}} = N_{\sim O}$), 4.4 - 4.9 (m, AcOCH), 5.6 - 6.1 (m, OCH), 87.92 (AcO), and 9.3 (s, 18-Me) (see Discussion for mass spectrum).

Acetylation of (IV[2a])(64mg.), with acetic anhydride in pyridine gave (IV[2b])(60mg.) as a gum, $[\alpha]_D$ + 37°(C, 1.2), $\nu_{max.}$ 1650 (O-N = O), and 1750 (C = O) cm.$^{-1}$, τ 4.6 - 5.3 (m, OCH), 5.15 (q. J_{AB} ca. 12 Hz. OCH_2), 8.00 and 8.05 (OAc), and 9.22 (s, 18-Me) (Found: C, 69.9; H, 9.14. $C_{31}H_{49}O_6N$ requires C, 70.02; H, 9.29%) (see Discussion for mass spectrum).

6β, 4a ξ-diacetoxy-9α,10-epoxy-3α,5-methano-4-oxa-A-homo-19-nor-5α,10α-cholestane (IV[6]).—Solution of steroid-syn-oxime (IV[3]) (50mg.) in acetic acid (5 ml.) was treated with sodium nitrite (60 mg.) in acetic acid (5 ml.) at 5°C. After 10 min. the reaction mixture was poured into water, extracted with ether and ethereal layer dried. Removal of solvent gave a gum which, after t.l.c. [elution benzene-ethyl acetate (3:1)], gave the hemi-acetal acetate (IV[6])(16mg.), $\nu_{max.}$ 1750 (C = O)cm.$^{-1}$, τ 3.88 (s, O-CH-O), 5.2 - 5.5 (m, AcOCH,OCH), 8.12 (s, AcO), and 9.25 (s, 18-Me) (see Discussion for mass spectrum).

Oxidation of the Ether (II[5]):- A solution of chromic oxide (1g.) in water (0.3ml.) and acetic acid (4ml.) was added to a solution of the ether (II[5]) (1g.)in acetic acid (4 ml.). The mixture was stored at room temperature for 2 hr. and was then poured into water and extracted thoroughly with ether. The other extracts were washed free of acid with sodium hydrogen carbonate solution, and were then washed with water. They were

finally dried. Removal of the solvent gave a crude product which, after t.l.c. [elution (x4) with benzene-ethyl acetate (5:1)], gave 6β-acetoxy-9α,10-epoxy-3β,5-oxaethano-19-nor-5β,10α-cholestan-11-one (V[1a])(420mg.), m.p. 122-126° (from aqueous methanol), $[\alpha]_D^+$ 10° (C, 1.0), $\nu_{max.}$ (KBr) 1710 and 1740 (C = O) cm.$^{-1}$, τ 5.0 - 5.3 (m, $W_{\frac{1}{2}}$ ca. 13 Hz., AcOCH), 5.6 - 5.8 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., OCH), 6.2 (q. J_{AB} ca. 7.9 Hz. OCH_2), 7.15 (d, J ca. 12 Hz., 12β-H), 8.0 (s, AcO), 9.13 (d, side-chain), and 9.22 (s, 18-Me) (see Discussion for mass spectrum) (Found: C, 73.7; H, 9.45. $C_{29}H_{44}O_5$ requires C, 73.7; H, 9.4%), 6β-acetoxy-8β,9-epoxy-3β,5-oxaethano-19-nor-5β,9β,10α-cholestan-11-one (V[2a])(117mg.) a gum, $\nu_{max.}$ 1720 and 1750 (C = O)cm.$^{-1}$, τ 4.5 - 4.8 (m, $W_{\frac{1}{2}}$ ca. 15 Hz., AcOCH), 5.4 - 5.7 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., OCH), 6.04 (s, OCH_2), 8.0 (s, AcO), 9.02 (s, 18-Me), and 9.12 (d, side-chain) (see Discussion for mass spectrum), 6β-acetoxy-3β,5-oxaethano-19-nor-5β-cholest-8(9)-en-11-one (V[3]) (96mg.) m.p. 145-146.5° (from aqueous acetone), $[\alpha]_D$ + 3.6° (C, 1.0), $\nu_{max.}$ (mull) 1630 (C = C), 1690 and 1750 (C = O) cm.$^{-1}$, τ 5.0 - 5.25 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., AcOCH), 5.5 - 5.8 (m, $W_{\frac{1}{2}}$ ca. 11 Hz., OCH), 6.26 (q. J_{AB} ca. 8.6 Hz., OCH_2), 7.26 (d, J ca. 14 Hz., 12β-H), 8.01 (s, AcO), 9.12 (d, side-chain), and 9.26 (s, 18-Me) (see Discussion for mass spectrum and u.v. results), and amorphous polar fraction (400 mg.) $\nu_{max.}$ (mull) 1750 (broad, C = O) and 3500 (broad -OH), τ 5.0 - 5.2 (m, AcOCH), 5.5 - 5.9 (m, -O-CH, and OCH_2), 6.7, 6.9, 7.0 and 7.2 (s, ?), 8.0 (s, AcO), and 9.28 (s,18-Me).

Hydrolysis of (V[1a]),(V[2a]) and polar fraction. - Solution of steroid in 1% aqueous methanolic potassium hydroxide was heated under reflux for 15 min., then poured into water, and extracted with ether. The ethereal layer was separated, dried and evaporated.

The α-epoxy-acetate (V[1a])(100 mg.) gave 9α,10-epoxy-3β,5-oxaethano-19-nor-5β,10α-cholestan-11-one-6β-ol (V[1b]) (93mg.), m.p. 119.5 - 121°(from aqueous methanol), $[\alpha]_D$ + 12° (C, 0.3), $\nu_{max.}$ 1720 (C = O), and 3530 (OH) cm.$^{-1}$, τ ($CDCl_3$) 5.4 - 5.65 (m, OCH), 5.85 (q, J_{AB} ca. 8.6 Hz., OCH_2), 6.3 - 6.6 (m, OCH), 6.94 (d, J ca. 12 Hz., 12β-H), 9.12 (d, side-chain), and 9.19 (s, 18-Me) (Found: C, 75.2; H, 10.2. $C_{27}H_{42}O_4$ requires C, 75.3; H, 9.85%). Polar fraction (300 mg.) gave an amorphous solid (198 mg.) which, after t.l.c. [elution (x3) benzene-ethyl acetate (1:3)], gave the triol (VII[7])(25 mg.) an amorphous solid $[\alpha]_D$ + 1.8°(C, 0.2), $\nu_{max.}$ 3500 (broad -OH) cm.$^{-1}$, τ ($CDCl_3$) 5.7 (q. J_{AB} ca. 8 Hz., OCH_2), 5.6 - 6.0 (m, OCH), and 9.28 (s, 18-Me) (see Discussion for mass spectrum) (Found: C, 74.5; H, 10.9. $C_{27}H_{46}O_4$ requires C, 74.6; H, 10.67%).

The β-epoxy-acetate (V[2a])(100mg.) gave 8,9-seco-6ξ-methoxy-3β,5-oxaethano-19-nor-5β,10α,14ξ-cholestan-8,11-dione (VI[7a])(83mg.) m.p. 117.5 - 119.5° (from aqueous methanol) $\nu_{max.}$ (KBr) 1712 (C = O)cm.$^{-1}$, τ 5.27 - 5.5 (m, 20CH), 6.63 (q, J_{AB} ca. 7.6 Hz., OCH_2), 6.06 (s,-OMe), and 9.31 (s, 18-Me) (see Discussion for mass spectrum) (Found: C, 75.42; H, 10.39. $C_{28}H_{46}O_4$ requires C, 75.29; H, 10.38%).

Ethers (V[4a]), (V[4b]), (V[5b]) and (V[6b]). - A solution of the ether (II[5]) (250mg.) in acetic acid (30ml.) was shaken, at room temperature, with perchloric acid (2 drops, 60% aqueous solution) and platinum oxide (250 mg.), in an atmosphere of hydrogen for 2 days. The solution was filtered, diluted with ether, washed free of acid ($NaHCO_3$), and dried. The mixture, obtained by removal of the solvent, gave, after t.l.c. [elution (x2) with benzene-ethyl acetate (10:1)], 6β-acetoxy-3β,5-oxaethano-19-nor-5β,9β-cholestane (V[4a]) (91mg.), a gum, $[\alpha]_D$ - 2.9° (C, 1.0), $\nu_{max.}$ (mull) 1745 (C = O) cm.$^{-1}$, τ 5.15 - 5.4 (m, $W\frac{1}{2}$ ca. 5Hz., AcOCH), 5.6 - 5.9 (m, $W\frac{1}{2}$ ca. 12Hz., OCH), 6.42 (q., J_{AB} ca. 7.9 Hz., OCH_2), 8.04 (s, AcO), 9.13 (d, side-chain), and 9.32 (s, 18-Me) (Found: C, 78.55; H, 10.65. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%), and a mixture of ether (V[5a])(and (V]6a])(108mg.). Hydrolysis of the mixture in 1% methanolic potassium hydroxide, and further t.l.c. [elution (x5) with benzene-ethyl acetate (3:1)], gave 3β,5-oxaethano-19-nor-5β,10α-cholest-6β-ol (V[5b])(27mg.), m.p. 162-163° (from aqueous methanol), $[\alpha]_D$ - 77° (C, 0.4), $\nu_{max.}$ (mull) 3400(OH) cm.$^{-1}$, τ 5.65 - 5.95 (m, $W\frac{1}{2}$ ca. 12 Hz., OCH), 5.95 - 6.4 (m, OCH and OCH_2), 9.13 (d, side-chain), and 9.34 (s, 18-Me) (Found: C, 80.5; H, 11.45. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%), and 3β,5-oxaethano-19-nor-5β,9β,10α-cholestan-6β-ol (V[6b]) (34mg.), m.p. 139-140° (from aqueous methanol), $[\alpha]_D$ - 3.0 (C, 0.8), $\nu_{max.}$ (mull) 3420 (OH) cm.$^{-1}$, τ 5.65 - 5.95 (m, $W\frac{1}{2}$ ca. 12 Hz., OCH), 6.05 - 6.45 (m, OCH and

OCH_2), 9.13 (d, side-chain), and 9.33 (s, 18-Me) (Found: C, 80.6; H, 11.35. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.55%). Hydrolysis of the ether (V[4a]) in 1% aqueous methanolic potassium hydroxide gave 3β,5-oxaethano-19-nor-5β,9β-cholestan-6β-ol (V[4b]), m.p. 128-130° (from aqueous methanol), $[\alpha]_D 0°$ (C, 1.0), $\nu_{max.}$ (mull) 3400 (OH) $cm.^{-1}$, τ 5.6 - 5.9 (m, $W\frac{1}{2}$ ca. 12 Hz., OCH), 5.9 - 6.6 (m, OCH and OCH_2), 9.13 (d, side-chain), and 9.30 (s, 18-Me) (Found:C, 80.65; H, 11.7. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%).

Ketones (V[4c]), (V[5c]) and (V[6c]).- A solution of Jones reagent (0.5 ml.) was added to a stirred solution of Analar acetone (10 ml./100 mg. of alcohol) at room temperature. After 10 min. the solution was poured into water, extracted with ether, washed free of acid ($NaHCO_3$), and dried. Removal of solvent gave the ketone which was crystallised from aqueous methanol.

The ether (V[4b])(37mg.) gave 3β,5-oxaethano-19-nor-5β,9β-cholestan-6-one (V[4c]) (20 mg.), m.p. 100-102° $[\alpha]_D$ - 32° (C, 0.2), $\nu_{max.}$ (KCl) 1720 (C = O) $cm.^{-1}$, τ 5.6 - 5.9 (m,OCH), 6.7 (q, J_{AB} ca. 8 Hz., OCH_2), and 9.32 (s, 18-Me) (Found: C, 80.75; H, 11.3. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.1%). The ether (V[5b])(250 mg.) gave 3β,5-oxaethano-19-nor-5β,10α-cholestan-6-one (V[5c])(150mg.), m.p. 125-126°, $[\alpha]_D$ - 91° (C, 1.0), $\nu_{max.}$ (KBr) 1716 (C = O) $cm.^{-1}$, τ 5.4 - 5.7 (m, OCH), 6.07 (q, J_{AB} ca. 8 Hz., OCH_2), and 9.33 (s, 18-Me) (Found: C, 80.7; H, 11.4. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.1%).

The ether (V[6b])(80 mg.) gave 3β,5-oxaethano-19-nor-5β,9β,10α-cholestan-6-one (V[6c])(69 mg.), m.p. 105-106° (from methanol), $[\alpha]_D$ + 5.3°(C, 1.5), $\nu_{max.}$(mull) 1720 (C = O) cm.$^{-1}$, τ 5.5 - 5.8 (m, OCH), 6.35 (q., J_{AB} ca. 8Hz., OCH_2), and 9.3 (s, 18-Me) (Found: C, 80.65; H, 11.1. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.1%).

The Diacetate (VII[1]) and Triacetates (VII[2]) and (VII[3]).- Borontrifluoride-ether (0.1 ml.) was added to a solution of (V[6b])(130mg.) in acetic anhydride [27] (8ml.) at room temperature. After 1 hr. the solution was poured into ice, set aside for 15 min., and extracted with ether. The ether extracts were washed free of acid ($NaHCO_3$) and dried. The product, obtained by removal of the solvent, after t.l.c. [elution with benzene-ethylacetate (3:1)], gave 6β-acetoxy--5-acetoxymethyl-19-nor-5β,9β,10α-cholest-2-ene (VII[1])(50mg.) as a gum, $[\alpha]_D$ + 38°(C, 0.8), $\nu_{max.}$ ($CHCl_3$) 1735 (C = O) cm.$^{-1}$, τ 4.3 (s, 2 = CH), 5.0 - 5.4 (m, AcOCH), 5.67 (q, J_{AB} ca. 12 Hz., CH_2OAc), 8.04 (s, 2AcO), 9.13 (d, side-chain), and 9.31 (s, 18-Me) (see Discussion for mass spectrum)(Found: C, 76.25; H, 10.4. $C_{31}H_{50}O_4$ requires C, 76.5; H, 10.35%), and a mixture of triacetates (VII[2]) and (VII[3])(63 mg.) (see Discussion for mass spectrum). Further t.l.c. [elution (x4) with benzene-ethylacetate (10:1)], gave 5-acetoxymethyl-3α,6β-diacetoxy-19-nor-5β,9β,10α-cholestane (VII[2])(30mg.), m.p. 102-3° (from aqueous methanol), $[\alpha]_D$ + 57°(c, 0.6), τ 5.0 - 5.6 (m, 2AcOCH), 5.68 (q., J_{AB} ca. 13 Hz., CH_2OAc), 7.96 (s, AcO),

8.04 (s, 2AcO), 9.10 (d, side chain), and 9.30 (s, 18-Me) (Found: C, 72.45; H, 9.9. $C_{33}H_{54}O_6$ requires C, 72.5; H, 9.95%), and 5-acetoxymethyl-3β,6β-diacetoxy-19-nor-5β,9β,10α-cholestane (VII [3])(10 mg.), m.p. 125-6° (from methanol), τ 4.8 - 5.1 (m, $W_{\frac{1}{2}}$ ca. 9 Hz., AcOCH), 5.1 - 5.6 (m, AcOCH), 5.62 (q., J_{AB} ca. 13 Hz., CH_2OAc), 7.97 (s, AcO) 8.03 (s, AcO), 8.08 (s, AcO), 9.14 (d, side-chain), and 9.33 (s, 18-Me)(see Discussion for mass spectrum).

Oxidation of the Ether (V[4a]) and the Ketone [5c]) with Chromic Acid.-- A solution of chromic oxide (100 mg.) in water (0.3 ml.) and acetic acid (5 ml.) was added to a solution of the steroid (100 mg.) in acetic acid (5 ml.). The mixture was heated on a boiling water-bath for 2 hr. and was then poured into water, and extracted with ether. The extracts were washed with sodium hydrogen carbonate (V[4a]) or sodium hydroxide (V[5c]) solution and were then dried. Removal of the solvent gave the crude product which was purified by t.l.c. [elution with benzene-ethylacetate (3:1)].

The ether (V[4a]) gave 6β-acetoxy-3α,5-methano-4-oxa-A-homo-19-nor-5α,9β-cholestan-4a-one (VII [4])(14mg.) m.p. 191-192, $[\alpha]_D$ + 10° (C, 0.8), $\nu_{max.}$ (KCl) 1750 and 1775 (C = O) $cm.^{-1}$, τ 4.8-4.95 (m, AcOCH), 5.1 - 5.4 (m, OCH), 7.82 (s, AcO), 9.13 (d, side-chain), and 9.28 (s, 18-Me) (see Discussion for mass spectrum) (Found: C, 75.55; H, 10.2. $C_{29}H_{46}O_4$ requires C, 75.95; H, 10.1%), and starting material (V[4a]) (10 mg.).

The ketone (V[5c]) gave 3α,5-methano-4-oxa-A-homo-19-nor-5α,10α-cholesta-4a,6-dione (VII[5])(10 mg.), m.p. 194-196°, $\nu_{max.}$ (KBr) 1720 and 1765 (C = O) cm.$^{-1}$ (see Discussion for mass spectrum) (Found: C, 78.00; H, 10.5. $C_{27}H_{42}O_3$ requires C, 78.20; H, 10.2%), 5α,10α--cholestan-6-one-3β-ol (VII[6]) (5 mg.), a gum, τ 5.5 - 6.1 (m, OCH), 9.1 (d, side-chain), and 9.3 (s, 18-Me) (see Discussion for mass spectrum), and starting material (V[5c]) (20 mg.).

Photolysis of nitrite ester 1[6e]:- The hydroxy-acetate (1[6c]) on treatment with nitrosyl chloride in pyride gave the nitrite ester (1[6e]). Photolysis of the nitrite ester (1[6e])(500 mg.) as previously described for (1[4e]) gave an oil. Preparative t.l.c. [elution with benzene-ethylacetate (3:1)], gave the keto-acetate (IV[1a])(50 mg.)$[\alpha]_D$+ 19° (c, 1.0)as a gum, ν_{max} 1720 and 1740 (C=O)cm.$^{-1}$, τ 5.3-5.6 (q, J apparent 10 and 5 Hz., AcOCH), 8.05 (s, AcO), 8.9 (s, 5-Me), 9.10 and 9.20 (d, side-chain, 18-Me), starting material (1[6c])(90 mg.), and 6β-acetoxy-9β,10-epoxy-5-oximino-19-nor-5β,9β-cholestan--3β-ol (IV[3 or 4a])(50mg.), a gum, $[\alpha]_D$+ 104° (c, 0.6), τ 2.50 (s,CH=N-O), 5.1-5.6 (m, AcOCH), 5.8-6.1 (m,OCH), 8.05 (s,AcO) 9.1 and 9.2 (d,side-chain and 18-Me) (see Discussion for mass spectrum).

Deoximation of (IV[3/4a])(35 mg.) with nitrous acid, as before, gave, after t.l.c.[elution with benzene-ethylacetate (3:1)],6β,4a--diacetoxy-9β,10-epoxy-3α,5-methano-4-oxa-A-homo-19-nor-5α,9β-cholestane (IV[6a])(15 mg.) a gum, $\nu_{max.}$ 1750 (C=O)cm.$^{-1}$, τ 3.78 (s,OCHO), 5.1-5.35 (m,AcOCH), 5.35-5.6 (m,OCH), 8.1 (s,2 OAc),9.08 and 9.18 (d,side-chain and 18-Me) (see Discussion for mass spectrum).

Mass Spectral Data

Comp.	Base m/e	Peak Formula (calculated mass)	Molecular ion m/e	Formula (calculated mass)	Relative Abundance (%)	m/e	Other ions Formula (calculated mass)	Relative Abundance (%)	Meta stable peaks m/e	transition
II[4a]	43		444.3594	$C_{29}H_{48}O_3$ (444.3603)	4	429		10	414	444-429
						384		4	247	444-331
						331		34	331	444-384
						271		18	222	331-271
						253		7	236	271-253
III[1a]	398		458.3403	$C_{29}H_{46}O_4$ (458.3396)	16	415		10.9	346	458-398
						383		2	376	458-415
						368		1	368	398-383
						343		15.2	340	398-368
									295	398-343
						314		24	248	398-314
IV[2k/5b]	43					517.3515	$C_{31}H_{49}O_6$ (517.3528)	38.3	404	517-457
						457.3307	$C_{29}H_{45}O_4$ (457.3307)	30	345	457-397
						397.3109	$C_{27}H_{41}O_2$ (397.3105)	44		
						289		20		

Mass Spectral Data (continued)

Comp.	Base m/e	Peak Formula (calculated mass)	Molecular ion m/e	Formula (calculated mass)	Relative Abundance (%)	Other ions m/e	Formula (calculated mass)	Relative Abundance (%)	Meta stable peaks m/e	transition
IV[3]	43		489		1.8	472		80	455	489-472
						430		9	350	472-412
						412		40	376	489-430
						402		16.4	366	402-384
						384		14.5	198	384-276
						289		3.6		
						276		5.5		
IV[4]	402. 3148	C H O 26 42 3 (402.3134)	489.3463	$C_{29}H_{47}NO_5$ (489.3454)	8.5	472.3429	$C_{29}H_{46}NO_4$ (472.3427)	4.6	455	489-472
						430.3311	$C_{27}H_{44}NO_3$ (430.3321)	12.3	350	472-412
						412	$C_{29}H_{36}$ (384.2817)	5.8	376	489-430
						384.2824	$C_{20}H_{33}O$ (289.2531)	55.5	366	402-384
						289.2527		7.7	208	402-289
						276.2453	$C_{19}H_{32}O$ (276.2453)	21.5	198	384-276
IV[6]	43		516.3461	$C_{31}H_{48}O_6$ (516.3451)	50	473		14.3	434	516-473
						457		50	405	516-457

Mass Spectral Data (continued)

Comp.	Base m/e	Peak Formula (calculated mass)	Molecular ion m/e	Formula (calculated mass)	Relative Abundance (%)	Other ions m/e	Formula (calculated mass)	Relative Abundance (%)	Meta stable peaks m/e	transition
III[5b]	364					424.3327	$C_{29}H_{44}O_2$ (424.3341)	4.7	312.5	424-364
						257		11.8	173	364-251
III[6b]	424.3336	$C_{29}H_{44}O_2$ 424.3341	484.3544	$C_{31}H_{48}O_4$ 484.3552	2.8	364		88	312.5	424-364
V[1a]	472.3184	$C_{29}H_{44}O_5$ (472.3189)	472	$C_{29}H_{44}O_5$	100	430.3084	$C_{27}H_{42}O_4$ (420.3082)	92	391	472-430
						413		20	359.6	472-412
						412		25	264	472-353
						353		36		
V[2a]	264.2458	$C_{18}H_{32}O$ (264.2453)	472.3194	$C_{29}H_{44}O_5$ (472.3189)	29	430		5.8		
						413.3059	$C_{27}H_{41}O_3$ (413.3056)	48	361.4	472-413
						412		6.9		

Mass Spectral Data (continued)

Comp.	Base m/e	Peak Formula (calculated mass)	Molecular ion m/e	Formula (calculated mass)	Relative Abundance (%)	Other ions m/e	Formula (calculated mass)	Relative Abundance (%)	Meta stable peaks m/e	transition
V[3]	456.3231	$C_{29}H_{44}O_4$ (465.3239)	456	$C_{29}H_{44}O_4$	100	396		34	343.9	456-396
						366.2919	$C_{26}H_{38}O$ (366.2923)	49	293.8	456-366
						353		27	273.3	456-353
VII[7]	151		434.3399	$C_{27}H_{46}O_4$ (434.3396)	30.8	416		46	362.8	398-380
								30.8	380.6	416-398
						398		23	398.7	434-416
						380		45		
						264			160.6	434-264
VI[7a]	414.3137	$C_{27}H_{42}O_3$ (414.3134)	446.3365	$C_{28}H_{46}O_4$ (446.3396)	18	386		12	359.9	414-386
						356		5	328.3	386-356
						278.2596	$C_{19}H_{34}O$ (278.2609)	21		
						263		16		

Mass Spectral Data (continued)

Comp.	Base m/e	Peak Formula (calculated mass)	Molecular m/e	Ion Formula (calculated mass)	Relative Abundance (%)	Other ions m/e	Formula (calculated mass)	Relative Abundance (%)	Meta stable peak m/e	transition
VII[1]	366		486		0.05	426		61	396.5	426-411
						411		4.3	337.4	366-351
						384		2.1	314.5	426-366
						354		14	292.5	426-353
						351		11		
VII[2]	426		546		0.33	486		28	373.4	486-426
						471		0.67	337.4	366-351
						413		3.9	314.5	426-366
						384		14		
						366		75	301.7	413-353
						353		45	292.5	426-353
VII[3]	43					486.3699	$C_{31}H_{50}O_4$	31	373.4	486-426
						471	(486.3709)	0.57	337.4	366-351
						426		69	314.5	426-366
						413		7.3	301.7	413-353
						384		8.9	292.5	426-353
						366		85		
						353		48		

Mass Spectral Data (continued)

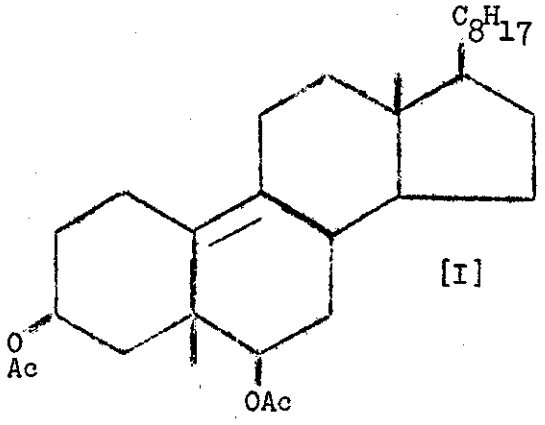
Comp.	Base m/e	Peak Formula (calculated mass)	Molecular ion m/e	Formula (calculated mass)	Relative Abundance (%)	Other ions m/e	Formula (calculated mass)	Relative Abundance (%)	Meta stable peak m/e	transition
VII[4]	415		458.3395	$C_{29}H_{46}O_4$ (458.3396)	19	398		78	375.9	458-415
						370		24	345.5	458-398
						354		50		
						43		71		
VII[5]	414		414		100	396		10	378.8	414-396
						370		4.6	323.9	359-341
						359		83		
						341		17		
VII [6]	125.0603	$C_7H_9O_2$ [125.0603]	388.3336	$C_{26}H_{44}O_2$ (388.3341	77	370		23	352	388-370
						215		16		
IV[3/4ε]	28		489.34		very weak	472.3427	$C_{29}H_{46}NO_4$ (472.3420)	33.3	360	(472-412)
						412		27		
IV[6a]	43		516		2.6	473		0.8	403	516-456
						456		4.3	345	456-397
						397		2.5		

Section 2

A Study of Westphalen type and related rearrangements

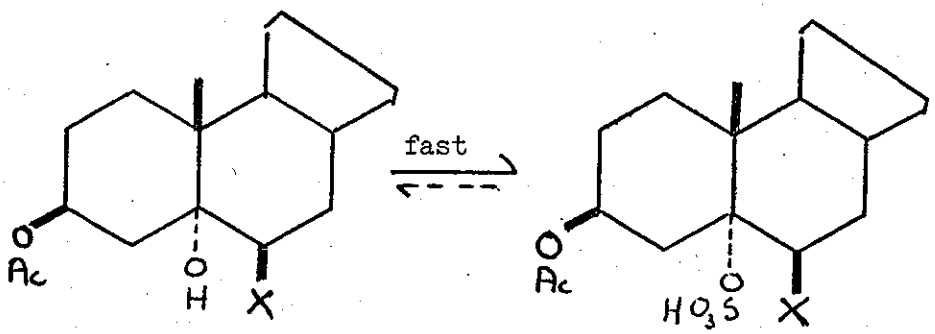
Introduction:-

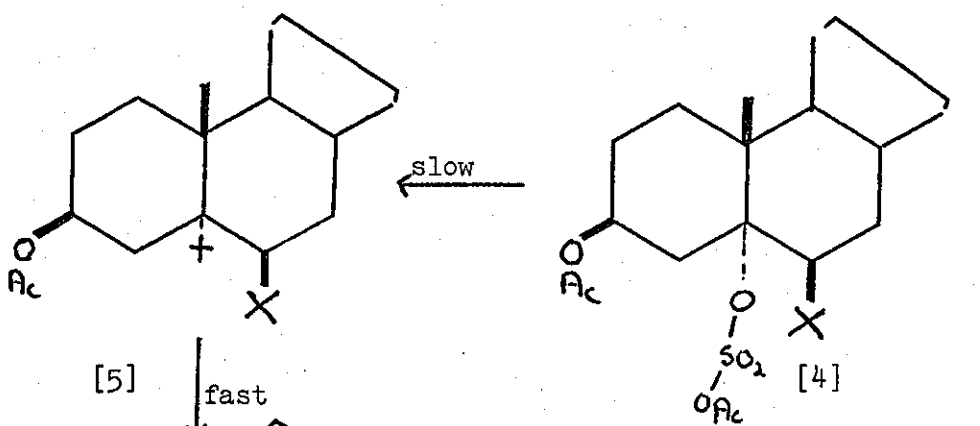
An unsaturated diol diacetate was obtained by Westphalen [37a,39a] while attempting to enforce acetylation of the tertiary alcohol of cholestane-3β,5α,6β-triol-3,6-diacetate. Petrow et al.[39b] in the late 30's, showed that Wagner-Meerwein rearrangement of the C(19)-methyl group from C-10 to C-5 had taken place. Further studies in the early 50's led to the formulation of the diol diacetate as [I][39c]

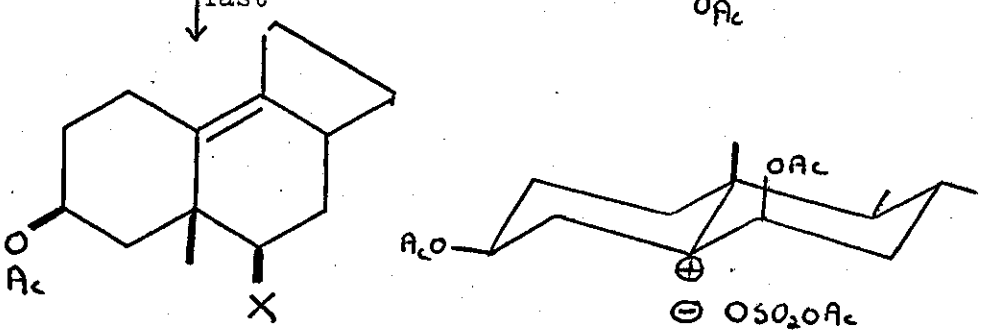


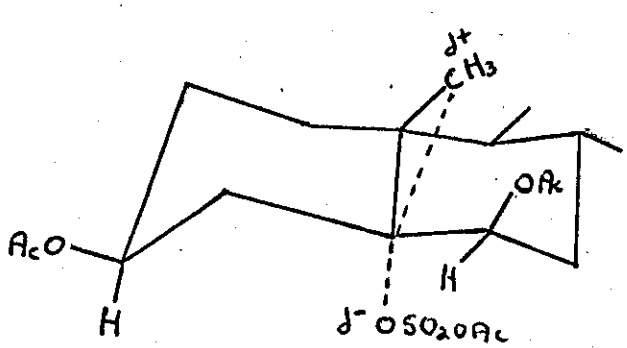
[I]

Chemical evidence for the β-configuration of the 5-methyl group in this structure has recently been published.[11] The Westphalen rearrangement is now common to a wide variety of 5α-hydroxy-steroids possessing electro-negative 6β-substituents, but the introduction of other substituents at C-6 i.e. electronegative 6α,[40a] 6β-methyl[40b] or 6-keto[40c] result in acetylation and/or simple dehydration. The rearrangement is usually carried out in acetic anhydride-acetic acid containing sulphuric acid or potassium hydrogen sulphate as the only effective acid catalyst for promoting rearrangement. Attempted rearrangement using other catalyst of varied acidity gives only acetylation of the 5α-hydroxy group.[41]


fast
Ac
H
X
[2]
Ac
HO3S
X
fast
[3]


slow
Ac
X
[5]
fast
Ac
X
[4]
SO2
OAc


Ac
X
[6]
AcO
OAc
⊖ OSO2OAc
[7]


δ+
CH3
AcO
OAc
H
H
δ- OSO2OAc

[8]

Kinetic data compiled by Kirk et al.[41] showed a first order dependance of reaction rate upon the concentration of each species, i.e. sulphuric acid, steroid and acetic anhydride. The apparent specific role of sulphuric acid as catalyst was indicated by the isolation of cholesteryl hydrogen sulphate (75%)[42] on treatment of cholesterol under Westphalen conditions. Analysis of the kinetic data excludes the possible protonation mechanism followed by loss of water and migration of the C(19)-methyl group, this being confirmed by the inertness of 5α-methoxyl derivative [41] under Westphalen conditions. The dependance of reaction rate upon the concentration of acetic anhydride was interpreted as involving the formation of a 5-acetyl sulphate which would be a better leaving group than 5-hydrogen sulphate.[42]

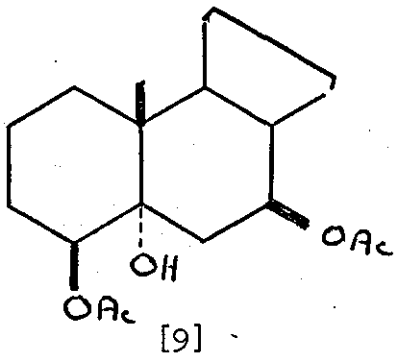
The route suggested which is consistent with the available data involves (a) rapid sulphonation giving the hydrogen sulphate [3] (b) acetylation giving the 5α-acetyl sulphate [4] (c) rate-determining loss of acetyl sulphate giving rise to the C(5)-carbonium ion [5] followed by migration of the C(19)-methyl group (see scheme).

The function of a 6β-substituent in the rearrangement has been rationalised in terms of steric compression arising from its 1,3-diaxial interaction with the C(19)-methyl group directing the fate of the carbonium ion intermediate [5].

Kirk et al.[41] have suggested that in addition to steric compression the electronegativity (-I) of the 6β-substituent could have an equal or even greater influence upon the reaction path.

If the above account of the specific need for a 6β-substituent is valid one would predict that the analogous 5α-hydroxy steroid possessing a 4β-electronegative group would undergo rearrangement. This was found to be so by Summers et al.[43] who reported the rearrangement of 4β,7β-diacetoxy cholestan-5α-ol [9] giving 4β-acetoxy-5β-methyl-Δ^{9}-compound[10] (66%) under Westphalen conditions. Hartshorn et al.[44] in a recent publication also found that the 4β-acetoxy-5α-oxygenated steroid [11] rearranged under Westphalen conditions. It is of interest to note that in the absence of an electronegative substituent in the B ring an increased yield of partial or complete backbone rearranged products was obtained. This was considered to be due to the greater ease with which the 8-9 hydride shift to form a C(8)transient carbonium ion could occur.

If the rearrangement, as suggested in the above account proceeds via a carbonium intermediate one might expect some rearrangement to occur with the 5β-hydroxy steroid [12]. This is not so as 5β-hydroxy steroid [12] is reported[45] to give only 3β,6β-diacetoxy cholest-4-ene and 3β-acetoxy-5α-cholestan-β^{6}-one under Westphalen conditions. This could be due to retention of configuration of the carbonium



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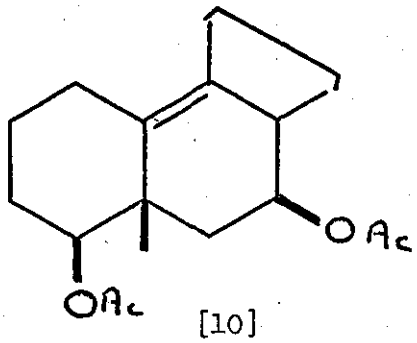

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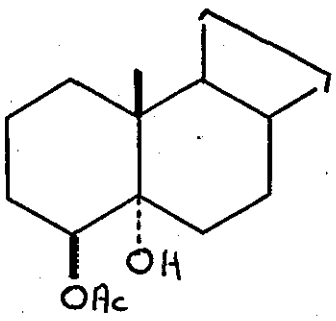
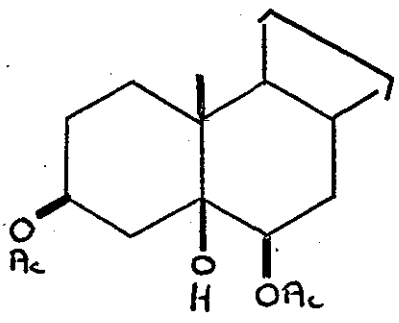
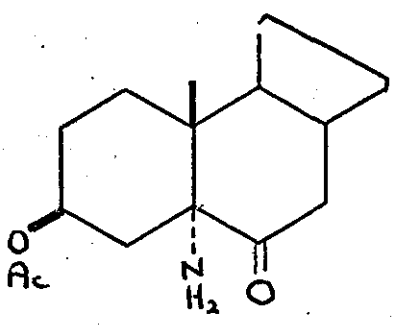


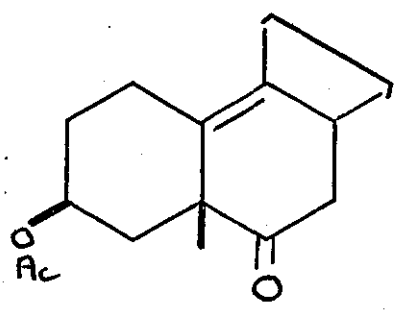
[11]



[12]



[13]



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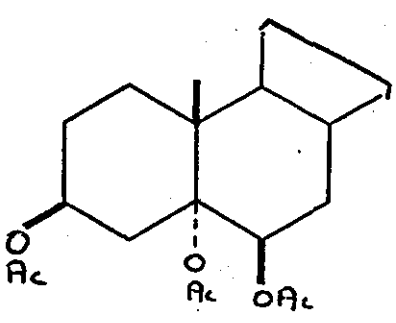

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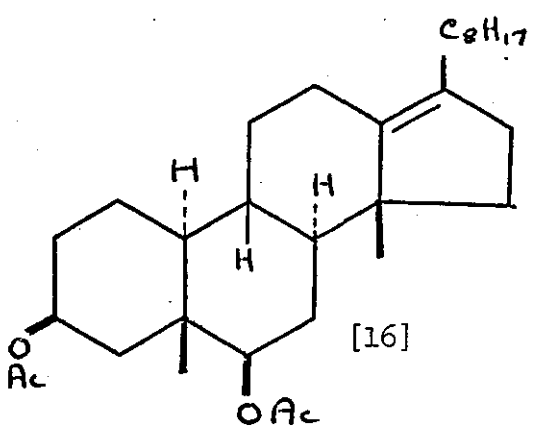


[16]

ion [7] by being associated with the departing acetyl sulphate anion as an ion pair while migration occurs, or it could also be interpreted as indicating the intervention of the migrating methyl group in the rate determining fission of the C(5)-O bond [8] (synchronous reaction). Available data does not allow one to distinguish between the two alternatives. The possibility of participation by the C(19)-methyl group giving rise to anchimeric assistance and/or steric acceleration[47] has to date received little attention and warrants investigation so that the nature of the rate-determining step can be clarified. It is of interest to note that Snatzke[46b] has suggested the possible intermediacy of a non-classical ion.

Westphalen-type rearrangements have been successfully carried out with other 5α-substituted steroids. Snatzke[46a] found that nitrous acid deamination of 5α-amino-steroids possessing electronegative 6β-substituents gave Westphalen rearranged products. Also deamination of the 5α-amino-6-keto-steroid [13] gave, surprisingly, the Westphalen-6-ketone [14]. This has been attributed to the ability of the diazonium ion formed to fragment to the required carbonium ion with a low activation energy by the loss of a molecule of nitrogen.[42]

A related reaction of interest discovered by Snatzke [46b] is the rearrangement of the 3,5,6-triacetate[15]. Under Westphalen conditions [15] gave only starting material but under forcing conditions the triacetate gave the Westphalen diacetate [1] and a rearranged product identified by Kirk et al.[48] as the 13,17-olefin [16]. The latter olefin is probably formed by stereospecific Wagner-Meerwein shifts of methyl and hydride groups at all ring junction positions. Similar backbone rearranged products were also formed on isomerisation of cholest-4-ene, cholest-5-ene,[49a] and 3α/β-amino-5-pregnene-20-ones[50] with acid. A backbone type rearranged product is also obtained (in part) on treatment of some 5,6α-epoxides with Lewis acids. The rearrangement of epoxides are usually complicated and a comprehensive account by Kirk and Hartshorn[49b] surveys the numerous reaction paths open to epoxides on treatment with Lewis acids. All the above reactions nominally proceed via a C-5 carbonium ion and it is not yet understood why under certain reaction conditions the rearrangement terminates at the 9,10-position while other conditions favour a complete and/or partial backbone rearrangement. The nature of the solvent medium and reagents in conjunction with the relief of conformational strain[49a] experienced in going to a backbone rearranged compound may well play an important role in

deciding the nature of the products obtained.

The Westphalen rearrangement of 5α-hydroxy steroids with varying substituents at C-4, C-6 and C-10 and the acid catalysed dehydration of 9-and 10-hydroxy-steroids are here investigated in an attempt to clarify the detailed mechanisms involved. Deamination of a 5α-amino steroid under aprotic conditions is also studied in order to determine the effect of solvent change upon the fate of the C(5)-carbonium ion.

Discussion.-

Snatzke and Veithen[46a] reported that deamination of 3β,6β-diacetoxy-5α-aminocholestane (1[3c]) in aqueous acetic acid and dioxan gave the Westphalen diol diacetate (1[5])(46%), the $\Delta^{1(10)}$-isomer (1[6]) (30%) and the Δ^{4}-isomer (II[1])(9%). This product distribution is similar to that obtained from Westphalen rearrangement of 5α-hydroxy-steroids (see introduction).

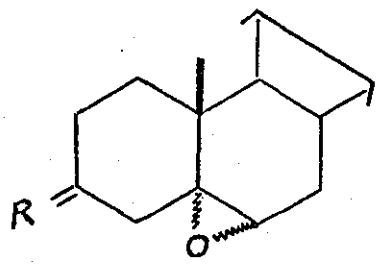
The attempted preparation of 5α-azido-3,3-ethylenedioxycholestan-6β-ol from the β-epoxide (1[1c]) proved unsuccessful. Epoxidation of 3,3-ethylenedioxycholest-5-ene with monoperphthalic acid in ether as described in the literature[51] gave a mixture of the α- and β-epoxides. Column chromatography of the mixture gave the β-epoxide (1[1c]) (60%) and the α-epoxide (1[1c]) (30%) The epoxides are assigned the α- and β-configuration on the basis of the ^{1}H n.m.r. spectra as the melting points observed did not agree with those quoted in the literature.[51] The deshielding of the 10-methyl observed in going from 5β,6β-epoxide to the 5α,6α-epoxide is analogous to the deshielding observed by Cross[16] for similar 5,6-epoxides.

The β-epoxide (1[1c]) on treatment with sodium azide and sulphuric acid in dimethyl sulphoxide gave only unchanged starting material whilst the corresponding α-epoxide (1[1c]) under the same conditions gave a quantitative conversion to the azide (1[2]). Resistance

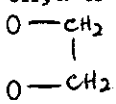
of the β-epoxide (1[1c]) to nucleophilic attack giving diequatorial substituents has been reported by other workers,[52] this resistance arising from the interaction between the incoming nucleophile and the bulky 3,3-ethylene dioxy-group at the α-face of the steroid molecule.

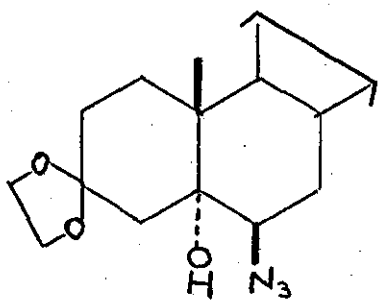
The amine (1[3c]) was prepared via the azide (1[3a]) by the method of Ponsold.[53] Reaction of the epoxide (1[1a])[54] with sodium azide and sulphuric acid in dimethyl sulphoxide gave the azide (1[3a]), the isomeric compound (1[4b]) and some starting material (1[1a]). The mixture on column chromatography gave (1[3a]) contaminated with the hydrolysed compound (1[4b]), and (1[4a]) contaminated with β-epoxide (1[1a]). Purification of (1[3a]) was effected by preparative thin layer chromatography and this on acetylation gave the azide (1[3b]). Reduction of (1[3b]) with hydrazine hydrate and Raney nickel gave the amine (1[3c]). The isomer (1[4a]), which was detected by Snatzke[46a] but not by Ponsold,[53] was subsequently obtained by way of the diol (1[4b]). The mixture of (1[4a]) and β-epoxide (1[1a]) was hydrolysed and chromatographed to give (1[4b]) and the β-epoxide (1[1b]). Acetylation of (1[4b]) gave the azide (1[4a]).

The hydrochloride of (1[3c]), in acetic acid, gave, on treatment with a saturated sodium nitrite solution, a product distribution identical to that obtained by Snatzke.[46a]

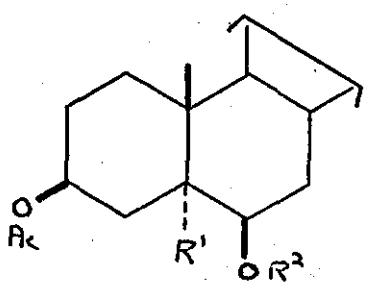


[1]

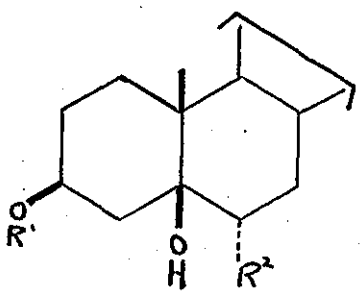
	R
(a)	β-OAc, α-H
(b)	β-OH, α-H
(c)	



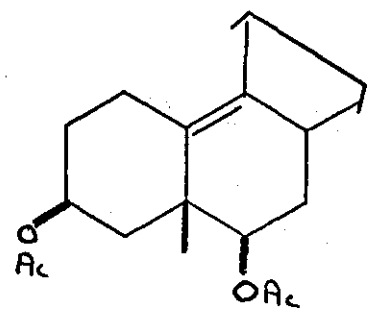
[2]



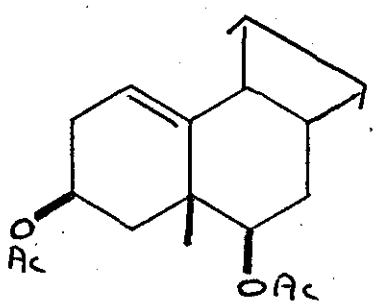
[3]	R^1	R^2
(a)	N_3	H
(b)	N_3	Ac
(c)	NH_2	Ac
(d)	OH	Ac



[4]	R^1	R^2
(a)	Ac	N_3
(b)	H	N_3
(c)	H	NH_2



[5]



[6]

The hydrochloride of (1[3c]), in chloroform, gave, on treatment with an excess of 3-methylbutylnitrite, and after preparative t.l.c., the Westphalen diol diacetate (1[5])(40%) and essentially pure $\Delta^{1(10)}$-isomer (1[6]) (47%). The ^{1}H n.m.r. spectrum of the latter suggested that it was contaminated with a little of the Δ^{4}-isomer (11[1]) ($< 10\%$), but one crystallisation from aqueous methanol gave pure $\Delta^{1(10)}$-isomer (1[6]).[46b]

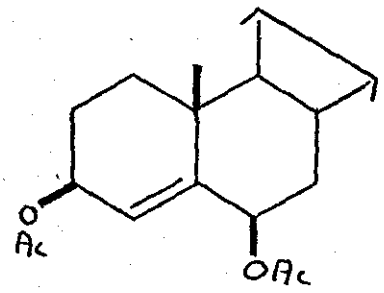
It appears that the change from protic to aprotic conditions results in an increased Hofmann versus Saytzeff control in the deamination. Since the Δ^{1}-isomer (1[6]) gives no detectable quantities of the $\Delta^{9(10)}$-isomer (1[5]) on standing in aqueous acetic acid for two hours, it seems unlikely that (1[6]) is first formed under protic conditions and then equilibrates to (1[5]). A possible explanation lies in the different size of the basic species[55] attacking the C(10)-carbonium ion, presumably an intermediate in both reactions. The removal of a proton from C-1 and C-9 by a water molecule is probably equally easy and under aqueous conditions the expected[56] Saytzeff elimination occurs. However, in the aprotic reaction, the base is probably 3-methylbutylnitrite and this will be more sterically demanding than water. The C-9 proton of a C(10)-carbonium ion intermediate appears, from inspection of models, to be subject to 1,3-diaxial interactions with hydrogen atoms at position 12, 14 and possibly 7, while the

proton at C-1 appears to be relatively unhindered. Consequently increased attack at C-1 and formation of more of the Hofmann product (1[6]) than in the reaction under protic conditions would be anticipated. It is noteworthy that 'backbone rearranged'[34] products were not detected.

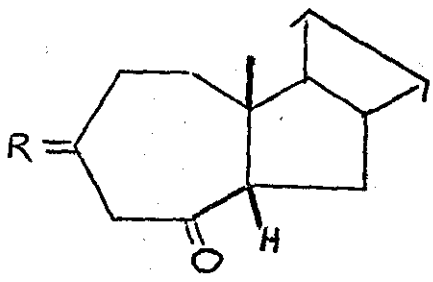
The indicated stereochemistry of the azide (1[4a]) was assumed by Snatzke and Veithen[46a] by analogy with the reported diequatorial opening (in part) of the β-epoxide (1[1a]) with lithium aluminium hydride.[57] The ^{1}H n.m.r. data for the diol (1[4b]) and azide (1[4a]) confirm this stereochemistry which is also consistent with the results of the deamination of the corresponding amine (1[4c]) described below. In the ^{1}H n.m.r. spectra of (1[4a])and (1[4b]) the C-3 methine proton signal, at τ 5.8 and 4.8 respectively, has a half-height band width of 7-9 Hz., which confirms its equatorial conformation and that the A/B ring junction is cis. The C-6 methine proton in (1[4b]) and (1[4a]) is axial, since the signal at τ 6.4 has a half-height band width of ca. 20 Hz.. Reduction of the dihydroxy-azide (1[4b]) with hydrazine hydrate and Raney nickel gave the amine (1[4c]), and deamination of this in aqueous acetic acid gave the anticipated A-homo-B-norketol (11[2a]). The ketol is assigned the cis-A/B-ring junction since it gives a positive c.d. curve and is closely analogous to the ketone (11[3b]) which gives a positive cotton effect.[58] The migration of the C(5)-C(10) bond in

the deamination is foreseeable, since it has the required antiperiplanar conformation with the departing equatorial diazonium group.[59] Oxidation of (11[2a]) with Jones reagent [33] gave the β-diketone (11[2b]) which in alkaline solution showed an intense u.v. absorption: $\lambda_{max.}$ 294 nm (ξ 20,800). In neutral solution only a weak absorption was evident; these data compare well with those reported[60] for the compound (11[4]). The availability of the ketol (11[5]), formed by Jones [33] oxidation of the diol (1[4b]) prompted us to investigate its possible retroaldolisation with strong base. Surprisingly, cholest-4-ene-3-6-dione [37b] (111[3]) was obtained. From thin layer chromatography, it appears that (111[3]) is formed by hydrolysis of an unstable intermediate which was shown to be the enamine (111[2]). The ^{1}H n.m.r. spectrum of (111[2]) showed important signals at τ 4.18 (s,=CH), 4.8-4.95 (m,=CH), and 6.5-7.2 (m, NH_2), the amine protons were exchanged by deuterium on shaking with D_2O. The i.r. spectrum showed important bands at 3460, 3380 (NH_2) 1675 (C=O) and 1640 (C=C) cm.$^{-1}$ The enamine (111[2]) was insufficiently stable to allow elemental analysis but a low resolution mass spectrum confirmed the molecular weight was 397. The u.v. spectrum of (111[2]) in ethanol showed bands at $\lambda_{max.}$ 256 (ξ 8750) and (ξ 7300) nm. On addition of sulphuric acid to the solution, the spectrum collapsed

to a single band at $\lambda_{max.}$ 273 (ε 16000) nm. The original spectrum was obtained by neutralising the solution with caustic soda. The band at 328 nm. in neutral solution is attributed to the dienone chromophore of (111[2]). No other examples of this type of enamine were reported in the literature but it appears that the γ -amino group exerts a bathochromic shift (ca. 50 nm.) which is larger than α- and β-hydroxyl and methoxyl groups.[62] The band at 256 nm. may be due to 4-en-3-one part of the chromophore which is cross-conjugated with the 6,7-en-6-amine system. Other cross-conjugated systems have similarly been reported to exhibit two bands in their u.v. spectra.[62] The band at 273 nm. in acid solution is probably due to the immonium salt (11[8b]). The spectrum of the imine (11[8a]) would be expected to be comparable with that of the ene-dione (111[3]) ($\lambda_{max.}$ 253 nm.[37b]) and a bathochromic shift to 273nm. on formation of the salt is not unreasonable. The conversion of the azide (11[5]) to the enamine (111[2]) presumably involves a base-catalysed β-elimination giving compound (11[6]) which decomposes in the enolate form (11[7]) to give the imine (11[8a]). This evidently tautomerises to the enamine (111[2]). This mechanism is analogous to that reported by Edwards and Purushothaman[64] for the reaction of the bromoketone (111[5a])[65] with sodium azide in dimethyl sulphoxide or lithium azide in dimethyl formamide. The diketone (111[5e]) was formed via the unstable azide



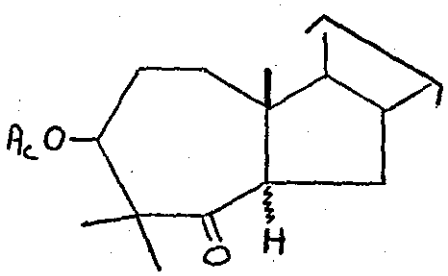
[1]



[2]

(a) R=β-OH,α-H

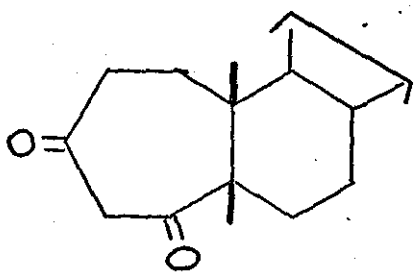
(b) R=O



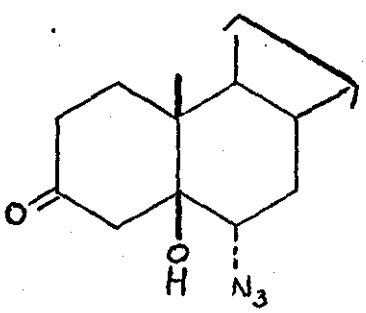
[3]

(a) 5α

(b) 5-β



[4]



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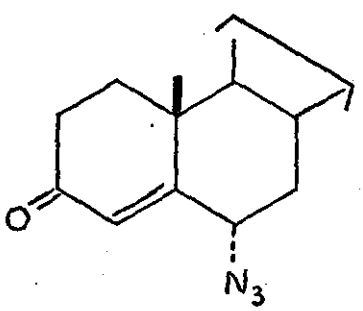

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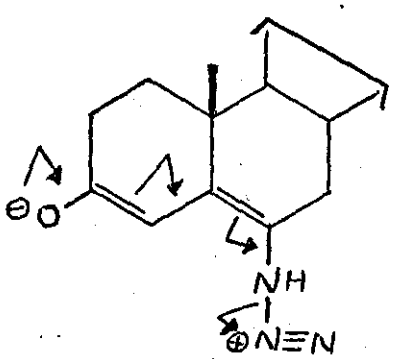

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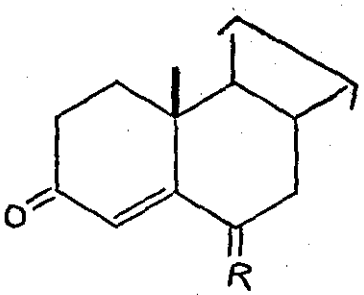
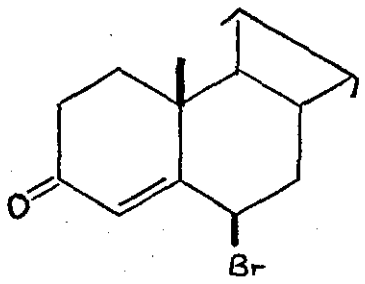


[8] (a) =NH

(b) $=NH_2^{\oplus}$



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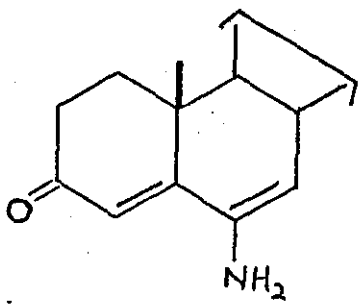

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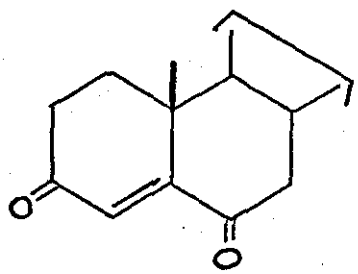

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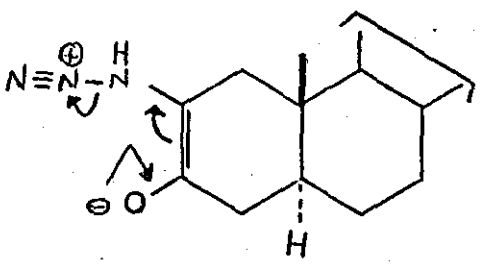

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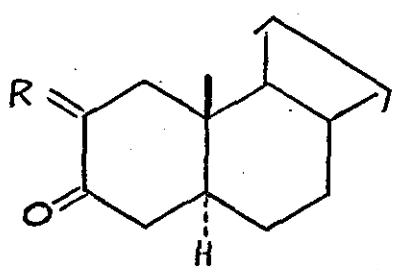


[5] R

(a) α-Br, β-H

(b) β-N_3, α-H

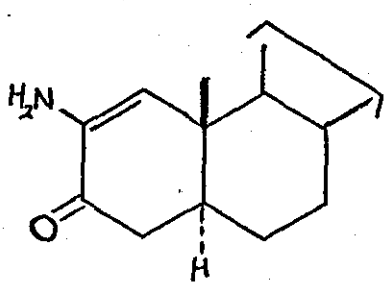
(c) NH

(d) $NH_2^{\oplus}$

(e) O

(f) β-Br, α-H

(g) α-N_3, β-H



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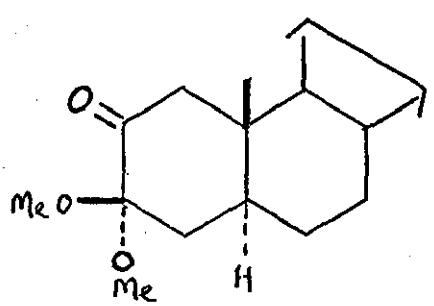
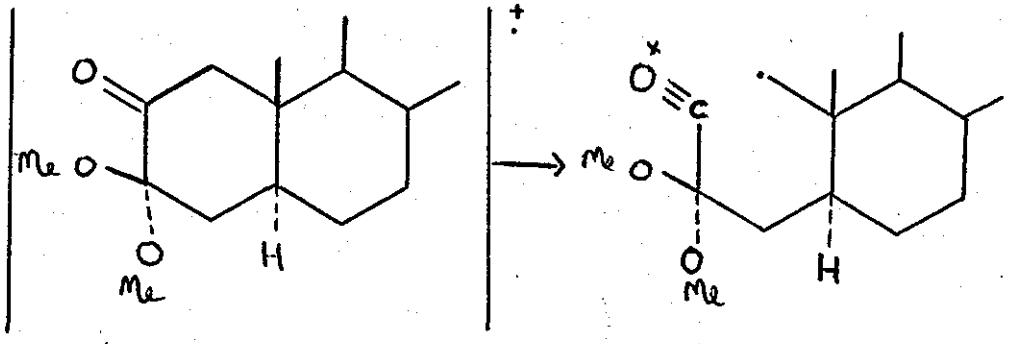
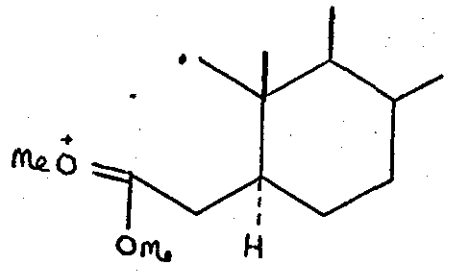


[7]

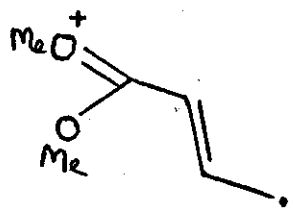
(111[5b]) and the imine (111[5c]) which were detected by i.r. spectroscopy but were not isolated. It was suggested that azide ion acts as a base and promotes the enolisation of the azide (111[5b]) to (111[4]). This is facilitated by the steric repulsion between the axial azido- and methyl-groups. Although such unfavourable interactions were not present in compound (11[6]) it is not surprising that it should revert to the enamine (11[8])in the basic medium employed. The azide (11[6])[66] appears to have similar stability to 2-azido-cyclohexanone[64] since it decomposes to the enamine (111[2]) only above 70° in dimethyl sulphoxide and sodium azide. Not surprisingly, treatment of the bromoketone (111[1][67] with sodium azide in dimethylsulphoxide at 100° rapidly gave the enamine (111[2]). Edwards and Purushothaman reported no u.v. or ^{1}H n.m.r. spectral data for the imine (111[5c]). An attempt was made to prepare the imine (111[5c]) by reaction of the bromoketone (111[5a]) with sodium azide in dimethyl sulphoxide at 100° so that its spectroscopic data could be compared with that of the enamine (111[2]). It was clear from these data that the product of this reaction was the enamine (111[6]) rather than its tautomer (111[5c]). The ^{1}H n.m.r. spectrum showed the presence of an olefinic proton (s, τ 4.09) and a primary amino-group (m, τ 6.3-6.9); the amine protons were exchanged by deuterium on shaking the sample with D_2O. The i.r. spectrum showed important bands

at 3500 and 3400 (NH_2), 1685 (C=C-C=O), and 1640 (C=C)cm.$^{-1}$ The mass spectrum confirmed the molecular weight was 399. The u.v. spectrum in ethanol exhibited a single band at 293 (ε 4330) nm. indicating that the α-amino-group exerts a bathochromic shift of about 65 nm. This figure is not unreasonable in view of the estimated effect of the γ-amino group. In acid solution the enamine (111[6a]) is converted to the immonium salt (111[5d]) since the u.v. spectrum has $\lambda_{max.}$ 231 (ε 6200) nm.(63) Treatment of the enamine (111[6]) with methanolic sulphuric acid gave the ketal (111[7]). The mass spectrum confirmed the structure of the ketal since it exhibited intense peaks at m/e 127 and m/e 114 (scheme below). The former ion has been observed in the mass spectrum of 3,3-dimethoxyandrostane.(68) Both are analogues of important ions in the mass spectrum of androstan-3-one ethylene ketal.(68) An intense peak at m/e 418 corresponds to the loss of carbon monoxide from compound (111[7]) and may be reasonably represented as shown (scheme). The chemical shift of the C(19)-methyl group signal (τ 9.29) in the ^{1}H n.m.r. spectrum confirmed the structure of the ketal (111[7]). The alternative 2,2-dimethoxy-3-oxo-structure would be expected to exhibit a C(19)-methyl group signal at τ 8.8.(22) A comparison of the stability of the 2α-azide (111[5g]) with that of the azides (11[6]) and (111[5b]) was desired.

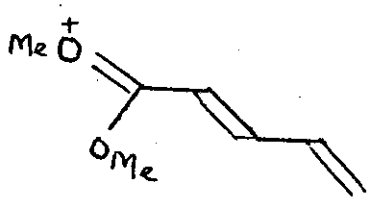




m/e 418



m/e 114



m/e 127

Synthesis of the azide (III[5g]) from the bromoketone (III[5f]) was not attempted since the latter is known to isomerise readily to the 2α-bromoketone (III[5a]). The preparation of (III[5g]) from the bromoacetoxy-compound (IV[1a])[69] by way of the azide (IV[1b]) was attempted. Unfortunately treatment of compound (IV[1a]) with sodium azide in dimethyl sulphoxide gave the allylic acetate (IV[2]) and no reaction occurred with sodium azide in refluxing methanol or n-butanol. The formation of the allylic acetate (IV[2]) may involve initial displacement of the bromine by dimethyl sulphoxide and a subsequent E_1 reaction,[49c] or a direct elimination of hydrogen bromide by way of an E_2 mechanism. The absence of any 2-keto-steroid (IV[1c]) in the product when the reaction was carried out in the presence of base i.e. collidine favours the latter mechanism. If solvent participation occurred the oxysulphonium ion (IV[3]) formed should break down in base via a sulphonium methylide giving the ketone (IV[1c]).[49c]

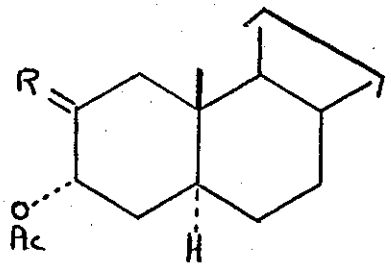
This line of investigation which has been recently reported by us,[70a,b] was not pursued any further.

The deamination results show that the type of solvent medium employed has little influence upon the nature of the products obtained. As mentioned previously Westphalen and more extensively rearranged compounds nominally involve C(5)- and C(10)-carbonium ions. An attempt to investigate

the importance of steric and electronic effects is made by studying the dehydration of 9- and 10-hydroxy-steroids and 5α-hydroxy-steroids with varying substituents at C-4, C-6 and C-10.

The 6β,10β-diols (IV[4a]) and (IV[7a]) were prepared as described in the previous chapter and briefly reported in a recent communication by us.(70c) Jones(33) oxidation of (IV[4a]) and (IV[7a]) gave the ketols (IV[4d]) and (IV[7b]) respectively.

Treatment of the diol (IV[4a]) with p-toluene sulphonyl chloride in dry pyridine gave a mixture of the 6-tosylate (IV[4c]) and the olefin (V[2]). The crude mixture on refluxing with lithium aluminium hydride in dry tetrahydrofuran gave the olefin (V[2]) (50%). The i.r. spectrum of (V[2]) shows a sharp hydroxyl band (at 3640 $cm.^{-1}$) and the mass spectrum does not exhibit a molecular ion but shows a fragment ion of molecular formula $C_{34}H_{48}O_2$ (M-4H) resulting from double dehydrogenation of molecular ion. Other important fragment ions are M-H_2O and M-(H_2O + C_7H_8O) ($C_{27}H_{42}$). The ^1H n.m.r. spectrum showed the presence of two olefinic protons (6-H and 7-H, τ 4.5-5.0) which exhibit an AB pattern (J ca. 11 Hz.). The expected AB pattern arising from coupling between the C-6, C-7 and C-8 protons giving an ABX system is not observed because, from inspection of models, the C(8)-H bond is approximately at right angles to the plane of the 6,7-olefin resulting in almost zero coupling with the olefinic protons.



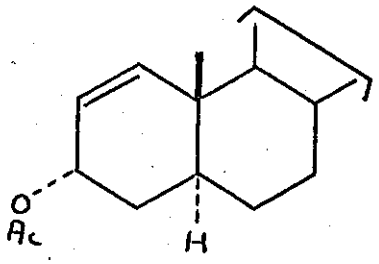
[1]

R

(a) β-Br, α-H

(b) α-N_3, β-H

(c) O



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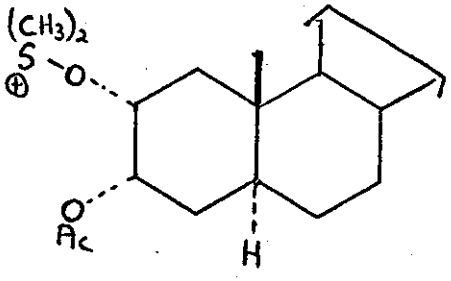

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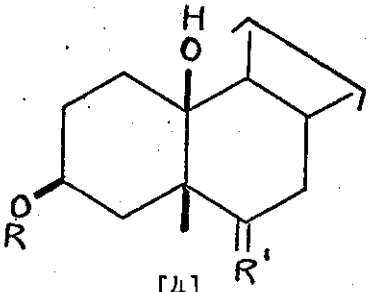
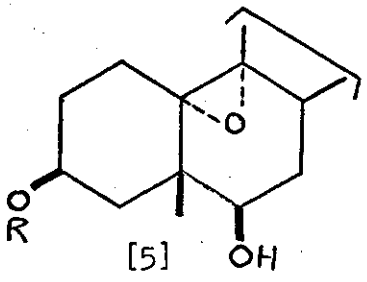


[4]

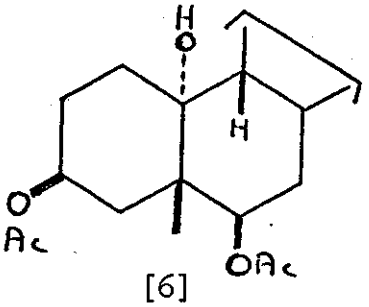
	R	R^1
(a)	$CH_2Ø$	β-OH, α-H
(b)	H	β-OH, α-H
(c)	$CH_2Ø$	β-OTs, α-H
(d)	$CH_2Ø$	O
(e)	H	H_2



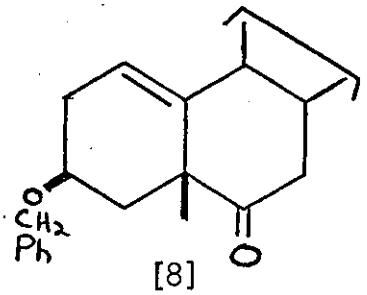
[5]

(a) R=H

(b) R=CH_2Ph



[6]



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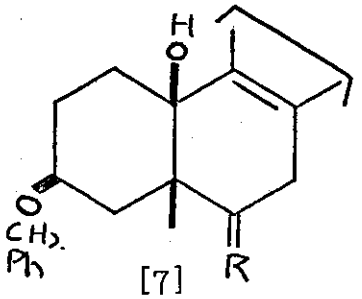


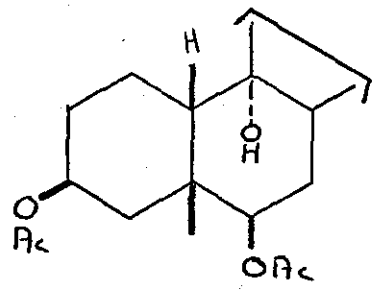
[7]

(a) β-OH, α-H

(b) O

Hydrogenation of the olefin (V[2]) with a palladium-charcoal catalyst, gave (IV[4e]). The i.r. spectrum of (IV[4e]) showed an hydroxyl band (at 3650 cm.$^{-1}$) and no benzyloxy bands indicating hydrogenolysis of the benzyloxy-group had occurred. This was confirmed from the ^{1}H n.m.r. spectrum of (IV[4e]) which showed no aromatic protons and the absence of olefinic protons showed that the 6,7-olefin had been fully hydrogenated.

Hydrogenolysis of (IV[5b]) with a palladium-charcoal catalyst, gave the diol (IV[5a]). Treatment of (IV[5a]) with lithium in ethylamine gave a mixture which after acetylation, with acetic anhydride in pyridine, and preparative t.l.c., gave the Westphalen diol diacetate (1[5]) (25%), alcohol-diacetates (IV[6]) (25%) and (V[1]) (41%). The structures of (IV[6]) and (V[1]) were deduced from spectroscopic and analytical data. The i.r. spectra of (IV[6]) and (V[1]) show sharp hydroxyl bands (at 3640 cm.$^{-1}$) and intense acetate carbonyl bands (at 1745 cm.$^{-1}$). In the ^{1}H n.m.r. spectrum of (IV[6]) the C-6 methine proton is in an axial conformation ($W\frac{1}{2}$ *ca.* 16 Hz.) showing the 10α-configuration. In the ^{1}H n.m.r. of (V[1]) the C-6 methine proton is in an equatorial conformation ($W\frac{1}{2}$ *ca.* 10 Hz.) showing the 10β-configuration. Compounds (IV[6]) and (V[1]) are given the 9β- and 9α-configuration respectively assuming diaxial opening of the epoxide (IV[5a]).



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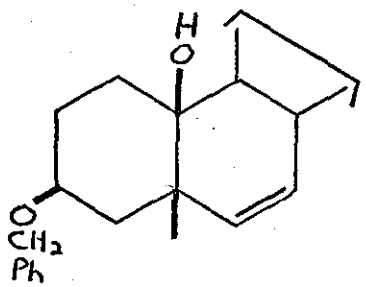

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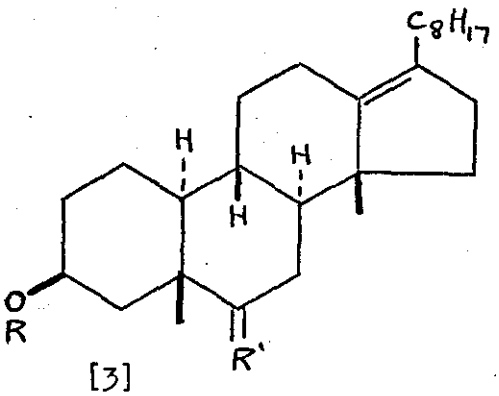
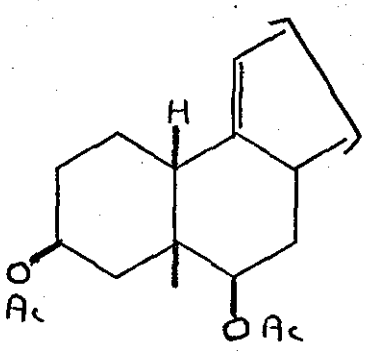


[3]

	R	R^1
(a)	$CH_2Ø$	β-OAc,α-H
(b)	$CH_2Ø$	O
(c)	Ac	H_2
(d)	$CH_2Ø$	β-OH;α-H



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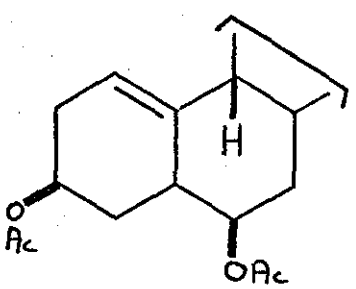

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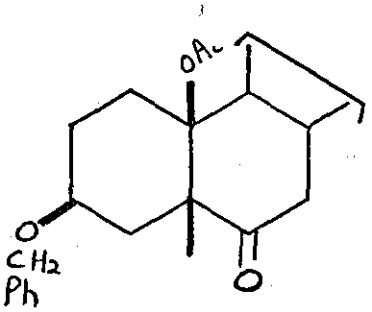

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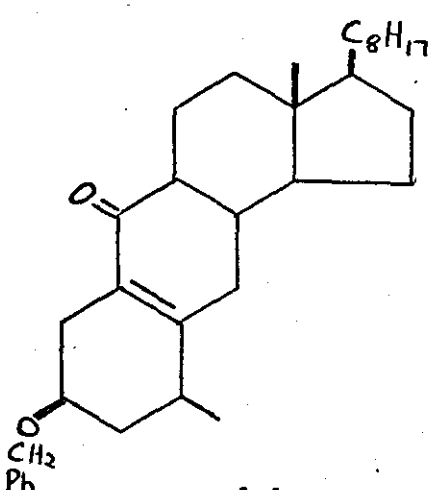


[7]

Treatment of the 6β,10β-diol (IV[4a]) and the 6-desoxy compound (IV[4e]) with toluene-p-sulphonic acid in acetic anhydride at 100° gave a high yield of the backbone rearranged products (V[3a]) (77%) and (V[3c]) (80%) respectively. The ^{1}H n.m.r. spectra of (V[3a]) and (V[3c]) are typical of compounds in this series.(71) (V[3a]) shows the characteristic C(21)-methyl doublet at τ 9.01 (lower branch of C(21)-Me doublet) and 9.11 (upper branch of C(21)-Me doublet, 14β-Me, and lower branch of side-chain doublet). The ^{1}H n.m.r. spectrum of (V[3c]) shows important peaks at τ 8.85 (s, 5β-Me), 9.02 (lower branch of C(21)-Me doublet) and 9.12 (upper branch of C(21)-Me doublet, 14β-Me, and lower branch of side-chain doublet). Double irradiation at 88 Hz. downfield from the C(21)-Me doublet caused its collapse to a singlet (τ 9.07) in both cases and this confirmed the presence of the $\Delta^{13(17)}$ double bond.(71) The low resolution mass spectrum of (V[3a]) showed a fragment ion (M-113) characteristic of backbone rearranged compounds.(71)

Treatment of the ketone (IV[4d]) with toluene-p-sulphonic acid in acetic anhydride at 100° gave the backbone rearranged product (V[3b]) (20%), the $\Delta^{1-(10)}$ compound (IV[8]) (25%) and the acetate (V[6]) (13%) which were separated by preparative t.l.c. Accurate mass measurement on the molecular ion in the mass spectrum of (V[3b]) showed it to have the molecular formula $C_{34}H_{50}O_2$. The ^{1}H n.m.r.

spectrum of (V[3b]) shows important peaks at τ 8.69 (s,5β-Me), 9.03 (shoulder, lower branch of C(21)-Me doublet), 9.04 (s,14β-Me), and 9.12 (upper branch of C(21)-Me doublet and lower branch of C(26)- and C(27)-Me doublets). These data are only consistent with the structure shown (V[3b]) and the failure of the ketone to isomerise with base to a Δ^{7}-6-ketone excludes the alternative $\Delta^{8(9)}$- and $\Delta^{8(14)}$-structures. Final confirmation of the structure of (V[3b]) was obtained by its preparation by Jones[33] oxidation of the alcohol (V[3d]) which was obtained by hydrolysis of (V[3a]). The ^{1}H n.m.r. spectrum of (IV[8]) shows a vinyl proton signal (τ 4.4-4.7) and the chemical shifts of the 5β-methyl and C(18)-methyl groups (τ 8.79, 9.32) suggest the $\Delta^{1(10)}$-structure for (IV[8]) rather than the possible alternative $\Delta^{9(11)}$-structure. The i.r. spectrum of (V[6]) showed strong carbonyl and acetate bands (at 1720 and 1740 cm.$^{-1}$). Elemental analysis and the ^{1}H n.m.r. spectrum of (V[6]) confirmed the presence of the acetate group (τ 8.08). Hence (V[6]) arises by direct acetylation of the 10β-hydroxy group in (IV[4d]).

Treatment of the alcohol-diacetates (IV[6]) and (V[1]) with toluene-p-sulphonic acid in acetic anhydride at 100° gave dehydration products and no skeletal rearranged products. The alcohol (IV[6]) gave, after preparative t.l.c., the Westphalen diacetate (1[5]) (50%) and the $\Delta^{1(10)}$-olefin

(V[5]) (11%). The ^{1}H n.m.r. spectrum of (V[5]) shows an olefinic proton signal (τ 4.5-4.7) and the chemical shift of the C(18)-methyl group (τ 9.32) suggests the $\Delta^{1(10)}$-structure for (V[5]) rather than the possible alternative $\Delta^{9(11)}$-structure. The mass spectrum of (V[5]) does not exhibit a molecular ion but accurate mass determination on the fragment ion (M-AcOH) showed it to have a molecular formula $C_{29}H_{46}O_2$. The alcohol (V[1]) gave, after preparative t.l.c., starting material (28%), Westphalen diacetate (1[5]) (6.5%), and the $\Delta^{9(11)}$-compound (V[4]) (36%). Spectroscopic and analytical data gave a clear indication as to the structure of (V[4]). The ^{1}H n.m.r. spectrum of (V[4]) shows an olefinic proton signal (τ 4.45-4.65) and the chemical shift of the C(18)-methyl group (τ 9.39) suggests the $\Delta^{9(11)}$-structure rather than the possible alternative $\Delta^{1(10)}$-structure. It was of interest to attempt the retroaldolisation of (IV[4d]) as this could confirm the mechanism postulated by Slates and Wendler,[30a] for the retroaldolisation of a 6-keto-5β-methyl-9α,10α-dihydroxy-steroid leading to an anthrasteroid. Treatment of (IV[4d]) with hot (20%) methanolic potassium hydroxide gave, as expected, the anthrasteroid (V[7]) (17%), starting material (17%) and a polar mixture (33%). Accurate mass measurement on the molecular ion (m/e 490) in the mass spectrum of(V[7]) shows the molecular formula to be $C_{34}H_{50}O_2$. The i.r. spectrum shows a carbonyl and an olefinic band (1680 and 1640 $cm.^{-1}$ respectively).

The u.v. spectrum of (V[7]) ($\lambda_{max.}$ 248 (ε 10,800) nm.) confirms the presence of an α,β-unsaturated ketone and is analogous to similar systems reported in the literature.(20) The ^{1}H n.m.r. spectrum shows a secondary methyl doublet at τ 9.00 (lower branch of the 5-methyl) and 9.10 (high-field branch of 5-methyl and low-field branch of the side-chain doublet). These data are only consistent with the structure (V[7]). It seems likely that (V[7]) is formed by retroaldolisation, giving a 5,10-seco-steroid, followed by an aldol condensation between the 6-keto-group and the C(1)-methylene-group.

The low yield of backbone-rearranged product obtained from the 6-ketone (IV[4d]) compared to that from the 6β, 10β-diol (IV[4a]) and the 6-desoxy-10β-alcohol (IV[4e]) is probably due to the greater electron-withdrawing properties of the 6-carbonyl- as compared to the 6-hydroxy-(or OAc) and 6-desoxy groups. The migration of a hydride ion from C-8 to C-9 will be more difficult in the ketone (IV[4d]). It has recently been suggested(44) that in the dehydration of 5α-hydroxy-steroids a 6β-acetoxy-group similarly inhibits the backbone rearrangement to a small extent. In contrast, under Westphalen conditions(14) the 10β-hydroxy-compound (IV[4a]) has recently been shown to give a mixture of the 9,10-olefin (60%) (see section 1) and the 13(17)-olefin (V[3a]) (40%). The decrease in yield of backbone-rearranged product obtained is probably due to the availability of

basic species i.e. acetate anion, from the solvent medium which result in competition between elimination, by an E_1 and/or E_2 type mechanism, and rearrangement to the backbone compound.

The marked difference in the course of rearrangement of the 6β,10β-diol (IV[4a]) and the 5α-hydroxy-6β-substituted compounds suggests that the two reactions do not involve the same C(10)-carbonium ion-like intermediate. Since the 10β-hydroxy-group and the 1α- and 9α-hydrogen atoms are in the anti-periplanar conformation, it seems likely that a discrete C(10)- carbonium ion is not involved in the dehydration of (IV[4a]), (IV[4d]), and (IV[4e]) and that the hydride shift or loss of proton from C-9, and in (IV[4d]) the loss of a proton from C-1, is concerted with the breakage of the C(10)-oxygen bond.

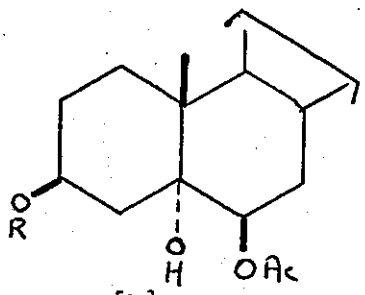
In the Westphalen rearrangement, the migrating methyl group and the 9α-hydrogen atom cannot be in a truly anti-periplanar conformation, and it is possible that a more C(10)-carbonium-ion-like intermediate is formed with subsequent loss of a proton from C-9 (or C-1). In the rearrangements of 4,5- and 5,6-epoxides the products generally obtained are the extensively rearranged $\Delta^{8(14)}$- and $\Delta^{13(17)}$-compounds, and in view of the above results and those reported recently by Hartshorn et.al.[71d] the differences in reagents and reactants may well play important roles in deciding the reaction path.

Since the $\Delta^{9(10)}$-compound (section 1, fig. (1[4a])) under identical conditions gave no detectable amount of the $\Delta^{13(17)}$-isomer it seems unlikely that the latter is formed by a protonation-deprotonation mechanism involving the initially formed $\Delta^{9(10)}$-compound. The absence of any backbone type rearranged $\Delta^{13(17)}$-product from the dehydration of (V[1]) is not surprising as from models this would give rise to the energetically unfavourable 5β,9β,10β-configuration, similarly the possible rearrangement of (IV[6]) to give a Δ^{4}-compound[61] would result in a 10β,9β,8β-configuration. The rearrangement of (~~V[1]~~ IV[6]) and (~~IV[6]~~ VII[5]) to give Δ^{4}- and $\Delta^{13(17)}$-compounds respectively, is unlikely due to the cis-configuration of their A/B- and B/C-ring junctions respectively.

It is of interest to note that the dehydration of the 10α-hydroxy-compound (IV[6]) leads to the expected high ratio of Saytzeff to Hofmann product (4.5:1) but, surprisingly, the dehydration of the 9α-hydroxy-compound (V[1]) gave the reverse with a high ratio of Hofmann to Saytzeff product (5.5:1). Under the conditions employed one would expect Saytzeff control of elimination to predominate in both cases as the transition states should have considerable cationic character. This anomaly can be rationalised as the loss of a C-10 (or C-8) hydrogen, for a transition state with cationic character, would be destabilised by its proximity to the electron withdrawing group at C-6.[44]

Recently Jones and his co-workers[58] reported that the diol (VI[3e]) dehydrated with toluene-p-sulphonic acid in benzene to give a mixture of the 5α- and 5β-6-ketones (VI[4a]) and (VI[4b]) and the A-homo-B-nor-5α- and 5β-ketones (11[3a]) and (11[3b]). Similarly dehydration of the triol (VI[3f]) in methanolic sulphuric acid gave the 5β-6-ketone (VI[4c]). It was felt that dehydration of 4,4-dimethyl-5α-hydroxy-steroids with electron-withdrawing substituents at C-6 would, under the Westphalen conditions[14] result in Westphalen type rearranged products. The rearrangement of 4,4-dimethyl,4β-methyl, and 4α-methyl-5α-hydroxy-compounds are described below.

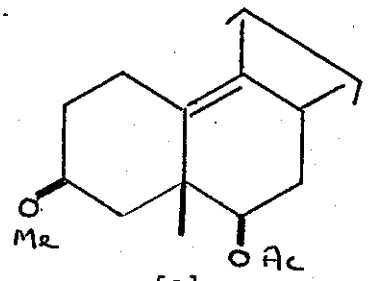
Compounds (VI[3a]), (VI[3b]), (VI[3c])[72] and (VI[3d])[58] were prepared from 4,4-dimethyl-Δ^5-compound (VI[5a]).[73] Cis-hydroxylation of compound (VI[5a]) gave the diol (VI[3e])[58,72] which on Jones oxidation[33] gave the ketol (VI[3c]).[58] Reduction of the ketol with sodium borohydride gave the diol (VI[3g]). Acetylation of the diols (VI[3e]) and (VI[3g]) (the latter with some difficulty) gave the required diacetates (VI[3a]) and (VI[3b]) respectively. Epoxidation of compound (VI[5a]) with monoperphthalic acid gave the α-epoxide (VII[1])[58] which on reduction with lithium in ethylamine gave the 6-desoxy-compound (VI[3d]).[58]



[1]

(a) R=Me

(b) R=Ac



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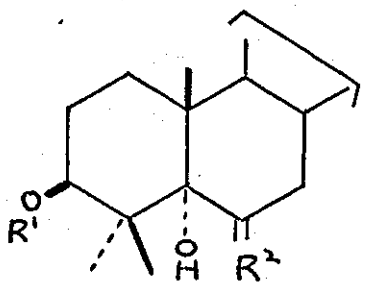
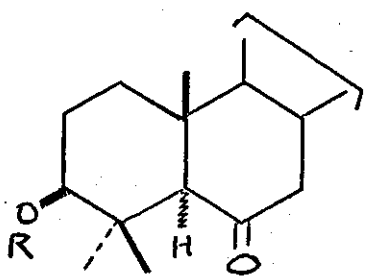


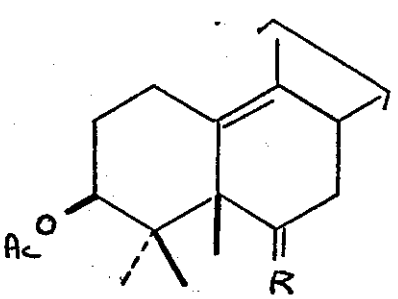
[3]

	R^1	R^2
(a)	Ac;	α-OAc, H
(b)	Ac;	β-OAc, H
(c)	Ac;	O
(d)	H ;	H_2
(e)	Ac ;	α-OH,H
(f)	H ;	α-OH,H
(g)	Ac ;	β-OH,H



[4]

	R
(a)	Ac ; 5-α
(b)	Ac ; 5-β
(c)	H ; 5-β



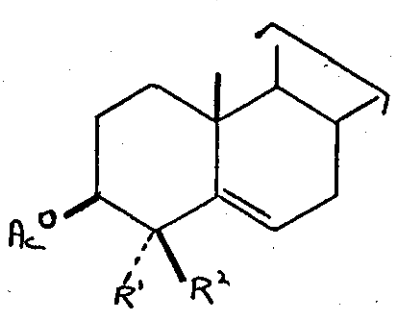
[6]

R

(a) α-OAc, β-H

(b) β-OAc,α-H

(c) O



[5]

(a) R^1=R^2=Me

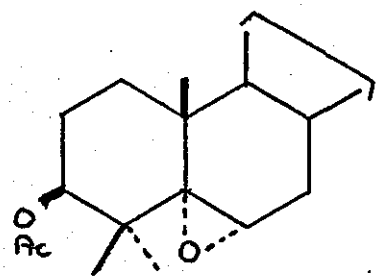
(b) R^1=Me;R^2=H

(c) R^1=H;R^2=Me

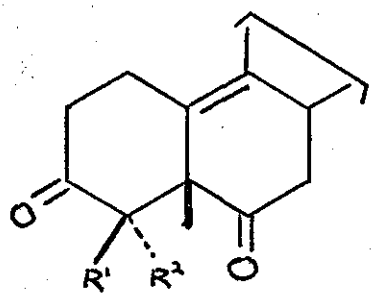
The 4β-methyl and 4α-methyl- Δ^5-compounds (VI[5c]) and (VI[5b]) respectively were prepared by the methods of Julia and Lavaux.[74] Oxidation of compound (VI[5c]) with osmium tetroxide gave the cis-diol (VIII[1a]) which on acetylation gave the 6α-acetate (VIII[1b]). Oxidation of the diol (VIII[1a]) with Jones reagent[33] gave the ketol (VIII[1c]) which was reduced with sodium borohydride in ethanol solution to give the 6β-alcohol (VIII[2a]). Acetylation of this gave the 6β-acetate (VIII[2b]). Similarly, oxidation of compound (VI[5b]) with osmium tetroxide gave the cis-diol (VIII[1d]) which on acetylation gave the 6α-acetate (VIII[1e]). Oxidation of compound (VI[5b]) with monoperphthalic acid and hydrolysis of the resultant epoxides with periodic acid[13] gave the diol (VIII[2c]). Acetylation of the diol (VIII[2c]) gave the 6β-acetate (VIII[2d]) and oxidation of the diol (VIII[2c]) with Jones reagent[33] gave the ketol (VIII[1f]).

The major products from the dehydration reactions of compounds (VI[3a]), (VI[3b]) and (VI[3c]) were the corresponding $\Delta^{9(10)}$-compounds (VI[6a]), (VI[6b]), and (VI[6c]).[74] respectively and these were isolated by preparative t.l.c. and identified mainly from their ^{1}H n.m.r. data which were typical of compounds in this series.[14] In the ^{1}H n.m.r. spectra of (VI[6b]) and (VI[6c]) the C-3 methine proton is in an equatorial

conformation ($W\frac{1}{2}$ ca. 6 Hz.) whilst the C-6 methine proton (in (VI[6b]) only), is in an axial conformation ($W\frac{1}{2}$ ca. 20 Hz.) indicating the 5β-configuration in both compounds. In the ^{1}H n.m.r. spectrum of (VI[6a]) the C-3 and C-6 methine protons are superimposed so the structure (VI[6a]) was assigned because of the low field position of the C(18)-methyl signal (τ 9.2). Hydrolysis of the diacetates (VI[6a]) and (VI[6b]) gave the corresponding diols which on oxidation gave the known $\Delta^{9(10)}$-diketone (VII[2a]).[25] In addition to the $\Delta^{9(10)}$-compound (VI[6a]), compound (VI[3a]) gave a small yield of a mixture of the $\Delta^{1(10)}$-compound (VII[3a]) and the backbone rearranged compound (VII[4a]). Hydrolysis of the mixture and t.l.c. allowed the separation of the diols (VII[3b]) and (VII[4b]). The ^{1}H n.m.r. spectrum of the former showed the presence of the C-1 vinylic proton (τ 4.5) and on oxidation it gave the α,β-unsaturated ketone (VII[5]) ($\lambda_{max.}$ 231 nm. (ε 9000)). Accurate mass determination on the molecular ion and the fragment ion of (VII[5]) and (VII[3b]) respectively confirmed the assigned structures (see table). The structure of the diol (VII [4b]) was assigned tentatively from its ^{1}H n.m.r. spectrum which showed important peaks at τ 8.92 (s, 4α-Me and 5β-Me), 9.02 (s, 4β-Me and low field branch of C(21)-Me doublet), and 9.16 (m, high field branch of C(21)-Me doublet, 14β-Me and side-chain.) The diol



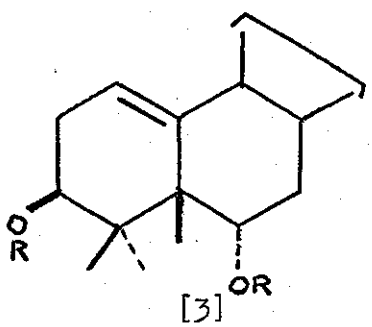
[1]



[2]

(a) $R_1=R_2=Me$

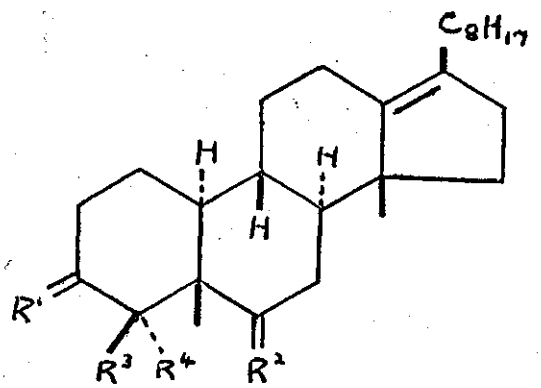
(b) $R_1=Me$ $R_2=H$



[3]

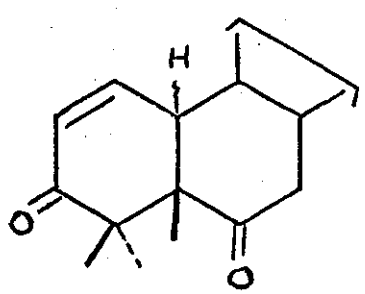
(a) R=Ac

(b) R=H

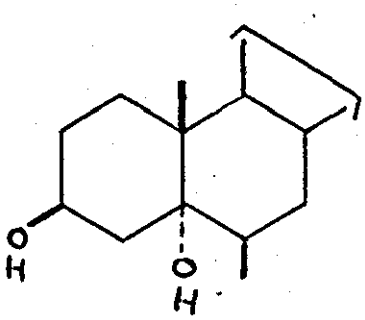


[4]

	R^1	R^2	R^3	R^4
(a)	β-OAc,H;	α-OAc,H	Me	Me
(b)	β-OH,H;	α-OH, H	Me	Me
(c)	O ;	O	Me	Me
(d)	β-OAc,H;	α-OAc,H	Me	H



[5]



[6]

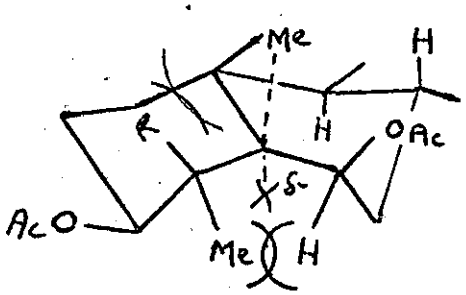
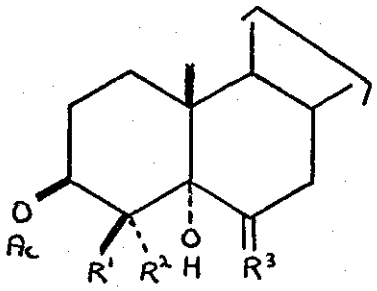


fig.

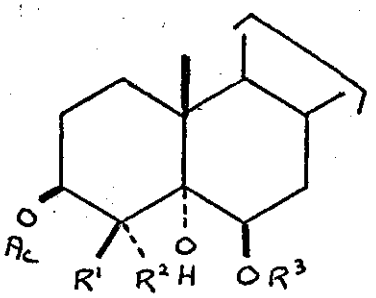
was oxidised to the diketone (VII[4c])[75] which showed an intense peak in the mass spectrum at m/e 313 corresponding to the loss of the side-chain. This fragmentation is very characteristic of $\Delta^{13(17)}$-compounds.[76] An unusual by-product was obtained from the oxidation of the diol (VII[3b]). This compound was isomeric with the ketone (VII[5]) (mass spectrum table) and showed a carbonyl band at 1765 cm.$^{-1}$ (presumably lactone). At present, a satisfactory structure to this compound cannot be assigned.

The major products in the reactions of compounds (VIII[1b]), (VIII[1c]) and (VIII[2b]) under Westphalen conditions[14] were the $\Delta^{9(10)}$-compounds (VIII[3a]), (VIII[3c]) and (VIII[3b]) respectively. These were isolated by preparative t.l.c. and identified mainly from their ^{1}H n.m.r. spectra which were typical of compounds in this series.[14] In the ^{1}H n.m.r. spectra of (VIII[3a]) and (VIII[3c]) the C-3 and C-6 methine protons are in equatorial conformations ($W_{\frac{1}{2}}$ ca. 6-8 Hz.) indicating the 5β-configuration in both compounds. In the ^{1}H n.m.r. spectrum of (VIII[3b]) the C-3 and C-6 methine protons are superimposed and the structure (VIII[3b]) was assigned because of the low field position of C(18)-Me signal (τ 9.2). In addition, hydrolysis of compounds (VIII[3a]), (VIII[3c]) and (VIII[3b]) and Jones oxidation[33] of the corresponding hydroxy-compounds gave the diketone (VII[2b]) (mass spectrum). The o.r.d. spectrum of the diketone (VII[2b]) is very similar to that of the 4,4-dimethyl-diketone (VII[2a])[75] suggesting



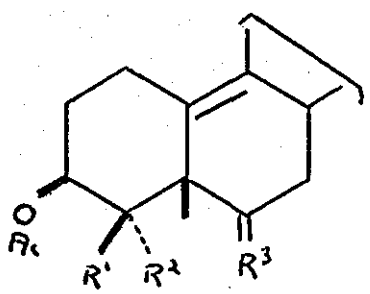
[1]

	R_1	R_2	R_3
(a)	Me	H	α-OH,β-H
(b)	Me	H	α-OAc,β-H
(c)	Me	H	O
(d)	H	Me	α-OH,β-H
(e)	H	Me	α-OAc,β-H
(f)	H	Me	O
(g)	H	H	α-OAc,β-H



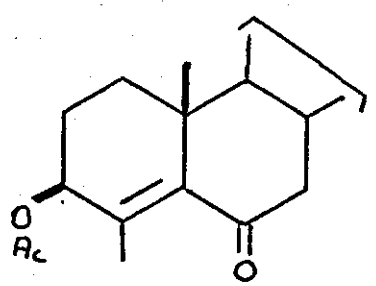
[2]

	R_1	R_2	R_3
(a)	Me	H	H
(b)	Me	H	Ac
(c)	H	Me	H
(d)	H	Me	Ac

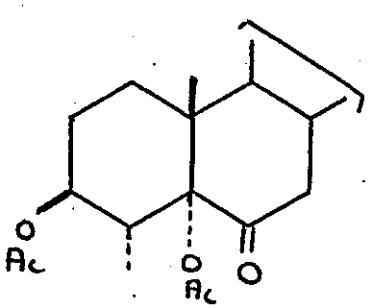


[3]

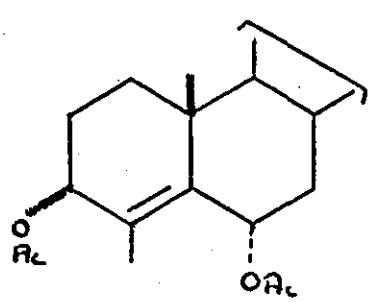
	R_1	R_2	R_3
(a)	Me	H	α-Ac,H
(b)	Me	H	β-Ac,H
(c)	Me	H	O
(d)	H	Me	β-OAc,H
(e)	H	Me	α-OAC,H



[4]



[5]



[6]

that the 4α-methyl group makes no appreciable contribution to the molecular amplitude of the latter. Models show that the 4α-methyl group in compound (VII[2a]) is approximately situated in the XZ plane in the octant projection for the 6-carbonyl group. This seems to confirm that due to vicinal effects the 6-carbonyl group is of prime importance in determining the sign and amplitude of the Cotton effect for the 3,6-diketones.[75] A small amount of slightly impure $\Delta^{13,17}$-compound (VII[4d]) was isolated from the reaction of the 6α-acetate (VIII[1b]). This was identified tentatively from the ^{1}H n.m.r. spectrum which showed important peaks at τ 8.85 (s, 5β-Me) and 9.08 (d, C(21)-Me).[71a] In addition, the mass spectrum of (VII[4d]) showed the important and characteristic fragmentation of the side chain[71b] after the loss of one molecule of acetic acid from the parent ion.

The major product from the dehydration of the 6β-acetoxy-4α-methyl-compound (VIII[2d]) under the usual conditions[14] was the Δ^9-compound (VIII[3d]). Compound (VIII[3d]) was identified by its ^{1}H n.m.r. data (see Experimental). The 6α-acetoxy-4α-methyl-compound (VIII[1e]) reacted very slowly and after 2 hours gave a considerable amount of unchanged starting material (23%) and a complex mixture from which the Δ^4-compound (VIII[6]) was separated by t.l.c. This, the major product, was not fully characterised from its ^{1}H n.m.r. spectrum which showed the presence of a vinylic methyl

group (τ 8.43). The signal was broadened by homoallylic coupling to the C-6 hydrogen atom indicating the retention of configuration at C-6.[77] The signal due to the C-3 hydrogen atom was superimposed on that for the C-6 hydrogen atom but its $W_{\frac{1}{2}}$ (ca. 6 Hz.) confirmed the 3α-configuration. The similar epimerisation of the 3-acetoxy-group (and not the 6-acetoxy-group) in Δ^4-compounds has previously been reported.[78] The 4α-methyl-6-oxo-compound (VIII[1f]) under dehydration conditions gave the acetate (VIII[5]) and the αβ-unsaturated ketone (VIII[4]) ($\lambda_{max.}$ 243 nm). The latter was also obtained by treatment of the 4α-methyl-6-oxo-compound (VIII[1f]) with thionyl chloride in pyridine. The former compound (VIII[5]) was identified from the ^{1}H n.m.r. spectrum which showed the presence of two acetoxy-groups (τ 7.88 and 8.07). Also hydrolysis of (VIII[5]) gave the corresponding diol which on acetylation gave starting material (VIII[1f]). Acetylation of 5α-hydroxy-6-keto-steroids under these conditions has been noted before[40c] and has been ascribed to the reluctance of these compounds to form carbonium ions at C-5 adjacent to the 6-carbonyl group.

The results described here show that provided the C(19)-methyl group suffers 1,3-syn-diaxial interaction with a β-substituent at C-4 and/or C-6 and provided an electron withdrawing substituent is present at C-6,

a Westphalen type rearrangement will occur. Compounds (VIII[1e]) and (VIII[1f]) do not have these requirements and react in a different way.

The reaction of the 6α-acetate (VI[3a]), under Westphalen conditions, differs from those reported for the hydroxy-compounds (VI[3e]) and (VI[3f]).[58] The course of the former reaction is probably influenced by the protection of the C-6 hydroxy-group by acylation thus eliminating some of the reaction paths open to the latter. It seems likely that the latter involves a C(5)-carbonium ion and it might be inferred that under Westphalen conditions the alternative concerted process operates.

The dehydration reactions of 4,4-dimethyl-6α-acetate (VI[3a]) and 4β-methyl-6α-acetate (VIII[1b]) gave in addition to the major product ($\Delta^{9(10)}$-) a small amount of the more extensively rearranged products (VII[4a]) and (VII[4d]) respectively. It has been suggested by Kirk and Hartshorn[42] that the direction of the dipole induced by the 6-substituent is of prime importance in directing the reaction path. The above results tend to indicate that this has little influence upon the migration of the C(19)-methyl but may well have a slight influence on the ability of the C-8 and C-9 protons to migrate.

The absence of any Δ^{4}-olefin from the dehydration of the 4β-methyl-compound (VIII[1b]) compared to the high yield obtained from (VIII[1e]) and reported[40a] for the

alcohol (VIII[1g]) suggests that a C(5)-carbonium ion is not involved. The rearrangement of the 6-ketones (VI[3c]) and (VIII[1c]) offers some evidence in support of a concerted mechanism as it is unlikely to proceed via the energetically unfavourable C(5)-carbonium ion.[40a] In the absence of 4β-methyl substituents 5α-hydroxy-6-ketones are acetylated under Westphalen conditions.[40] It has been suggested that the carbonyl group destabilises the formation of the C(5)-carbonium ion allowing the intermediate acetyl sulphate to be attacked by a molecule of free alcohol.[79] Formation of a C(5)-carbonium ion from (VI[3c]) and (VIII[1c]) would be similarly destabilised but a concerted process would be subject to steric acceleration.

The reaction of the 6-desoxy-compound (VI[3d]) to give the Δ^5-olefin is similar to the reaction of the 5α-hydroxy-6β-methyl-compound (VII[6]).[80] Both reactions presumably proceed via C(5)-carbonium ions and indicate that the steric effect of the 4- or 6-substituent alone is insufficient to ensure rearrangement.

The rearrangement of compound (VI[3b]), and (VIII[2d]) in 0.01 M solution in acetic acid which were 0.05M in sulphuric acid and 0.5 M in acetic acid[14,41] were followed polarimetrically at 25°C. The high rate of reaction of compound (VIII[2b]) did not allow an accurate determination of k in 0.5 M acetic anhydride. At the

lower concentration (0.15 M) reasonably consistent values were obtained. A plot of log (α-α_{∞}) against time were linear indicating that the reaction under these conditions was first order in steroid concentration as are the normal Westphalen rearrangements.[49a] Relative rates were calculated by reference to the values for the 3β-methoxy-5α-hydroxy-compound (VI[1a]) which were in good agreement to those previously obtained.[14, 41] The last column in table below shows the estimated rates of compounds (VI[3b]), (VIII[2b]), and (VIII[2d]) relative to that of the 3β-acetoxy-5α-hydroxy-compound (VI[1b]). These figures are deduced from the known[14] relative rates of compounds (VI[1a]) and (VI[1b]) (ratio ca. 3:1)

Compound	$[Ac_2O]$=0.14M k $sec.^{-1}$	k rel.	$[Ac_2O]$=0.5M k $sec.^{-1}$	k rel.	k rel.
(VIII[2b])	$53\pm6\times10^{-3}$	51	-	-	158
(VIII[2d])	-	-	$3.1\pm0.1\times10^{-3}$	1.1	2.0
(VI[3b])	-	-	$2.9\pm0.1\times10^{-3}$	1	1.8
(VI[1a])	$1.04\pm0.02\times10^{-3}$	1	$4.9\pm0.02\times10^{-3}$	1.7	3.1
(VI[1b])[14]	-	-	-	-	1
(IX[2a])	$7.56\pm0.16\times10^{-3}$	7.3	$36.8\pm1.5\times10^{-3}$	12.7	22.6

From inspection of the calculated relative rates it appears that the rates of the reactions of compounds (VI[3b]), (VIII[2d]), and (VI[1b]) are very similar. At first sight, this may seem unreasonable if the angular

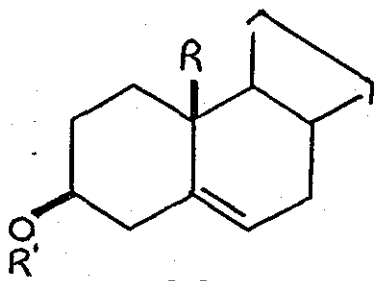
methyl migration is concerted with the heterolysis of the C(5)-O bond, since considerable relief of the syn-1,3-diaxial interaction between the 4β-methyl group and the angular methyl group in (VI[3b]) should occur. Also, there would be some relief of the similar interaction between the 6β-acetoxy-group and the 4β-methyl group. However, models suggest such relief of strain will be counteracted to some extent by compression between the 4α-methyl group and the 6α-hydrogen (VII(fig.)). This compression appears to be governed, in part, by the residual compression between the 4β-substituent and the migrating C(19)-methyl group, accounting for the similarity in the rates of reactions of compounds (VI[3b]) and (VIII[2d]). It is also possible, but perhaps unlikely, that the same detailed mechanism does not apply for compounds (VI[3b]), (VIII[2d]), and (VI[1b]) and that similarity in reaction rates is fortuitous. These data do not however exclude the possible intermediacy of a discrete C(5)-carbonium ion. Two alternative C(5)-carbonium ion mechanisms may be considered; the carbonium ion may be appreciably flattened or it may be reactant-like, existing as an intimate ion pair. The former mechanism seems unlikely as an appreciable increase in the reaction rate of the 4,4-dimethyl-compound (VI[3b]) would be expected due to some relief of steric compression between the 4β-methyl, the angular methyl, and the 6β-acetoxy-group in the transition state. However, the latter

mechanism would certainly account for the similarity of rates of compounds (VI[3b]) and (VI[1b]) and there is evidence[81] to suggest that similar carbonium ions are reactant-like. However, the very rapid rate for compound (VIII[2b]) militates against this mechanism and a concerted mechanism seems best to explain all the data.

Although it is reasonable that the rearrangements discussed above and those reported for 5α-hydroxy steroids under Westphalen conditions in the literature[42] proceed in a concerted fashion the alternative carbonium ion mechanism cannot be completely excluded at this stage. In addition, if the reactions are concerted, it is not possible to say whether a protonated cyclopropane intermediate and/or a C(10)-carbonium ion are involved.

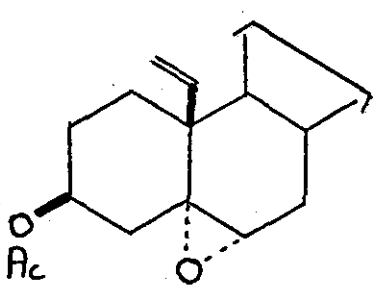
In an attempt to resolve these questions we decided to study some 10-substituted steroids. In particular it was felt that various 10-alkyl and -benzyl compounds, with varying substituents at C-6, might provide useful kinetic as well as general information on the reaction mechanisms. It was envisaged that these compounds could be synthesised from the 19-oxo-derivative (IX[1d]) prepared as described in the literature.[82]

Tosylation of the alcohol (IX[1d]) with toluene-p-sulphonylchloride in pyridine gave the crude 3-tosylate ester which on refluxing in methanol gave the 3β-methyl ether compound (IX[1b])(70%). This was identified from its ^{1}H n.m.r. spectrum which showed important peaks at

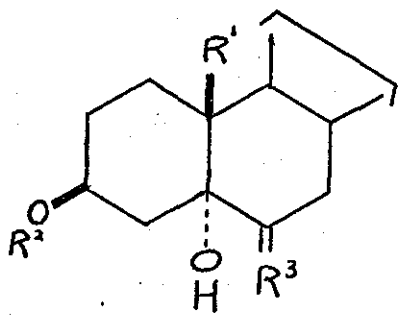


[1]

	R	R^1
(a)	CH_2OH	Ac
(b)	CHO	Me
(c)	CHO	Ac
(d)	CHO	OH
(e)	$HC=CH_2$	Me
(f)	CH_2CH_3	Me
(g)	$HC=CH_2$	H
(h)	$HC=CH_2$	Ac
(i)	CH_2OAc	Ac

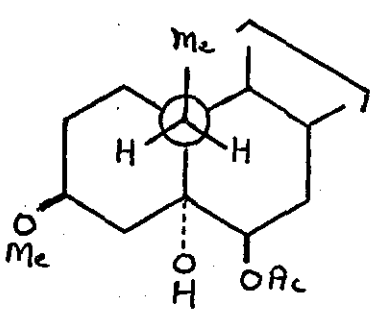


[3]



[2]

	R^1	R^2	R^3
(a)	CH_2CH_3	Me	β-OAc,α-H
(b)	$CH=CH_2$	Ac	β-OAc,α-H
(c)	CH_2CH_3	Me	β-OH,α-H
(d)	CH_2CH_3	Me	α-OH,β-H
(e)	CH_2CH_3	Me	α-OAc,β-H
(f)	CH_2OAc	Ac	α-OH,β-H
(g)	CH_2OAc	Ac	O
(h)	CH_2OAc	Ac	β-OAc,α-H
(i)	$CH_2=CH$	Ac	β-OH,α-H
(j)	CH_2CH_3	Me	O



[4]

τ 0.4 (s,CHO) 4.2-4.4 (m, olefin), and 6.82 (s,OMe). Treatment of (IX[1b]) with methylene-triphenylphosphorane (83) in dry ether gave the diene (IX[1e]) (60%). The i.r. spectrum of (IX[1e]) showed no aldehyde band indicating the absence of the 19-oxo-group. The ^{1}H n.m.r. showed a complex four proton multiplet at τ 4.1-5.2 which confirmed the presence of the 10-ethenyl group. Selective hydrogenation of the diene (IX[1e]) with palladium charcoal catalyst gave the 10-ethyl compound (IX[1f]). The ^{1}H n.m.r. spectrum showed only a single proton multiplet between τ 4.0-5.0 which showed that selective hydrogenation had occurred.

Oxidation of the olefin (IX[1f]) with performic acid and hydrolysis with methanolic potassium hydroxide gave the diol (IX[2c]). Acetylation of this gave the 6β-acetate (IX[2a]). The i.r. spectrum of (IX[2a]) showed a strong acetate carbonyl band and a sharp hydroxyl band (at 1745 and 3610 cm.$^{-1}$). In the ^{1}H n.m.r. spectrum of (IX[2a]) the C-3 and C-6 methine protons are in axial ($W\frac{1}{2}$ *ca.* 18 Hz.) and equatorial ($W\frac{1}{2}$ *ca.* 6 Hz.) conformations respectively indicating the 5α-configuration at C-5 and the β-configuration of the 6-acetoxy-group. Oxidation of the diol (IX[2c]) with Jones reagent (33) gave the ketol (IX[2j]). The i.r. spectrum of (IX[2j]) showed strong carbonyl and hydroxyl bands (at 1710 and 3600 cm.$^{-1}$).

Oxidation of compound (IX[1f]) with osmium tetroxide gave the *cis*-diol (IX[2d]) which on acetylation gave the

acetate (IX[2e]). In the ^{1}H n.m.r. spectrum of (IX[2e]) the C-6 methine proton signal has a half height band width of ca. 19 Hz., which confirms its axial conformation.

Attempted reduction of the ketal (IX[2j]) with sodium metal in ethanol gave a complex mixture of products which, after acetylation and preparative t.l.c., gave the alcohol-acetate (X[4a]) (12%) and (X[4b]) (10%). The structures of these products were deduced from spectroscopic and analytical data. The i.r. spectra of (X[4a]) and (X[4b]) showed intense acetate carbonyl bands (at 1740 $cm.^{-1}$) and hydroxyl bands (at 3500 and 3550 $cm.^{-1}$). The ^{1}H n.m.r. spectra confirmed the presence of two methine protons (3-H and 6-H), one acetoxy-group, and one methoxy-group. In the spectrum of (X[4a]) the C-3 and C-6 methine protons are in equatorial conformations ($W_{\frac{1}{2}}$ ca. 8 and 6 Hz. respectively) and this indicates the 5β-configuration at C-5 and the β-configuration of the 6-acetoxy group. In the spectrum of (X[4b]) the C-3 and C-6 methine protons are in equatorial and axial conformation ($W_{\frac{1}{2}}$ ca. 8 and 20 Hz.) respectively and this indicates the 5β-configuration at C-5 and the α-configuration of the 6-acetoxy group. It thus appears that epimerisation at C-5 occurs prior to reduction of the carbonyl. This could occur in the basic medium employed through an A-homo-B-nor-compound.[85a]

The α-epoxide (IX[3]) was prepared by the method of Watanabe et al.[84] Hydrolysis of (IX[3]) with periodic acid in acetone[13] gave the diol (IX[2i]). Acetylation

with acetic anhydride in pyridine gave the 6β-acetate (IX[2b]). This was identified from its ^{1}H n.m.r. spectrum which confirmed the presence of ~~four~~ three olefinic protons, two methine protons, and two acetate groups.

The attempted opening of the olefin (IX[1a]) with performic acid resulted in epoxidation and attempted cleavage of the crude epoxide with periodic acid[13] gave back unchanged epoxide. Permanganate[85b] oxidation of (IX[1i]) gave a complex mixture from which no identifiable products were isolated. Oxidation of (IX[1i]) with osmium tetroxide gave the cis-diol (IX[2f]) which on oxidation with Jones reagent[33] gave the ketol (IX[2g]). The i.r. spectrum of (IX[2g]) showed intense carbonyl bands (1710 and 1740) and an hydroxy-band (at 3450). Reduction of the ketol (IX[2g]) with sodium borohydride in ethanol gave a crude diol which on acetylation gave the 6β-acetate (IX[2h]). The ^{1}H n.m.r. spectrum of (IX[2h]) confirmed the presence of an axial and equatorial methine (C-3 and C-6 with $W\frac{1}{2}$ ca. 22 and 8 Hz. respectively), three acetoxy-groups, and the O-CH_2 group.

Treatment of (IX[1d]) with methyl lithium in dry ether gave the 19-methyl-19-hydroxy-compound (XI[1a]) which on acetylation with acetic anhydride-pyridine gave the 19-methyl-19-acetoxy-compound (XI[1b]). The diacetate (XI[1b]) on hydrolysis with sodium carbonate in methanol gave the alcohol-acetate (XI[1c]) which on treatment with

trimethylorthoformate and perchloric acid gave the acetoxy-methyl ether (XI[1d]). Hydrolysis of (XI[1d]) overnight with methanolic potassium hydroxide gave the alcohol-methyl ether (XI[1e]) which on oxidation with Jones reagent[33] gave the 10-acetyl-compound (XI[2a]). Spectroscopic and analytical data for all the above compounds gave a clear indication as to their structures. The i.r. spectrum of (XI[2a]) showed a strong carbonyl band at 1710 $cm.^{-1}$ indicating the presence of the 10-acetyl-group. The ^{1}H n.m.r. spectrum confirmed the presence of an olefinic proton, a methoxy-group and a low-field methyl signal (τ 7.95) due to the 10-acetyl-group.

Treatment of (XI[2a]) with methyl lithium in ether and benzene, to give the required 10-iso-propyl derivative, gave only unchanged starting material, similarly treatment with methylene triphenylphosphorane, at elevated temperatures gave no reaction. It is of interest to note that the attempted reaction of (IX[1b]) with methyl lithium gave only unchanged starting material in contrast to (IX[1d]). A possible explanation for this difference is that the 3-O-Li group formed may promote polarisation of the 10-formyl-group and assist attack by a molecule of methyl lithium. In view of this result it was felt that the 10-acetyl-3-hydroxy-compound (XI[2b]) might well react with methyl lithium. (XI[2b]) was prepared by the method described by Caspi et.al.[86] in the androstane series. The alcohol-acetate (XI[1c]) on

treatment with dihydropyran in chloroform gave the 3-tetrahydropyranyl ether derivative which after treatment with lithium aluminium hydride, followed by chromic acid oxidation, and treatment of resulting crude product with mineral acid gave the 10-acetyl-3-hydroxy-compound (XI[2b]). Treatment of (XI[2b]) with methyl lithium unfortunately gave only unchanged starting material. In addition the possible route to 10-n-propyl-derivatives by treatment of (IX[1d]) with ethyl lithium and ethylidene triphenylphosphorane gave only unchanged starting material. This lack of reactivity must be due to steric crowding around the reacting centre which inhibits the formation of a reacting complex in the former and a betaine intermediate in the latter. Treatment of (IX[1d]) with phenyl lithium in ether gave, surprisingly, the diols (XI[3]) and (XI[4]). Their structures were deduced from spectroscopic and analytical data. The i.r. spectra of (XI[3]) and (XI[4]) showed strong intramolecularly hydrogen bonded hydroxy-bands at 3640 cm.$^{-1}$ This indicates that the oxygen function at C-19 is conformationally held over the A-ring in both cases due to partial bonding with 3β-hydroxy-group. Both ^{1}H n.m.r. spectra showed a five proton signal τ 2.5-3.0 indicating the presence of a phenyl group. In both cases the 19-H signal was broad ($W_{\frac{1}{2}}$ ca. 5 Hz.) indicating considerable allylic coupling with the ortho-protons of the phenyl group. The compound (XI[4]) is assigned the S-configuration due to the

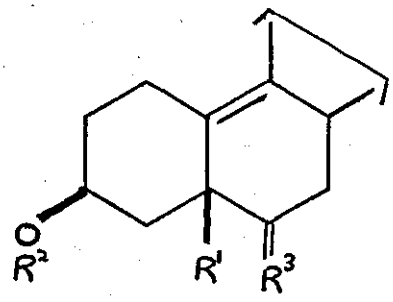
high field position of the C(18)-methyl in the ^{1}H n.m.r. spectrum at τ 9.7 compared to 9.45 in the spectrum of (XI[3]). This large difference becomes understandable on inspection of models. In the S-alcohol the aromatic ring is conformationally held over the B- and C-rings and one of the protons of the C(18)-methyl lies underneath the aromatic ring causing the upfield shift of the C(18)-methyl resonance.

A mixture of the alcohols (XI[3]) and (XI[4]) on acetylation gave a mixture of the mono-acetate (XI[6]) and the diacetate (XI[5]). Oxidation of the crude mixture with Jones reagent[33] followed by hydrolysis gave after t.l.c. starting material and the 10 benzoyl-compound (XI[7b]). The i.r. spectrum showed a carbonyl band at 1675 $cm.^{-1}$ and a hydrogen bonded hydroxyl band at 3640 $cm.^{-1}$ In the ^{1}H n.m.r. spectrum of(XI[7b]) the aromatic protons do not appear as a singlet due to the deshielding influence of the 19-carbonyl group and the two ortho-protons appear as a multiplet (at τ 2.05-2.3) at lower field than the meta- and para-protons (at τ 2.5-2.8). In view of the large degree of hydrogen bonding observed in the i.r. spectrum, it would be reasonable to assume that the 19-carbonyl group is conformationally held over the A-ring. Inspection of models show that the benzene ring would then be held over the C- ring and directly over the C(18)-methyl group. This is confirmed by the high field position

of the C(18)-methyl resonance in the ^{1}H n.m.r. spectrum (τ 9.9). Attempts to reduce the benzoyl-group to give the required 10-benzyl-compound by Wolf-Kishner, Huang-Minlon and catalytic reduction have to date failed and this line of investigation requires further attention.

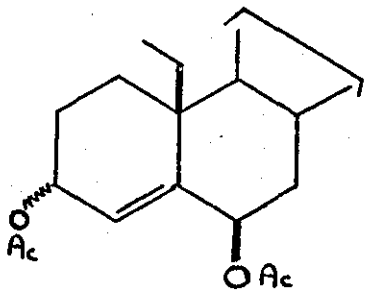
The major products from the dehydration of (IX[2a]) and (IX[2j]) under Westphalen conditions were the $\Delta^{9(10)}$-compounds (X[1a]) and (X[1b]). These were identified from their spectroscopic and analytical data. In the ^{1}H n.m.r. spectra of (X[1a]) and (X[1b]) the C-3 methine proton is in an equatorial conformation ($W\frac{1}{2}$ ca. 8-9 Hz.) indicating the β-configuration of the 5-ethyl group. In the former the C-6 methine proton is in an axial conformation confirming the equatorial conformation of the 6-acetate group. The low field position of the C(18)-methyl (τ 9.21 and 9.25) is characteristic of compounds of this type.[14] The appearance of a triplet centred at τ 9.5 in the latter which is assigned to the methyl protons of the 5β-ethyl group indicates that the 5β-ethyl group is conformationally held so that the methyl protons lie in the shielding cone of the C-6 carbonyl group. Hydrolysis and oxidation of (X[1a]) to give the keto-acetate (X[1b]) confirmed that both were 9,10-olefins.

In addition to the $\Delta^{9(10)}$-compound (X[1a]) the hydroxy-acetate (IX[2a]) gave small amounts of the Δ^4-compound (X[2]). The ^{1}H n.m.r. spectrum showed the absence of a

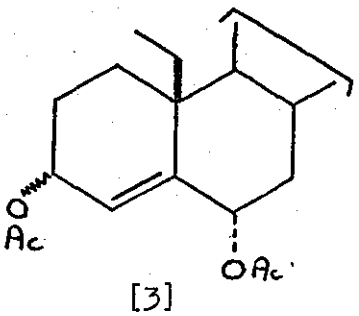


[1]

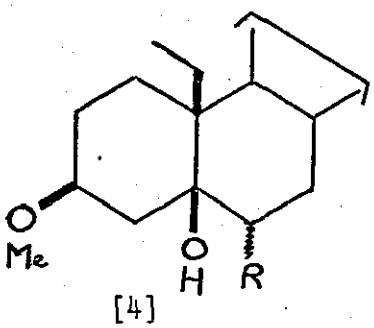
	R^1	R^2	R^3
(a)	CH_2CH_3	Me	β-OAc, α-H
(b)	CH_2CH_3	Me	O
(c)	$CH{=}CH_2$	Ac	β-OAc, α-H
(d)	$CH{=}CH_2$	H	β-OH, α-H
(e)	CH_2CH_3	H	β-OH, α-H



[2]



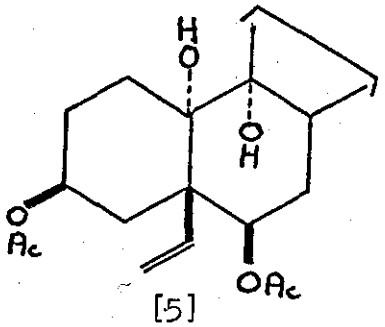
[3]



[4]

(a) R_1 β-AcO

(b) R_2 α-AcO



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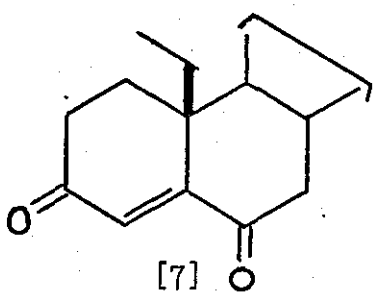

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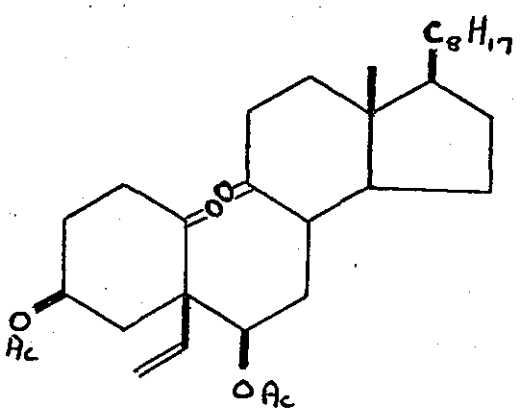

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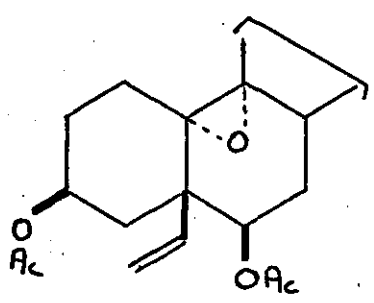

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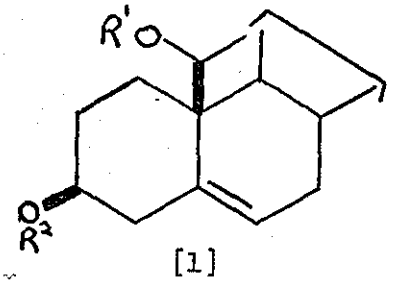
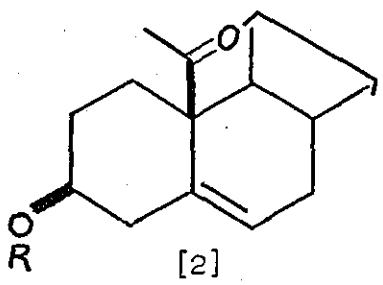


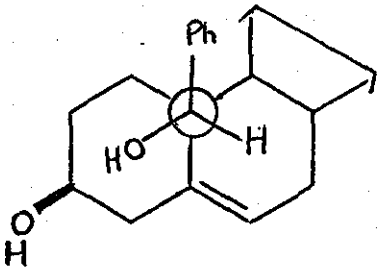
[1]

	R^1	R^2
(a)	H	H
(b)	Ac	Ac
(c)	Ac	H
(d)	Ac	Me
(e)	H	Me



[2]

	R
(a)	Me
(b)	H



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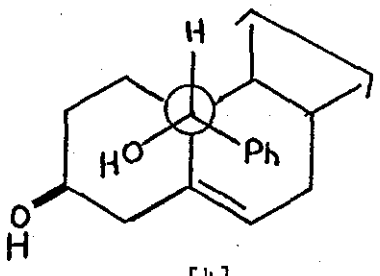

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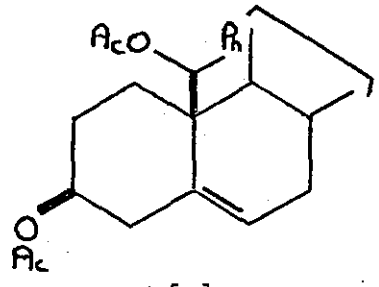
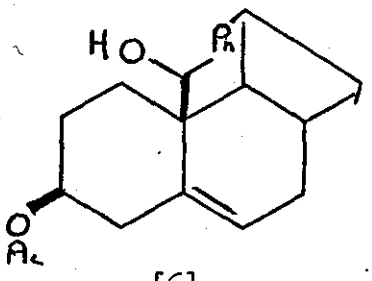
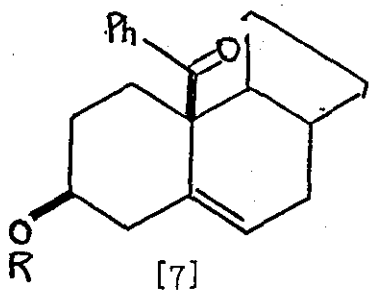


[5]



[6]



[7]

(a) Ac

(b) H

3-methoxy-group and the presence of two acetoxy-groups (τ 8.08) indicating that under the acid conditions employed the 3β-methoxy-group has been cleaved and displaced by an acetate group. The stereochemistry at C-3 is not assigned as the ^{1}H n.m.r. spectrum indicates it to be a mixture of 3α- and 3β-isomers.

The hydroxy-acetate (IX[2e]) gave a high yield of Δ^4-compound (X[3]). The ^{1}H n.m.r. spectrum showed the absence of a methoxy-group and the presence of two acetate groups. As in the above case cleavage of the methyl ether occurs probably due to allylic activation by elimination giving 4,(5)-olefin. The stereochemistry at C-3 is not assigned. Conformation of the structures of the diacetates (X[2]) and (X[3]) was obtained by hydrolysis and oxidation to the 3,6-dione (X[7]). The structure was deduced from spectroscopic and analytical data. The i.r. spectrum showed a strong carbonyl band (at 1695 cm.$^{-1}$) A strong absorption in the u.v. spectrum at $\lambda_{max.}$ 248 n.m. is typical of compounds of this type.[20]

Dehydration of (IX[2b]) gave surprisingly the rearranged compound (X[1c]). Accurate mass measurement on the fragment ion M-60 showed it to have a molecular formula $C_{30}H_{46}O_2$. The ^{1}H n.m.r. spectra of (X[1c]) and its hydrolysed derivative (X[1d]) showed the presence of two methine protons ($W\frac{1}{2}$ ca. 10 and 16 Hz.), three olefinic protons exhibiting an ABC-pattern and a low-field C(18)-methyl (τ 9.2) resonance, the former and the latter being

typical of compounds in this series obtained above. Hydrogenation of (X[1d]) with palladium charcoal (5%) as catalyst gave the saturated derivative (X[1e]) which exhibited an ^{1}H n.m.r. spectrum similar to that of (X[1a]).

The rearrangement of a 0.01M solution of (IX[2a]) was followed as previously described for the 5α-hydroxy-steroids and rate data obtained is given in the above table. It can be seen that the 10β-ethyl compound (IX[2a]) rearranges at a rate 7.3 times greater than the rearrangement of compound (VI[1a]) to (VI[2]). The stable conformation of compound (IX[1a]) is probably close to that represented in (IX[4]). The 19-methyl group suffers an interaction with the 11β-hydrogen atom and two skew interactions with the C(1)-C(10) and C(9)-C(10) bonds. These interactions are thus probably largely responsible for raising the ground state energy of compound (IX[2a]) relative to that of compound (VI[1a]). From models it is difficult to see how relief of these interactions may occur by flattening at C-5 necessary in the transition state leading to a planar carbonium ion. However if the alkyl group migration, as suggested above, is concerted with C(5)-O-bond cleavage such steric relief in the transition state will occur, and this would explain the observed increase rate. Such relief would also explain the rearrangement of the 6-keto-compound (IX[2j]) in view of the results reported

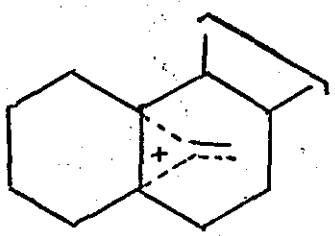
for the 10-methyl analogue.[40c] It was rather surprising that the 6α-acetate (IX[2e]) gave only Δ^4-compounds. This must be because the extra interactions detailed above are not sufficient to raise the transition state for elimination above that for a concerted rearrangement. In addition the unfavourable conformational change which the 6α-acetate undergoes in a concerted process will contribute to the high energy of the transition state. In the 6-keto-derivative the transition state for acetylation is raised above that required for a concerted rearrangement thus giving the 9,10-olefin in high yield.

The rate of reaction of the 10-ethenyl compound (IX[2b]) was not measured but after 3 hr. t.l.c. of the reaction mixture showed considerable amounts of unreacted material. This indicates that the reaction rate is very slow.

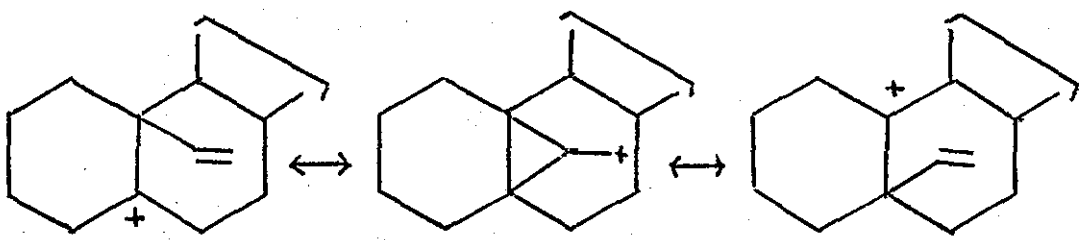
In view of the slow rate it seems likely that a discrete carbonium ion is not formed in the rate determining step because if thiswere so the rate of ethenyl/migration and ethyl would be expected to be similar. Hence migrating group participation giving rise to the cyclopropyl intermediate (or transition state)(A) probably occurs. The slow reaction rate may be due to the electron withdrawing effect of the ethenyl group analogous to that observed for phenyl migrations.[87]

In addition, the resulting cyclopropyl transition state or intermediate involves a contribution in one of its resonance forms from a primary carbonium ion [Ċ] which would be energetically unfavourable.

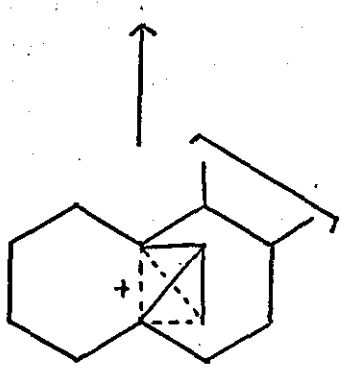
A deuteration experiment detailed below indicates that a cyclopropane intermediate as opposed to just a transition state is involved in the ethenyl migration. 19-Dideutromethylene-derivative of (IX[2b]) was prepared from dideutromethylene triphenylphosphorane by the method described above. Mass spectral analysis of the deuterated reactant (IX[2b]) and the deuterated product (X[1c]), resulting from Westphalen rearrangement, showed ions at m/e 456, 457 and 458; and 438, 439 and 440 respectively, corresponding to the d_o (11.0%), d_1 (38.4%), and d_2(50.6%); and d_o (9.0%), d_1 (37.5%), and d_2 (53.0%) species of the fragment ions M -60 respectively. The above results indicate that during the Westphalen rearrangement all the deuterium atoms are retained and no exchange with solvent occurs. The ^1H n.m.r. spectra of the deuterated reactant and product show a fall in intensity of the tertiary olefin signal and a corresponding increase in intensity of the terminal olefinic signal (12%). This indicates that during rearrangement scrambling of the deuterium atoms has taken place and this seems likely to occur by the formation of a cyclopropyl intermediate [A]. However the above result does not preclude the possibility of a cyclobutyl intermediate [E].



A



B C D



E

The attempted introduction of oxygenated functions at the C-5 position detailed in Section I prompted the investigation of selective oxidation of the 5β-ethenyl group detailed below.

Treatment of the diene (X[1c]) with monoperphthalic acid in ether at room temperature gave in high yield the 9α,10α-epoxide(X[8]). No direct evidence is available to assign the α-configuration to the epoxide but this is tentatively assigned on the basis that the major product obtained on oxidation of a similar 9,10-olefin in section I is the α-epoxide. Oxidation of the diene (X[1c]) with oxmium tetroxide in pyridine gave after 24 hrs. at room temperature a high yield of the cis-diol (X[5]). Low resolution mass spectrum showed a fragment ion m/e 472 corresponding to M-60 and subsequent fragmentation with loss of two molecules of water (see table) confirming the presence of two hydroxyl groups. The diol is assigned the 9α,10α-configuration due to the high field position of the C(18)-methyl signal in the ^{1}H n.m.r. spectrum as the 9β-hydroxy-group would be expected to have a deshielding influence upon the C(18)-methyl resonance. Further oxidation of the diol (X[5]) with lead tetraacetate gave the diketone (X[6]).

The results detailed in this section and others reported in the literature[14,17] clearly indicate that the Westphalen rearrangement of 5α-hydroxy-steroids require

the presence of a 4- or 6-electron withdrawing substituent. It is clear that these substituents play an important role sterically and electronically in controlling the dehydration and that these need not be located in one particular group. The rate data leave little doubt as to the synchronous nature of the heterolysis of the C(5)-O bond and the alkyl group migration which implies that the function of the syn-axial substituent (at C-4 or C-6) is to provide steric acceleration in the Westphalen rearrangement.

EXPERIMENTAL.-

Solutions were dried over anhydrous sodium sulphate. Column chromatography was carried out with deactivated (grade III) Camag or Woelm neutral alumina. Merck Kieselgel PF_{254} silica gel was used for preparative t.l.c. I.r. spectra were determined with Perkin-Elmer 237 and 257 spectrophotometers, u.v. spectra were determined for solutions in ethanol with a Unicam SP800 spectrophotometer and ^1H n.m.r. spectra were determined (for solutions in carbon tetrachloride unless otherwise specified) at 60 Mc/sec. with a Perkin-Elmer R10 spectrometer. Rotations were measured at 22° with a Bendix polarimeter 143C for solutions in chloroform. Mass spectra were determined on A.E.I. M.S.9 and M.S.12 mass spectrometers.

Epoxides (1[1c]).- Cholest-5-en-3-one ethylene ketal (2.0 g.) in dry ether (30 ml.) was treated with monoperphthalic acid-ether solution (100 ml., 0.65 N) and the mixture stirred at room temperature for 24 hr. The ether solution was then washed with 2N sodium hydroxide solution, water, dried and evaporated. Chromatography of the resulting white solid, with 10% benzene-light petroleum ether as eluent gave the β-epoxide (1[1c])(1.2g.) m.p. 124-5° [lit.[51] m.p. 126-127°] τ 6.17 (s, OCH_2CH_2), 7.3 (d, J ca. 3Hz. C<O>CH), 9.09 (s, 19-Me), and 9.34, s, 18-Me),. further elution with 20% benzene-light petroleum ether gave the α-epoxide (1[1c])(0.6g.) m.p. 141-3° (from ether) [lit.[51] m.p. 118-120°], 6.16 (m, OCH_1CH_2O) 7.4 (d, J ca. 5Hz., C<O>CH),9.09 (s, 19-Me), and 8.95 (s, 18-Me).

5α-Azido-3β-acetoxy-5α-cholestan-5-ol(1[3a]), 6α-azido-5β-cholestan-3β,5-diol (1[4b]) and 6β-azido-5α-cholestan-5-ol-3-one ethylene ketal (1[2]).- The β-epoxide 1[1a](2g.) and sodium azide (6 g.) in dimethyl sulphoxide (200 ml.) containing a few drops of 98% sulphuric acid were heated for 48 hr. on a steam-bath. The mixture was poured into brine and extracted with chloroform; the extract was dried and evaporation of the solvent gave a mixture of azides (1[4a]) and epoxide (1[1a]) (1.1g.). Elution with 5% ether-light petroleum ether gave a mixture of the azide (1[3a]) and the hydrolysis product (1[4b]). Preparative t.l.c. of the latter mixture on silver nitrate-impregnated silica (10%) gave the azide (1[3a]) (647 mg.), m.p. 184-188° (lit.,[46a] 188°) $\nu_{max.}$ 3350 (OH), 2090 (N_3), and 1740 and 1710 (C=O, partially hydrogen bonded) cm.$^{-1}$, τ 4.7-5.3 (m, AcOCH), 6.1-6.4 (m, OCH), 8.0 (s, AcO), 8.84 (s, 19-Me), and 9.35 (s, 18-Me), and the azide (1[4b]) (227 mg.), m.p. 126-8°, $[\alpha]_D$+ 40°, $\nu_{max.}$ 3440 (OH) and 2090 (N_3) cm.$^{-1}$, τ 5.7-5.9 (m, OCH), 6.2-6.7 (m, N_3CH), 9.1 (s, 19-Me), and 9.35 (s, 18-Me) (Found: C, 72.85; H, 10.35; N, 9.2 $C_{27}H_{47}N_3O_2$ requires C, 72.75; H, 10.65; N, 9.45%).

The mixture (1[4a]) and (1[1a]) was heated under reflux in 10% aqueous methanolic potassium hydroxide for 15 min., poured into water, and extracted with ether. The crude product was chromatographed; elution with 20% ether-light petroleum ether gave the azide (1[4b]), (700 mg.), m.p. 125-6° (see above). Elution with 40% ether-light petroleum gave the β-epoxide (1[1b])(200 mg.).[54]

The epoxide (1[1c]) (150 mg.) under identical conditions gave the azide (1[2])(110 mg.) m.p. 82-3° (from methanol). $\nu_{max.}$ 3400 (OH) and 2100 (N_3) cm.$^{-1}$, τ 70.15 (m, OCH_2CH_2O) 6.6-6.8 (m, CHN_3), 8.91 (s, 19-Me), and 9.3 (s, 18-Me).

5-Azido-3β,6β-diacetoxy-5α-cholestane (1[3b]) and 3β-acetoxy-6α-azido-5β-cholestan-5-ol (1[4a]).- The appropriate azide was treated with an excess of acetic anhydride in pyridine at room temperature overnight. The solution was poured into cold water, set aside for a few minutes and extracted. The extract was washed successively with water, sodium hydrogen carbonate solution until neutral, and finally water, and dried. Removal of the solvent left the crude acetate which was crystallised from methanol.

(a) Azide (1[3a]) (640 mg.) gave azide (1[3b])(540 mg.), m.p. 146-148°, $[\alpha]_D$- 73° (lit.[53] m.p. 146°, $[\alpha]_D$-70°), $\nu_{max.}$ 2095 (N_3) and 1740 (AcO) cm.$^{-1}$ τ 4.8-5.3 (m, 2 AcOCH), 7.96 and 8.05 (each s, AcO), 8.86 (s, 19-Me), and 9.34 (s, 18-Me).

(b) Azide (1[4b]) (700 mg.) gave azide (1[4a])(630 mg.), m.p. 115-6°, $[\alpha]_D$+ 41°, (lit.[46a], m.p. 112-115°, $[\alpha]_D$+ 40.5°), $\nu_{max.}$ 3600 (OH), 2100 (N_3), and 1740 (AcO) cm.$^{-1}$, τ 4.7-4.9 (m, AcOCH), 6.2-6.6 (m, CHN_3), 7.92 (s, AcO), 9.06 (s, 19-Me), and 9.35 (s, 18-Me).

5-Amino-3β,6β-diacetoxy-5α-cholestane (1[3c]) and 3β-acetoxy-6α-amino-5β-cholestan-5-ol (1[4c]).- To the azide in ethanol was added hydrazine hydrate (1 ml.per 300 mg. of azide) and a

little Raney nickel. The mixture was heated under reflux for 15 min., ether was added, and the solution was set aside until gas evolution ceased. It was then washed with water and dried, and the solvent was removed to leave the crude amine which was purified by t.l.c. and crystallised from methanol.

(a) Azide (1[3b])(600 mg.) gave the amine (1[3c])(500 mg.), m.p. 141-142°, $[\alpha]_D$-32°(lit.[46a], m.p. 142-145°, $[\alpha]_D$-36.8°), $\nu_{max.}$ 3310 and 3390 (NH_2), 1740 (AcO), and 1610 (NH_2) cm.$^{-1}$, τ 4.5-5.2 and 5.3-5.6 (each m, AcOCH), 7.99 and 8.07 (each s, AcO), 8.86 (s, 19-Me), and 9.32 (s, 18-Me).

(b) Azide (1[4b])(200 mg.) gave the amine (1[4c])(180 mg.), m.p. 141-3°, $[\alpha]_D$+ 33°, $\nu_{max.}$ 3400 broad (OH and NH_2) cm.$^{-1}$, τ ($CDCl_3$) 5.8-6.1 (m, CHO), 7.0-7.4 (m, $CHNH_2$), 9.1 (s, 19-Me), and 9.35 (s, 18-Me) (Found: C, 76.95; H, 11.85; N, 3.5. $C_{27}H_{49}NO_2$ requires C, 77.25; H, 11.75; N, 3.35%).

Aprotic Deamination of the Amine (1[3c]).- Dry hydrogen chloride was bubbled briefly through a solution of the amine (1[3c]) (150 mg.) in dry ether. The solvent was removed in vacuo and the residual hydrochloride was treated in chloroform with an excess of 3-methyl butyl nitrite (5 drops). The solution was set aside at room temperature for 1.5 hr. and then evaporated to dryness in vacuo. Preparative t.l.c. gave (1[5])(59 mg.), m.p. 126-127°(from aqueous acetone), $[\alpha]_D$+ 85.5° (lit.[46b], m.p. 127°, $[\alpha]_D$+ 84°), $\nu_{max.}$ 1740 (AcO) cm.$^{-1}$, τ 4.8-5.1 and 5.1-5.6 (each m, AcOCH), 8.0 (s,AcO), 8.82 (s, 19-Me), and

9.18 (s, 18-Me) and (1[6])(68 mg.), m.p. 81-82°(from methanol), $[\alpha]_D$-7°(lit.[46b] m.p. 85°, $[\alpha]_D$-10°, $\nu_{max.}$ 1740 (AcO) cm.$^{-1}$, τ 4.5-4.8 (m, CH=C), 4.8-5.6 (m, 2AcOCH), 7.99 and 8.02 (each s, AcO), 8.80 (s, 19-Me), and 9.33 (s, 18-Me).

Deamination of the Amine (1[4c]).- The amine (1[4c])(500 mg.) in 80% aqueous acetic (50 ml.) at 10° was treated with concentrated sodium nitrite solution (containing 2g.). After 1 hr., the solution was poured into water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution until neutral, and then water, and finally dried. Removal of the solvent left an oil (400 mg.) which after preparative t.l.c. gave the A-homo-B-nor-ketol (II [2a])(220 mg.), m.p. 148° (from methanol)$[\alpha]_D$+ 21°, $\nu_{max.}$ 3400 (OH) and 1695 (C=O) cm.$^{-1}$, τ 6.1-6.6 (m, CHO), 7.2-7.6 (m, CH_2COCH), 8.85 (s, 19-Me), and 9.35 (s, 18-Me), c.d. (cyclohexane) $\lambda_{max.}$ 293, 298, and 307 nm; $\Delta\xi$ + 1.40; + 1.55; and + 1.39 (Found: C, 80.85; H, 11.35. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%).

6α-Azido-5β-cholestan-5-ol-3-one (11[5]) and A-homo-B-nor-5β-cholestan-3,4a-dione (11 [2b]).-The appropriate alcohol was treated in Analar acetone at 20° with an excess of chromic acid solution [chromium trioxide (6.25g.) in 20% sulphuric acid (25 ml.)[33]] for 15 min. The solution was diluted with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution until neutral and then with water, and dried. The solvent was removed to leave the crude ketone which was crystallised.

(a) The azide (1[4b])(260 mg.) gave the ketol (II[5])(250 mg.), m.p. 182-184°(decomp.) (from methanol), $[\alpha]_D$+ 84° $\nu_{max.}$ 3490 (OH), 2100 (N_3), and 1720 (C=O) cm.$^{-1}$, τ ($CDCl_3$) 6.1-6.5 (m, N_3CH), 8.97 (s,19-Me), and 9.28 (s,18-Me) (Found: C, 73.15; H, 10.0; N, 9.45. $C_{27}H_{45}N_3O_2$ requires C, 73.1; H, 10.2; N, 9.45%).

(b) The ketol (II[2a])(25 mg.) gave the diketone (II [2b]) (22 mg.), m.p. 138-139° (from aqueous acetone), $\nu_{max.}$ 1695 (C=O) cm.$^{-1}$, τ 6.4-6.8 (m, $COCH_2CO$), 8.99 (s, 19-Me), and 9.35 (s, 18-Me), $\lambda_{max.}$ (KOH-EtOH) 294 nm (ε 20,800) (Found: C, 81.05; H, 11.25. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.05%).

Attempted Retroaldolisation of 6α-Azido-5β-cholestan-5-ol-3-one (II[5]).- The ketol (II[5]) (50 mg.) was heated under reflux in methanolic potassium hydroxide (50 mg. in 8 ml.) for 0.5 hr.. The solution was poured into water and extracted with ether-chloroform (1:1). Removal of the solvent gave the slightly impure enamine (III[2])(40 mg.). Immediate preparative t.l.c. [elution with benzene:ethyl acetate (3:1)], gave the enamine (III[2]). τ 4.18 (s, =CH), 4.8-4.95 (m, =CH), 6.5-7.2 (m, NH_2), 8.90 (s, 19-Me), 9.13 (d side-chain), and 9.26 (s, 18-Me), (see Discussion for i.r., u.v., and mass spectral data).

Enamine (III[2]) from 6β-Bromocholest-4-en-3-one (III[1]).- A mixture of the bromoketone (III[1])(200 mg.)[67] and sodium azide (200 mg.) in dimethyl sulphoxide (20 ml.) was heated on a boiling water bath for 10 min. and poured into water.

Extraction with ether gave the enamine (III[2]) (180 mg.) (spectroscopic data were as above).

Enamine (III[6]) from 2α-Bromo-5α-cholestan-3-one (III[5a]).- A mixture of the bromoketone (III[5a]) (1g.)[65] and sodium azide (2 g.) in dimethyl sulphoxide (60 ml.) was heated on a boiling water bath for 2 hr. and poured into water. Extraction with ether gave the crude amine (III[6]). Immediate preparative t.l.c., [elution with benzene:ethylacetate (1:1)], gave the pure enamine (III[6]) (320 mg.), τ 4.09 (s, =CH), 6.3-6.9 (m, NH_2), 9.04 (s, 19-Me), 9.13 (d, side-chain), and 9.32 (s, 18-Me) (see Discussion for i.r., u.v., and mass spectral data).

3,3-Dimethoxy-5α-cholestan-3-one (III[7]).- A solution of the enamine (III[6]) (60 mg.) in methanol (10 ml.) and concentrated sulphuric acid (2 drops) was heated under reflux for 2 hr. and poured into water. Extraction with ether gave a solid which crystallised from methanol to give the ketal (III[7]) (30 mg.) m.p. 105-106°, $[\alpha]_D$+ 70° (c,0.4), τ 6.77 (s, OMe), 6.91 (s, OMe), 9.14 (d, side chain), 9.29 (s,19-Me), and 9.36 (s, 18-Me), $\nu_{max.}$(CCl_4) 1744 (C=O) cm.$^{-1}$, (Found C, 78.85; H, 11.5. $C_{29}H_{50}O_3$ requires C, 77.95; H, 11.3%) (see Discussion for mass spectral data).

3α-Acetoxy-5α-cholest-1-ene (IV[2]).- A mixture of the bromoacetate (IV[1a])[69] (200 mg.) and sodium azide (500 mg.) in dimethyl sulphoxide (10 ml.) was heated on a boiling water bath for 15 minutes and poured into water. Extraction with ether

gave a solid which crystallised from methanol to give the allylic acetate (IV[2]) m.p. 76-78°, $[\alpha]_D$-40° (c, 1.1), τ 3.8-4.6 (m, HC=CH-, J ca. 5Hz.), 4.8-5.1 (m, AcOCH), 8.06 (s, AcO), 9.15 (d, side-chain), 9.21 (s, 19-Me), and 9.35 (s, 18-Me). (Found C, 81.05; H, 11.35. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.3%).

9α,10-Epoxy-5-methyl-19-nor-5β,10α-cholestan-3β,6β-diol (IV[5a]).- An ethyl acetate solution of hydroxy-epoxide (IV[5b])(1.25 g.) was shaken with 10% palladium on charcoal catalyst, in an atmosphere of hydrogen at room temperature until the uptake of hydrogen ceased. The solution was filtered and evaporated, giving the diol (IV[5a])(1.05g.) m.p. 173-174° (from aqueous methanol), $[\alpha]_D$+ 26° (c, 0.7), $\nu_{max.}$(KBr) 3400 (broad, OH) cm.$^{-1}$, τ 5.55 - 5.9 (m, OCH), 6.00 - 6.4 (m, OCH) 8.84 (s, 5-Me), and 9.25 (s, 18-Me) (Found: C, 76.87; H, 11.01 $C_{27}H_{46}O_3$ requires C, 77.46; H, 11.08%).

3β,6β-Diacetoxy-5-methyl-19-nor-5β,9β,10α-cholestan-10-ol (IV[6]), and 3β,6β-Diacetoxy-5-methyl-19-nor-5β-cholestan-9α-ol (V[1]).- A solution of epoxide (IV[5])(1.2g.) in anhydrous ethylamine (50 ml.) was treated with finely cut lithium metal (500 mg.) at 0°C and the mixture shaken until a permanent blue colour appeared. The solution was kept at room temperature for a further 0.5 hr., water carefully added, extracted with ether, ether layer was dried and evaporated. The resulting amorphous solid was acetylated with acetic anhydride in pyridine giving an oil. Preparative t.l.c. [elution (x2) with benzene-ethyl acetate (10:1)],

gave the diacetate (1[5]) (300 mg.) m.p. 124-125°, $[\alpha]_D$+ 80°(c, 1.2), [lit.[46b] m.p. 128°, $[\alpha]_D^+$ 85°] the alcohol (V[1])(500 mg.) m.p. 165-166° (from aqueous methanol), $[\alpha]_D$+ 3.5° (c, 2.8), $\nu_{max.}$ 1745 (AcO) and 3640 (sharp, OH) cm.$^{-1}$, τ 4.7-5.00 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., AcOCH), 5.3-5.5 (m, $W_{\frac{1}{2}}$ ca. 6Hz., AcOCH), 8.07 (s, AcO), 8.05 (s,AcO), 8.91 (s, 5-Me), and 9.3 (s, 18-Me) (Found: C, 73.82; H, 10.32. $C_{31}H_{52}O_5$ requires C, 73.76; H, 10.4%), and the alcohol (IV[6]) (300 mg.) as a gum, $[\alpha]_D$+ 16.5° (c, 3.0), $\nu_{max.}$ 1745 (AcO) and 3640 (sharp, OH) cm.$^{-1}$, τ 4.9-5.4 (m, 2 AcOCH, estimated $W_{\frac{1}{2}}$ ca. 8 Hz. and 16 Hz.), 8.00 (s, AcO), 8.03 (s, AcO), 8.85 (s, 5-Me), and 9.35 (s, 18-Me).

3β-Benzyloxy-5-methyl-19-nor-5β-cholestan-6-one-10-ol (IV[4d]) and 3β-Benzoyloxy-5-methyl-19-nor-5β-cholest-8(9)-en-6-one-10-ol (IV [7b]).- A solution of steroid in acetone at 0° was treated with chromic acid solution[33] for 5 min. The solution was diluted with water, extracted with ether. The ether layer was washed with water, dried and evaporated giving the crude ketone.

The diol (IV[4a])(450 mg.) gave the ketol (IV[4d]) (400 mg.) m.p. 111-2°, $[\alpha]_D$ - 36° (c, 2.3) $\nu_{max.}$ 1715 (C=O) and 3650 (sharp, OH) cm.$^{-1}$, τ 2.75(s,phenyl), 5.4-5.8 (q, J_{AB} ca. 12 Hz., O-CH_2-), 6.2-6.5 (m, OCH), 8.75 (s, 5-Me), and 9.32 (s, 18-Me) (Found: C, 80.07; H, 9.88 $C_{34}H_{54}O_3$ requires C, 79.95; H, 10.66%).

The diol (IV[7a])(92 mg.) gave the ketol (IV[7b])(24 mg.) m.p. 167-170° (from methanol) $\nu_{max.}$ 1720 (C=O) and 3550 (sharp, OH) cm.$^{-1}$, τ 2.65 (s, phenyl), 5.4 (s, OCH_2) 6.1-6.6 (m, OCH), 8.88 (s, 5-Me), and 9.22 (s,18-Me) (see Discussion for mass spectral data).

3β-Benzyloxy-5-methyl-19-nor-5β-cholest-6-en-10-ol (V[2]).- A solution of diol (IV[4a])(200 mg.) and p-toluene sulphonyl chloride (200 mg.) in pyridine (20 ml.) was allowed to stand at room temperature for 4 days. The mixture was poured into water, extracted with ether, and the organic layer dried. Evaporation of the solvent gave an oil which, after t.l.c. [elution with benzene-ethylacetate (20:1)], gave an oil (150 mg.), and starting material (IV[4a]).

The oil (150 mg.) was then dissolved in dry tetrahydrofuran (25 ml.) and treated with lithium aluminium hydride (100 mg.) at room temperature for 1 hr. After the addition of methanol (5 ml.) the mixture was poured into water and extracted with ether. Evaporation of the ether extract gave an oil which, after t.l.c. [elution with benzene-ethylacetate (20:1)], gave (V[2])(90 mg.) as a gum, $[\alpha]_D$- 28° (c, 1.8), $\nu_{max.}$ 3640 (OH) cm.$^{-1}$, τ 2.75 (s,phenyl), 4.5-5.00) (m, AB of ABX system, CH=CH), 5.57 (s, OCH_2) 6.3-6.6 (m, OCH), 8.82 (s, 5-Me), and 9.3 (s, 18-Me) (see Discussion for mass spectral data).

5-Methyl-19-nor-5β-cholestan-3β,10-diol(IV[4e]).- An ethylacetate solution (20 ml.) of the alcohol (V[2])(80 mg.) was stirred with 10% palladium-charcoal as catalyst, in an atmosphere of hydrogen

for 0.5 hr. The solution was filtered and evaporated to give (IV[4e])(68 mg.) m.p. 116-117°, $[\alpha]_D$+ 27.5° (c, 1.3), $\nu_{max.}$ 3650 (OH) cm.$^{-1}$, τ 5.85-6.1 (m, OCH), 8.88 (s, 5-Me) and 9.35 (s, 18-Me) (Found: C, 79.84; H, 12.26 $C_{27}H_{48}O_2$ requires C, 80.1; H, 12.0%).

Dehydration of alcohols (IV[4a])(IV[4d])(IV[4e])(IV[6]) and(V[1]).- Acetic anhydride solution of steroid (0.036 M) was treated with p-toluene sulphonic acid (200 mg.) and the mixture heated on a steam bath for 0.5 hr. The reaction mixture was then cooled, poured into water and extracted with ether. The organic layer was dried and solvent evaporated.

The diol (IV[4a])(900 mg.), after t.l.c. [elution (x2) with benzene-ethylacetate (20:1)], gave 6β-acetoxy-3β-benzyloxy-5-methyl-18,19-bisnor-5β,8α,9β,10α,14β-cholestan-13(17)-ene (V[3a]) (700 mg.) a gum, $[\alpha]_D$ + 27° (c, 1.3), $\nu_{max.}$ 1740 (AcO) cm.$^{-1}$, τ 2.75 (s,phenyl), 5.4-5.8 (m, OCH_2,OCH), 6.20-6.5 (m,$W_{\frac{1}{2}}$ ca. 9 Hz. AcOCH), 8.02 (s, AcO), 8.9 (s, 5-Me), 9.01 and 9.11 (d, 21-Me), and 9.2 (s, 18-Me) (Found: C, 80.72; H, 10.2. $C_{36}H_{54}O_3$ requires C, 80.85; H, 10.18%).

The ketol (IV[4d])(80 mg.), after t.l.c. [elution with benzene-ethylacetate (10:1)], gave a mixture (35 mg.) and 10β-acetoxy-3β-benzyloxy-5-methyl-19-nor-5β-cholestan-6-one (V[6])(10 mg.) a gum, $\nu_{max.}$1720 (C=O) and 1740 (AcO) cm.$^{-1}$ τ 2.78 (s, phenyl), 5.4-5.7 (s, OCH_2), 6.3-6.6 (m $W_{\frac{1}{2}}$ ca. 8 Hz., OCH), 8.08 (s,OAc), 8.68 (s, 5-Me), and 9.35 (s, 18-Me) (Found:

C, 78.5; H, 9.99. $C_{36}H_{54}O_4$ requires C, 78.5; H, 9.88%). Further t.l.c. of the mixture [elution (x2) of silver nitrate impregnated silica, with chloroform-petroleum ether (60/80) (1:1)] gave 3β-benzyloxy-5-methyl-19-nor-5β-cholest-1(10)-ene-6-one (IV[8])(20 mg.) as a gum, τ 2.78 (s, phenyl), 4.4-4.65 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., C = C H), 5.4-5.6 (s, OCH_2), 6.1-6.4 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., OCH), 8.79 (s,5-Me), and 9.32 (s, 18-Me), and 3β-benzyloxy-5-methyl-18,19-bi s nor-5β,8α,9β,10α,14β-cholest-13(17)-en-6-one (V[3b])(16 mg.), a gum, $\nu_{max.}$ 1720 (C = O) cm.$^{-1}$, τ 2.75 (s, phenyl), 5.4-5.6 (s, OCH_2), 6.1-6.4 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., OCH), 8.68 (s, 5-Me), and 9.04 and 9.12(d)(see Discussion for mass spectral data).

The diol (IV[4e])(52 mg.) t.l.c. [elution with benzene-ethylacetate (10:1)], gave 3β-acetoxy-5-methyl-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-ene (V[3c])(40 mg.) a gum, $[\alpha]_D$+ 9° (c, 0.8), τ 4.9-5.1 (m, $W_{\frac{1}{2}}$ ca. 9 Hz., AcOCH), 8.05 (s, AcO), 8.85 (s, 5-Me), 9.1 (s, 14-Me), 9.02 and 9.12 (d, 21-Me).

The alcohol-diacetate (V[1])(140 mg.), after t.l.c. [elution with benzene-ethylacetate (10:1)], gave the W stphalen diol-diacetate (1[5]) (9 mg.) m.p. 123-4° $[\alpha]_D$ + 82° (lit.,[46b] m.p. 127-8°, $[\alpha]_D$ + 85°), 3β,6β-diacetoxy-5-methyl-19-nor-5β-cholest-9(11)-ene (V[4])(50 mg.) m.p. 101-102° (from methanol), $[\alpha]_D$- 1.7° (c, 0.8), τ 4.45-4.65 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., C = CH), 4.9-5.15 (m, $W_{\frac{1}{2}}$ ca. 9 Hz., AcOCH) 5.3-5.5 (m, $W_{\frac{1}{2}}$ ca. 6 Hz., AcOCH), 8.00 (s, AcO), 8.05 (s,OAc), 8.85 (s, 5-Me), and 9.38 (s, 18-Me) (Found C, 76.42; H,10.45

$C_{31}H_{50}O_4$ requires C, 76.50; H, 10.36%), and starting material (V[1])(40 mg.).

The alcohol-diacetate (IV)[6])(40 mg.), after t.l.c. [elution with benzene-ethylacetate (10:1)], gave the Westphalen diol-diacetate (1[5])(20 mg.) m.p. 126-127° (lit[46b], m.p. 127-8°) and 3β,6β-diacetoxy-5-methyl-19-nor-5β,9β-cholest-1(10)-ene (V[5])(6 mg.), a gum $[\alpha]_D$+ 10.5° (c, 0.7), $\nu_{max.}$ 1745 (AcO) cm.$^{-1}$, τ 4.5-4.75 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., C:CH), 4.9-5.2 (m, $W_{\frac{1}{2}}$ ca. 6 Hz., AcOCH), 5.2-5.45 (m, $W_{\frac{1}{2}}$ ca. 13 Hz., AcOCH), 8.00 (s, AcO), 8.05 (s, AcO) 8.95 (s, 5-Me), and 9.32 (s, 18-Me) (see Discussion for mass spectral data).

3β-Benzyloxy-5α/β-methyl-19-nor-anthracholest-6(1)-ene-10-one (V[7]).- A methanolic solution of steroid (IV)[4d])(300 mg. in 5 ml.) was treated with 20% potassium hydroxide in methanol (30 ml.) and the mixture refluxed for 7 hr. The solution was then poured into water and extracted with ether. The organic layer separated, dried and evaporated gave an oil which, after t.l.c. [elution (x2) with benzene-ethylacetate (10:1)], gave the anthra-steroid (V[7])(50 mg.), a gum, $[\alpha]_D$+ 115° (c, 0.8), $\lambda_{max.}$ 284 (ϵ 10,800) nm., $\nu_{max.}$ 1640 (C=C), and 1680 (C=O) cm.$^{-1}$, τ 2.75 (s, phenyl), 5.35-5.55 (s, CH_2O), 6.00-6.6 (m, OCH), 9.00 and 9.10 (d, J ca. 6 Hz., 5-Me), and 9.22 (s, 18-Me) (see Discussion for mass spectrum) and a mixture (50 mg.) containing numerous polar components from the t.l.c.

3β,6α-Diacetoxy-4,4-dimethyl-5α-cholestan-5-ol (VI[3a]), and 3β,6α-diacetoxy-4α-methyl-5α-cholestan-5-ol (VIII[1e]), and 3β,6α-diacetoxy-4β-methyl-5α-cholestan-5-ol (VIII[1b]).- A solution of the steroid in pyridine(10 ml./0.4 g. steroid) was treated with osmium tetroxide (0.3 g. per 0.4 g. steroid) and the mixture kept at 21° for 96 hr. with occasional shaking. A solution of sodium sulphite, in water and pyridine (1:1) was added and the mixture shaken for 2 hr. After extraction with chloroform and repeated washings the organic layer was saturated with hydrogen sulphide and the solution washed with water. Evaporation of the solvent gave the crude diol-acetates.

The crude diols in pyridine and excess acetic anhydride were heated on a steam bath for the period specified. Addition of water and removal of the solvent under reduced pressure gave the diacetates.

The olefin (VI[5a])(500 mg.) gave the crude diol (VI[3e]) (450 mg.).[58,72] The crude diol (VI[3e])(140 mg.), after 24 hr., gave the diacetate (VI[3a]), m.p. 115-117° (from methanol), $[\alpha]_D$ - 18° (c, 0.6), τ 4.8-5.2 (m, 2 AcOCH), 7.98 (s, AcO), 8.04 (s, AcO), 8.74 (s, 4β-Me), 8.88 (s, 19-Me), 9.0-9.22 (d, 4α-Me, 26-Me, and 27-Me), and 9.33 (s, 18-Me)(Found: C, 74.5; H, 10.9 $C_{33}H_{56}O_5$ requires C, 74.4; H, 10.6%).

The olefin (VI[5c])[74] (1.1 g.) gave the crude diol (VIII [1a])(1.0 g.).

The crude diol (VIII[1a])(300 mg.), after 4 hr., gave the diacetate (VIII[1b])(300 mg.) m.p. 200-201° (from methanol),

$[\alpha]_D$-5° (c, 1.9), τ 4.5-5.0 (m, 2AcOCH), 8.0 (s, 2AcO), 9.0 (s, 19-Me), 9.07 and 9.18 (d, 4β-Me), 9.12 and 9.22 (d, side-chain), and 9.4 (s, 18-Me) (Found: C, 74.15; H, 10.32 $C_{32}H_{54}O_5$ requires C, 74.09; H, 10.49%).

The olefin (VI[5b])(300 mg.) gave the crude diol (VIII[1d])(250 mg.). The crude diol (VIII[1d]) (250 mg.), gave, after t.l.c. [elution with benzene-ethylacetate (3:1)], the diacetate (VIII[1e])(185 mg.) m.p. 175-6° (from methanol), $[\alpha]_D$+ 68° (c, 0.4), τ 4.9-5.5 (m, 2AcOCH), 8.05 (s, 2AcO), 8.95 (s, 19-Me), 9.10 and 9.20 (d, side-chain), 9.15 and 9.25 (d, 4α-Me), and 9.33 (s, 18-Me) (Found: C, 74.18; H, 10.58 $C_{32}H_{54}O_5$ requires C, 74.09; H, 10.49%).

3β-Acetoxy-4α-methyl-5α-cholestan-5,6β-diol (VIII[2c]).- The olefin (VI [5b])(600 mg.)(74) in ether (20 ml.) was treated with monoperphthalic acid solution (50 ml.)(60 g./litre) and the mixture stirred overnight. The mixture poured into water and the usual work up gave a mixture of α-and β-epoxides (600 mg.).

The crude epoxide mixture (600 mg.) in acetone (30 ml.) was treated with periodic acid dihydrate solution (250 mg./5 ml.H_2O) and the mixture refluxed for 1 hr. The mixture poured into water and the usual work up gave the crude diol (VIII[2c])(400 mg.) which was used without further purification.

3β-Acetoxy-4,4-dimethyl-5α-cholestan-5-ol-6-one (VI[3c])

3β-Acetoxy-4β-methyl-5α-cholestan-5-ol-6-one (VIII[1c])

3β-Acetoxy-4α-methyl-5α-cholestan-5-ol-6-one (VIII[1f]).-

A solution of Jones(33) reagent (0.4 ml./200 mg. steroid)

was added to a stirred solution of the diol in acetone (15 ml./200 mg. alcohol) at 0°C. After 4 min. the solution was poured into water and the usual work up gave the ketol.

The diol (VI[3e])(200 mg.) gave the ketol (VI[3c]) (180 mg.) m.p. 157-159° (from methanol), $[\alpha]_D$ 0° (Lit.[72] m.p. 158-160°, $[\alpha]_D$ - 1.1°) (Found: C, 76.4; H, 10.5 $C_{31}H_{52}O_4$ requires C, 76.2; H, 10.7%).

The diol (VIII[1a])(700 mg.) gave the ketol (VIII[1c]) (600 mg.) m.p. 202-203°, $[\alpha]_D$ - 26.5° (c, 0.5), $\nu_{max.}$ 1720-1730 (AcO, C=O) and 3300-3600 (broad OH) cm.$^{-1}$ τ 4.7-5.0 (m, AcOCH), 8.07 (s, AcO), 9.10 and 9.2 (d, side-chain), 9.05 and 9.15 (d, 4β-Me), 9.15 (s, 19-Me), and 9.38 (s, 18-Me) (Found: C, 75.67; H, 10.74 $C_{30}H_{50}O_4$ requires C, 75.9; H,10.62%).

The diol (VIII[2c])(200 mg.) gave the ketol (VIII[1f]) (130 mg.) m.p. 166-167° $[\alpha]_D$ - 11° (c, 0.18), τ 5.02 - 5.5 (m, AcOCH), 8.00 (s, AcO), 9.1 and 9.2 (d, 4α-Me, side-chain) 9.2 (s, 19-Me), and 9.36 (s, 18-Me) (Found: C, 75.59; H, 10.78 $C_{30}H_{50}O_4$ requires C, 75.9; H, 10.6%).

3β,6β-Diacetoxy-4,4-dimethyl-5α-cholestan-5-ol (VI[3b]), 3β,6β-diacetoxy-4β-methyl-5α-cholestan-5-ol (VIII[2b]), 3β,6β-diacetoxy-4α-methyl-5α-cholestan-5-ol (VIII[2d]).-

A solution of the ketol in ethanol (20 ml./150 mg.) was treated with an excess of sodium borohydride (100 mg.) and set aside for 1 hr. The solution was acidified with acetic acid and diluted with water. The usual work up gave the crude diol.

A pyridine solution of the crude diol and excess acetic anhydride was heated on a boiling water bath overnight. Water added and evaporation gave the diacetate.

The ketol (VI[3c])(150 mg.) gave the crude diol (VI[3g]) (140 mg.) τ 4.8-5.2 (m, AcOCH), 5.9-6.15 (m, OCH), 8.01 (s, AcO), 8.63 (s, 4β-Me), 8.68 (s, 19-Me), 9.0-9.2 (d, 4α-Me; 27-Me), and 9.32 (s, 18-Me).

The crude diol (VI[3g])(140 mg.) gave the diacetate (VI[3b]), m.p. 115-117° (from methanol), $[\alpha]_D$- 18° (c, 0.6), τ 4.8-5.2 (m, 2AcOCH), 7.98 (s, AcO), 8.04 (s,AcO), 8.74 (s, 4β-Me), 8.88 (s,19-Me), 9.0-9.22 (d, 4α-Me, 27-Me) and 9.33 (s, 18-Me) (Found: C, 74.5; H, 10.9 $C_{33}H_{56}O_5$ requires C, 74.4; H, 10.6%).

The ketol (VIII[1c])(200 mg.) gave the crude diol (VIII[2a]) (190 mg.). The crude diol (VIII[2a])(190 mg.) gave the diacetate (VIII[2b])(180 mg.), m.p. 167-168° (from methanol), $[\alpha]_D$- 40° (c, 0.4), τ (weak) 4.6-5.4 (m, 2AcOCH), 7.98 (s, AcO), 8.04 (s, AcO), 8.80 and 8.92 (d, 19-Me and 4β-Me) 9.1 and 9.2 (d, side chain), and 9.3 (s, 18-Me) (Found: C, 73.74; H, 10.51 $C_{32}H_{54}O_5$ requires C, 74.09; H, 10.49%).

The diol (VIII[2c]) (180 mg.), after acetylation at room temperature overnight, gave the diacetate (VIII[2d])(140 mg.) m.p. 136-8° (from methanol), $[\alpha]_D$ 0° τ 5.0-5.6 (m, 2AcOCH), 8.0 (s,AcO), 8.05 (s,AcO), 8.88 (s, 19-Me), 9.1 and 9.2 (d, side-chain), 9.12 and 9.22 (shoulders, 4α-Me), and 9.33 (s,18-Me) (Found:C,73.80;H,10.67 $C_{32}H_{54}O_5$ requires C, 74.09;H,10.49%).

General procedure for dehydration of 5α-hydroxy steroids.- A solution of the steroid (100 mg.) in acetic acid (6 ml.) and acetic anhydride (1 ml.) was treated with sulphuric acid (0.1 ml.; 4g. H_2SO_4/25 ml.acetic acid) and set aside for the period specified. The solution was poured into brine and the resultant mixture was extracted with ether. The ether extracts were washed with water (x2) and evaporation gave the crude product.

The diacetate (VI[3a])(80 mg.) after 1 hr., gave an oil. Preparative t.l.c. [elution with benzene-ethylacetate (40:1)], gave 3β,6α-diacetoxy-4,4,5-trimethyl-19-nor-5β-cholest-9(10)-ene (VI[6a])(24 mg.), an oil $[\alpha]_D$+ 4.4°(c,0.9), τ 5.3-5.6 (m,2AcOCH), 8.02 (s, 2AcO), 8.74 (s,5β-Me), 8.93 (s, 4α-Me), 9.06 (s, 4β-Me), and 9.20 (s,18-Me) (Found: C, 76.70; H, 10.8 $C_{33}H_{54}O_4$ requires C, 77.00; H, 10.60%), a mixture of compounds (VII[3a]) and (VII[4a]) (11 mg.) and starting material (12 mg.).

The mixture (VII[3a],VII[4a])(30 mg.) in 1% methanolic potassium hydroxide was refluxed for 6 hours. The usual work up, followed by t.l.c. [elution with benzene-ethylacetate (3:1)], gave 3β,6α-dihydroxy-4,4,5-trimethyl-19-nor-5β-cholest-1(10)-ene (VII[3b])(14 mg.),an oil, τ 4.5 (m,HC=C), 5.4-5.8 and 5.9-6.1 (m, AcOCH), 8.85 (s, 5β-Me), 9.0-9.3 (m, 4α-Me, 4β-Me, 21-Me, 26-Me, 27-Me), and 9.38 (s, 18-Me), (see Discussion for mass spectral data), and 3β,6α-dihydroxy-4,4,5,14-tetramethyl-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-ene (VII[4b])(8mg.), an oil, τ 6.1-6.8 (m, OCH),

8.92 (s,4α-Me and 5β-Me), 9.02 (s, 4β -Me and low-field branch of 21-Me doublet), 9.16 (m, high-field branch of C-21 Me doublet, C-26 Me, 27-Me, and 14β-Me).

The diacetate (VI[3b])(90 mg.) after 30 min. gave an oil (80 mg.). Preparative t.l.c. [elution with benzene-ethylacetate (10:1)], gave 3β,6β-diacetoxy-4,4,5-trimethyl-19-nor-5β-cholest-9(10)-ene (VI[6b])(45 mg.) an oil, $[\alpha]_D$ + 100° (c, 0.9), τ 4.7-5.2 (m, AcOCH), 5.3-5.55 (m, AcOCH) 8.0, (s,OAc), 8.06 (s,OAc), 8.72 (s,5β-Me), 9.03 (s,4β-Me), 9.10 (s,4α-Me), and 9.21 (s, 18-Me) (Found: C,76.95; H, 10.7 $C_{33}H_{54}O_4$ requires C,77.0; H,10.66%).

The ketol (VI[3c])(100 mg.) after 2 hours gave an oil (90 mg.). Preparative t.l.c.[elution with benzene-ethylacetate (10:1)], gave 3β-acetoxy-4,4,5-trimethyl-19-nor-5β-cholest-9-en-6-one (VI[6c]) (60 mg.), m.p. 95-97°,$[\alpha]_D$-55° (c, 0.4) (lit.(75) m.p. 95-96°, $[\alpha]_D$-53°). 5.3-5.5 (m, AcOCH), 7.99 (s, OAc), 8.72 (s, 5β-Me), 9.04 (s,4β-Me), 9.08 (s,4α-Me), and 9.26 (s, 18-Me).

The diol (VI[3d])(400 mg.) after 30 min., and t.l.c. [elution with benzene-ethylacetate (40:1)], gave 3β-acetoxy-4,4-dimethyl-cholest-5-ene (VI[5a]) (280 mg.), identical in all respects to an authentic sample, and mixture (20 mg.) τ 3.0-4.0 (olefinic protons) $\lambda_{max.}$ (EtOH) 244 nm.

The diacetate (VIII[1b])(240 mg.) after 1 hr., and t.l.c. [elution with benzene-ethylacetate (10:1)], gave 3β,6α-diacetoxy-4β,5-dimethyl-19-nor-5β-cholest-9(10)-ene (VIII[3a])(90 mg.), m.p. 138-139°(from methanol), $[\alpha]_D$+ 108° (c,1.8), 4.9-5.15

(m,AcOCH), 5.15-5.4 (m,AcOCH), 8.0 (s,AcO), 8.08 (s,AcO), 8.85 (s, 5-Me), 9.12 and 9.22 (d,4β-Me and part of side-chain doublet),and 9.20 (s,18-Me) (Found: C, 76.91; H, 10.55 $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.47%) and a mixture of (VIII[3a]) and (VII[4d]). Further t.l.c. of the mixture [elution (x2) benzene-ethylacetate (10:1)] gave 3β,6α-diacetoxy-4β,5,14-trimethyl-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-ene (VII[4d])(10 mg.) as an oil, τ 4.9-5.4 (m, 2AcOCH), 8.05 (s, 2AcO), 8.85 (s,5β-Me), 9.03 (s, low-field branch of 21-Me doublet), 9.13 (s, 14β-Me, and low-field branch of side chain doublet, high-field branch of 21-Me doublet), 9.20 and 9.30 (d, 4β-Me) (see Discussion for mass spectral data).

The diacetate (VIII[2b])(60 mg.) after 1 hr., and t.l.c. [elution with benzene-ethylacetate (10:1)], gave 3β,6β-diacetoxy-4β,5-dimethyl-19-nor-5β-cholest-9(10)-ene (VIII[3b])(26 mg.) an oil, $[\alpha]_D$+ 50° (c, 0.6) 5.0-5.22 (m, 2AcOCH), 8.00 (s, AcO), 8.05 (s,AcO), 8.9 (s,5β-Me), 9.06(s,low-field branch of the 4β-Me doublet), 9.10 and 9.20 (d, side-chain, high-field branch of 4β-Me doublet, C-18 Me)(Found: C, 77.1; H, 10.3 $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.47%).

The ketol (VIII[1c]) (140 mg.) after 2 hr., and t.l.c. [elution with benzene-ethylacetate (10:1)], gave 3β-acetoxy-4β,5-dimethyl-19-nor-5β-cholest-9(10)-en-6-one (VIII[3c]) (80 mg.), m.p. 128-129° (from methanol), $[\alpha]_D$-61° (c, 1.5), τ 4.9-5.1 (m, AcOCH), 8.00 (s, AcO), 8.80 (s,5β-Me), 9.10 and 9.20 (d, side-chain and low-field branch of the

4β-Me doublet, 9.25 (s, 18-Me), and 9.32 (s, high-field branch of 4β-Me doublet),(Found: C, 78.74; H, 10.62 $C_{30}H_{48}O_3$ requires C, 78.78; H, 10.59%).

The diacetate (VIII[2d]) (45 mg.), after 1 hr. and t.l.c. [elution with benzene-ethylacetate (19:1)], gave 3β,6β-diacetoxy-4α,5-dimethyl-19-nor-5β-cholestan-9(10)-ene (VIII[3d]) (17 mg.), an oil, $[\alpha]_D$ + 67° (c, 0.3), τ 5.0-5.4 (m, 2AcOCH), 8.00 (s, 2AcO), 8.78 (s, 5β-Me), 9.1 and 9.2 (d, side-chain, 4α-Me and 18-Me) (Found: C, 76.25; H, 10.45 $C_{32}H_{54}O_4$ requires C, 76.76; H, 10.47%).

The ketol (VIII[1f]) (90 mg.), after 3 hr. and t.l.c. [elution with benzene-ethylacetate (19:1)], gave 3β-acetoxy-4-methyl-cholest-4-en-6-one (VIII[4]) (18 mg.), m.p. 99-101°, $\nu_{max.}$ 1700 (conj. C=O) and 1740 (AcO) cm.$^{-1}$ $\lambda_{max.}$ 243 (ε 6,500) nm., τ 4.6-5.0 (m, AcOCH), 8.00 (s, AcO), 8.45 (s, 4-Me), 9.04 (s, 19-Me), and 9.3 (s,18-Me) (Found: C, 79.2; H, 10.62 $C_{30}H_{54}O_3$ requires C, 78.89; H, 10.59%), 3β,5-diacetoxy-4α-methyl-5α-cholestan-6-one (VIII[5]) (24 mg.), an oil, τ 5.1-5.6 (m, AcOCH), 7.9-(s,AcO), 8.05 (s,AcO), 9.08 and 9.13 (d, side-chain), 9.15 and 9.26 (d, 19-Me and 4α-Me), and 9.35 (s, 18-Me), and starting material (14 mg.).

Hydrolysis of (VIII[5]) (24 mg.) with 1% methanolic potassium hydroxide, and after the usual work up acetylation overnight with acetic anhydride in pyridine gave starting material (VIII[1f]) (10 mg.), m.p. 165-7°. The diacetate

(VIII[1e])(120 mg.) after 2½ hr. and t.l.c. [elution with benzene-ethylacetate (19:1)], gave a mixture (24 mg.) and starting material (27 mg.). Preparative t.l.c. of the mixture [elution (x2) with benzene-ethylacetate (40:1)], gave 3ξ,6α-diacetoxy-4-methylcholest-4-ene (VIII[6]) (10 mg.) τ4.6-4.9 (m, 2AcOCH), 8.05 (s, 2AcO), 8.4 (s, broad, 4-Me), 8.88 (s, 19-Me), and 9.32 (s, 18-Me) and (VIII[3e]) tentatively assigned the structure, 3β,6α-diacetoxy-4α,5-dimethyl-19-nor-5β-cholest-9(10)-ene, τ 8.02 (s,AcO), 8.78 and 8.9 (d, 4α-Me and 5β-Me) and 9.25 (s, 18-Me).

Dehydration of (VIII[1f]) with thionyl chloride.- A solution of ketol (VIII[1f]) (18 mg.) in pyridine (9 ml.) was treated with thionyl chloride (three drops) at 0°C for 0.5 hr. The mixture poured into water and extracted with ether. The ether extracts, dried and evaporated, gave 3β-acetoxy-4-methylcholest-4-en-6-one (VIII[4]) (10 mg.), m.p. 99-101°, identical in all respects to sample previously obtained.

4,4,5-Trimethyl-19-nor-5β-cholest-9-en-3,6-dione (VII[2a]), and 4β,5-Dimethyl-19-nor-5β-cholest-9-en-3,6-dione (VII[2b]).- A small sample of each of the diacetates (VI[6a]), (VI[6b]), (VIII[3a]), (VIII[3b]) and (VIII[3c]) was separately hydrolysed by heating under reflux in a 1% methanolic potassium hydroxide solution overnight. The diols thus obtained were oxidised with chromic acid in acetone and purified by t.l.c.

The diacetates (VI[6a]) and (VI[6b]) each gave the Δ^9-dione (VII[2a]) m.p. 116-117° (from methanol), o.r.d.$[\phi]_{318}$ -16,900°,

$[\emptyset]_{270}$+ 19,435°, $[\emptyset]_{246}$ + 13,945° (lit.[75] m.p. 110-120°, $[\emptyset]_{321}$ - 13,750°, $[\emptyset]_{273}$ + 14,600°, $[\emptyset]_{245}$ + 11,200°).

The diacetates (VIII[3b]) (VIII[3a]) and (VIII[3c]) each gave the Δ^9-dione (VII[2b]) an oil, o.r.d. $[\emptyset]_{318}$-18,440°, $[\emptyset]_{270}$+ 18,440, $[\emptyset]_{250}$ + 16,200°. τ 9.1 and 9.2 (d, side-chain, 18-Me, 5β-Me, and low-field branch of 4β-Me doublet) and 9.31 (s, high-field branch of 4β-Me doublet) (see Discussion for mass spectrum).

Oxidation of diols (VII[3b]) and (VII[4b]).- Both compounds were treated with chromic acid in acetone under conditions described above. The diol (VII[3b]) (14 mg.) after t.l.c. [elution with benzene-ethylacetate (10:1)], gave 4,4,5-trimethyl-19-nor-5β,10α/β-cholest-1-ene-3,6-dione (VII[5]), m.p. 134-136°, $\nu_{max.}$ 1700 (broad) $cm.^{-1}$, $\lambda_{max.}$(EtOH) 231 nm. (ε 9000) (see Discussion for mass spectral data), and an unknown lactone $\nu_{max.}$ 1765 $cm.^{-1}$, (see Discussion for mass spectral data).

The diol (VII[4b]) (8 mg.) gave 4,4,5,14-tetramethyl-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-en-3,6-dione (VII[4c])[75], an oil (see Discussion for mass spectral data).

3β-Methoxy-19-oxocholest-5-ene (IX [1b]).- 3β-Hydroxy-steroid (IX[1d])[82] (1 g.) in dry pyridine (30 ml.) was treated with p-toluene sulphonyl chloride (1 g.) and the mixture allowed to stand at room temperature overnight. The solution was then poured into ice, extracted with ether and the ether extracts washed with water, dried and evaporated. The resulting oil was dissolved in methanol and refluxed for 2 hr. on a steam bath.

Water was then added till the solution became turbid, cooling gave the crystalline product (IX[1b]) (700 mg.) m.p. 71-2° (aq.methanol), $\nu_{max.}$ 1730 (C=O) and 2720 (H-C=O) cm.$^{-1}$, τ 0.4 (s, HC=O), 4.2-4.4 (m, C=CH), 6.82 (s, OMe), and 9.4 (s, 18-Me) (Found: C, 81.12; H, 11.22 $C_{28}H_{46}O_2$ requires C, 81.1; H, 11.18%).

3β-Methoxy-19-methylenecholest-5-ene (IX[1e]).- A 2.0 M hexane solution of butyl lithium (2.5 ml.) was added to a suspension of methyl triphenyl phosphonium bromide (2.02 g.) in ether (25 cc) and the mixture stirred under nitrogen for 1 hr. The steroid (1X[1b]) (1 g.) dissolved in ether (25 ml.) was then added and the mixture stirred for 2 hr., and refluxed for a further 4 hr. After cooling the mixture was poured into water, extracted with ether and the ether extracts dried and evaporated. The resulting oil after column chromatography, elution with petroleum ether (60/80) gave the 19-vinyl steroid (1X[1e]) (600 mg.) m.p. 82-4° (from methanol), $[\alpha]_D$- 102° (c, 0.4), τ4.1-5.2 (m, 4H, C=CH, and $HC=CH_2$), 6.82 (s, OMe), 6.9-7.5 (m, OCH), and 9.43 (s,18-Me) (Found: C, 84.34; H, 11.75 $C_{29}H_{48}O$ requires C, 84.4; H, 11.72%).

3β-Methoxy-19-methylcholest-5-ene (1X[1f]).- An ethylacetate solution of the steroid (IX[1e]) (1g.) was stirred with 10% palladium on charcoal catalyst, in an atmosphere of hydrogen at room temperature until the uptake of hydrogen had ceased. The solution was filtered and evaporated and the resulting oil, on crystallisation from methanol, gave (1X[1f])(1 g.) m.p. 81-2°

$[\alpha]_D$- 53° (c, 0.4), τ 4.4-4.7 (m, C=CH), 6.8 (s, OMe), 6.7-7.3 (m, OCH), and 9.3 (s, 18-Me) (Found: C, 83.41; H, 12.15 $C_{29}H_{50}O$ requires C, 83.99; H, 12.15%).

6β-Acetoxy-3β-methoxy-19-methyl-5α-cholestan-5-ol (IX[2a]).- A solution of steroid (IX[1f]) (2g.) in 98% formic acid (20 ml.) was stirred vigorously at 50°C, for 5 min. After cooling to room temperature the suspension was then treated with 30% H_2O_2 (2.0 ml.) and stirring continued overnight. Boiling water (30 ml.) was added and after cooling the mixture was extracted with ether, washed with sodium hydroxide solution, water and evaporated. The resulting oil was treated with 10% potassium hydroxide solution (2 ml.) in methanol.(60 ml.). The usual work up gave 3β-methoxy-19-methyl-5α-cholestane-5,6β-diol (IX[2c]) (1.8 g.) m.p. 203-4°, $[\alpha]_D$- 3° (c, 2.0), τ 6.2-6.8 (m, 2 OCH), 6.68 (s, OMe), and 9.3 (s, 18-Me) (Found:C,77.8; H, 11.67 $C_{29}H_{52}O_3$ requires C, 77.62; H, 10.70%). Acetylation of (IX[2c]) with acetic anhydride-pyridine gave a quantitative yield of the 6β-acetate (IX[2a]) as an oil $[\alpha]_D$- 25° (c, 0.4), $\nu_{max.}$ 1745 (C=O) and 3610 (OH) cm.$^{-1}$, τ 5.3-5.5 (m, $W_{\frac{1}{2}}$ ca. 6 Hz., AcOCH), 6.3-6.8 (m, 2OCH), 6.8 (s, OMe), 8.0 (s,AcO), and 9.3 (s, 18-Me) (Found: C 75.56; H,10.76 $C_{31}H_{54}O_4$ requires C, 75.87; H, 11.09%).

3β,6β-Diacetoxy-19-methylene-5α-cholestan-5-ol (IX[2b]).- A solution of the α-epoxide (IX[3])[84] (250 mg.) and periodic acid dihydrate (150 mg.) in aqueous acetone was heated under reflux for 30 min. Water was added to precipitate

the product which on filtration gave 3β-acetoxy-19-methylene-5α-cholestan-5,6β-diol (IX[2i]) (200 mg.) m.p. 199-200°(from methanol) $[\alpha]_D$+ 8° (c, 0.25) (Found: C, 76.76; H, 10.08 $C_{30}H_{50}O_4$ requires C, 75.9; H, 10.62%). Acetylation of (IX[2i]) with acetic anhydride-pyridine gave a quantitative yield of the hydroxy-acetate (IX[2b]) as an oil, $[\alpha]_D$-24° (c, 0.2), τ 3.2-3.9 (m, X proton of AEX system, HC=C) 4.5-5.3 (m, $C=CH_2$,2AcOCH), 7.95 s, AcO), 8.08 (s,AcO), and 9.42 (s, 18-Me)

6α-Acetoxy-3β-methoxy-19-methyl-5α-cholestan-5-ol (IX[2e])
3β-Acetoxy-10-acetoxymethyl-5α-cholestan-5,6α-diol (IX[2f]).- A solution of steroid in pyridine (10 ml./0.4 g. steroid) was treated with osmium tetroxide (0.3 g. per 0.4 g. steroid) and the mixture left at 21° for 96 hr. Chloroform (100 ml.) was added and the solution saturated with hydrogen sulphide. Filtration through a short alumina (grade III) column and evaporation gave the cis-diol.

The olefin (IX[1f]) (200 mg.), gave (IX[2d]), which on treatment with acetic anhydride in pyridine and preparative t.l.c.[elution with benzene-ethylacetate (3:1)], gave the hydroxy-acetate (IX[2e]) (150 mg.) m.p. 166-8° (from methanol) $[\alpha]_D$ + 36° (c, 1.1), τ 5.00-5.4 (m, AcOCH), 6.4-6.9 (m, OCH),6.78 (s,OMe), 8.05 (s,AcO), and 9.35 (s, 18-Me) (Found: C, 75.93; H, 11.12 $C_{31}H_{54}O_4$ requires C, 75.87; H,11.09%).

The olefin (IX[1i]) (450 mg.) gave the diol (IX[2f])

(350 mg.) m.p. 149-151° (from methanol) $[\alpha]_D$ 0°, τ 4.9-5.3 (m, AcOCH), 5.6-6.2 (m,$AcOCH_2$), 6.2-6.9 (m, OCH) 8.00 (s, 2AcO), and 9.35 (s, 18-Me) (Found: C, 71.19; H, 9.94 $C_{31}H_{52}O_6$ requires C, 71.50; H, 10.07%).

3β-Methoxy-19-methyl-5α-cholest-5-ol-6-one (IX[2j]) and 3β-acetoxy-10-acetoxymethyl-5α-cholestan-5-ol-6-one (IX[2g]).- A solution of Jones[33] reagent (0.4 ml./200 mg. steroid) was added to a stirred solution of the diol in acetone (15 ml./200 mg. steroid) at 0°C. After 3 min. the solution was poured into water and the usual work up gave the ketol.

The diol (IX[2d]) (100 mg.) gave the ketol (IX[2j]) (100 mg.) m.p. 204-5° (from methanol) $[\alpha]_D$ - 44.5° (c, 0.3), $\nu_{max.}$ 1710 (C=O) and 3600 (OH) cm.$^{-1}$ τ 6.75 (s,OMe) and 9.3 (s, 18-Me) (Found: C, 78.11; H, 11.46 $C_{29}H_{50}O_3$ requires C, 77.97; H, 11.28%).

The diol (IX[2f]) (310 mg.) gave the ketol (IX[2g]) (290 mg.) as an oil $[\alpha]_D$ - 37.5° (c, 0.45), $\nu_{max.}$ 1710 (C=O), 1740 (AcO), and 3450 (broad,OH) cm.$^{-1}$ τ 4.7-5.3 (m, AcOCH), 5.5-6.0 (m,OCH_2), 8.02 (s,AcO), 8.1 (s,AcO) and 9.33 (s,18-Me) (~~see Discussion for mass spectral data~~).

3β,6β-Diacetoxy-10-acetoxymethyl-5α-cholestan-5-ol (IX[2h]).- A solution of the ketol (IX[2g]) (200 mg.) in ethanol (25ml.) was treated with sodium borohydride (200 mg.) and stirred for 1 hr. at room temperature. The solution was acidified with acetic acid, diluted with water and the usual work up gave the crude diol.

A pyridine solution of the crude diol and excess acetic anhydride was allowed to stand at room temperature overnight. Addition of water and evaporation, under vacuo, gave the crude triacetate (IX[2h]) (200 mg.). Preparative t.l.c.[elution with benzene:ethylacetate (10:1)] gave pure triacetate (IX[2h]) (137 mg.), an oil, $[\alpha]_D$-30° (c, 1.0), $\nu_{max.}$ 1740 (AcO) and 3500 (OH) cm.$^{-1}$, τ 4.7-5.2 (m, AcOCH), 5.2-5.6 (m, AcOCH), 5.6-6.0 (m, OCH_2), 7.9 (s,AcO) 8.00 (s,AcO), 8.1 (s,AcO), and 9.3 (s, 18-Me).

Dehydration of (IX[2a]),(IX[2b]),(IX[2e]),(IX[2h]), and (IX[2j]).- Conditions identical to those detailed above. The hydroxy-acetate (IX[2a]) (200 mg.) after 15 min. gave an oil (150 mg.). Preparative t.l.c. [elution with benzene-ethylacetate (19:1)] gave 6β-acetoxy-3β-methoxy-5-ethyl-19-nor-5β-cholest-9(10)-ene (X[1a]) (100 mg.), an oil, $[\alpha]_D$+ 47° (c, 0.6), τ 5.2-5.6 (m, $W_{\frac{1}{2}}$ ca. 16 Hz., AcOCH), 6.5-6.8 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., OCH), 6.8 (s,OMe) 8.05 (s,AcO), 9.1 and 9.2 (d, 21-Me), and 9.21 (s, 18-Me) (Found: C, 78.74; 10.95 $C_{31}H_{52}O_3$ requires C, 78.65; H, 11.09%) and 3ξ,6β-diacetoxy-19-methylcholest-4-ene (X[2]) (20 mg.), an oil, $[\alpha]_D$+ 40° (c,0.6), $\nu_{max.}$ 1740 (AcO) cm.$^{-1}$, τ 4.05-4.35 (m,$W_{\frac{1}{2}}$ 9 Hz., C=CH), 4.6-5.1 (m, 2AcOCH), 8.08 (s,2AcO), and 9.3 (s,18-Me) (Found: C, 77.03; H, 10.55 $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.47%).

The hydroxy-acetate (IX[2b]) (80 mg.) after 6 hr. gave an oil (70 mg.). Preparative t.l.c. [elution with benzene:

ethylacetate (10:1)] gave 3β,6β-diacetoxy-5-ethenyl-19-nor-5β-cholest-9(10)-ene (X[1c]) (44 mg.), oil, $[\alpha]_D$+ 73° (c, 1.0), τ 4.0-5.6 (m, $HC=CH_2$,2AcOCH), 8.05 (s,AcO), 8.1 (s, AcO), 9.08 and 9.18 (d, 21-Me and 18-Me) (see Discussion for mass spectrum).

The hydroxy-acetate (IX[2e]) (60 mg.) after 15 min. gave an oil (60 mg.). Preparative t.l.c. [elution with benzene: ethylacetate (10:1)] gave 3ξ,6α-diacetoxy-19-methylcholest-4-ene (X[3]) (40 mg.), oil, $[\alpha]_D$ + 21° (c, 0.7). τ 4.4-4.6 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., HC=C), 4.7-5.1 (m, 2AcOCH), 7.98 (s,AcO), 8.05 (s,AcO), and 9.32 (s, 18-Me).

The hydroxy-triacetate (IX[2h]) (100 mg.), after 3 hr., t.l.c. indicated mainly unchanged starting material; further treatment for 18 hr. gave a mixture (10 mg.) τ 4.1-4.4 (m,HC=) 7.9-8.05 (m,3AcO), and 9.3 (s, 18-Me).

The ketol (IX[2j]) (120 mg.) after 15 min. gave an oil (60 mg.). Preparative t.l.c.[elution with benzene:ethyl-acetate (10:1)] gave 3β-methoxy-5-ethyl-19-nor-5β-cholest-9(10)-en-6-one (X[1b]) (20 mg.), oil. $[\alpha]_D$- 41° (c,0.4), $\nu_{max.}$ 1745 (C=O) $cm.^{-1}$, τ 6.4-6.7 (m, $W_{\frac{1}{2}}$ ca. 9 Hz., CHO) 6.75 (s, MeO), 9.25 (s, 18-Me), 9.38, 9.5, and 9.6 (t, CH_3 portion of 5-ethyl) (Found: C, 81.26; H, 11.32 $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.29%).

Sodium in ethanol reduction of (IX[2j]).- A solution of the ketol (IX[2j]) (250 mg.) in absolute ethanol (50 ml.) was treated, over 20 min., with sodium metal and refluxing continued for a further 20 min. The excess sodium was destroyed by

addition of more ethanol. The solution was poured into water, extracted with ether, and the ether extract washed and dried. Evaporation gave an oil which was shown by t.l.c. to contain numerous products. Acetylation of the crude oil with acetic anhydride in pyridine followed by preparative t.l.c. [elution with benzene-ethylacetate (10:1)] gave 6β-acetoxy-3β-methoxy-19-methyl-5β-cholestan-5-ol (X[4a]) (30 mg.), oil $[\alpha]_D$ 0°, $\nu_{max.}$ 1740 (C=O) and 3500 (OH) cm.$^{-1}$, τ 5.2-5.4 (m, $W_{\frac{1}{2}}$ ca. 6 Hz., AcOCH), 6.3-6.6 (m, $W_{\frac{1}{2}}$ ca. 8 Hz., OCH), 6.7 (s,OMe), 8.04 (s,AcO), and 9.32 (s, 18-Me) (Found : C, 76.2; H, 11.70 $C_{31}H_{54}O_4$ requires C, 75.87; H, 11.09%), and 6α-acetoxy-3β-methoxy-19-methyl-5β-cholestan-5-ol (X[4b]) (15 mg.) m.p. 138-40° (from aq. methanol), $[\alpha]_D$ + 120° (c, 0.2), $\nu_{max.}$ 1740 (C=O) and 3550 (OH) cm.$^{-1}$, τ 4.9-5.3 (m, $W_{\frac{1}{2}}$ ca. 20 Hz. AcOCH), 6.3-6.5 (m, $W_{\frac{1}{2}}$ ca. 8 Hz. OCH), 6.7 (s, OMe), 8.05 (s,AcO), and 9.35 (s, 18-Me) (Found: C, 75.77; H, 10.84 $C_{31}H_{54}O_4$ requires C, 75.87; H, 11.09%).

Hydrolysis and oxidation of (X[1a],(X[2], and (X[3]).- The steroids were hydrolysed with 1% potassium hydroxide in methanol and after the usual work up the crude alcohols were oxidised with Jones reagent[33] as previously described.

The methoxy-acetate (X[1a]) (20 mg.) gave 3β-methoxy-5-ethyl-19-nor-5β-cholest-9(10)-en-6-one (X[1b])(10 mg.) identical in every respect to the sample previously obtained.

The diacetates (X[2]) (20 mg.) and (X[3]) (10 mg.) gave 19-methylcholest-4-en-3,6-dione (X[7] (12 mg. and 6 mg.

respectively), m.p. 119-20° (from methanol), $[\alpha]_D$ - 34° (c,0.2), $\nu_{max.}$ 1695 (conj. C=O) cm.$^{-1}$, $\lambda_{max.}$ 248 n.m. (ϵ 11.500) (Found: C, 81.33; H, 10.86 $C_{28}H_{44}O_2$ requires C, 81.5; H, 10.75%).

Hydrolysis and hydrogenation of (X[1c]).- A solution of the diacetate (X[1c]) (30 mg.) in 1% methanolic potassium hydroxide was refluxed on a steam bath for 15 min. Work up in the usual manner gave 5-ethenyl-19-nor-5β-cholest-9(10)-en-3β,6β-diol (X[1d]), oil, τ 3.8-5.4 (m, $HC=CH_2$, ABC system), 5.9-6.3 (m, $W_{\frac{1}{2}}$ ca. 10 Hz., OCH), 6.4-6.9 (m, OCH), 9.1 and 9.2 (d, 21-Me and 18-Me).

A solution of the diol (X[1a]) (15 mg.) in ethylacetate was treated with 5% palladium on charcoal (10 mg.) and the mixture stirred under an atmosphere of hydrogen for 1 hr. The solution was filtered and evaporation of the solvent gave 5-ethyl-19-nor-5β-cholest-9(10)-en-3β,6β-diol (X[1e]) (14 mg.), oil, τ 6.0-6.3 (m,OCH), 6.4-6.8 (m, OCH), 9.1 and 9.2 (d, 21-Me and 18-Me). (Found: C, 81.24; H, 11.51 $C_{28}H_{48}O_2$ requires C, 80.71; H, 11.61%).

3β,6β-Diacetoxy-5-ethenyl-19-nor-5β-B-seco-cholestan-9,10-dione (X[6]). A solution of the diene (X[1c]) (60 mg.) in pyridine (3 ml.) was treated with oxmium tetroxide (30 mg.) and the mixture kept at room temperature for 24 hr. Usual work up gave, after preparative t.l.c.,[elution with benzene-ethylacetate (3:1)], 3β,6β-diacetoxy-5-ethenyl-19-nor-5β,10α-cholestan-9α,10-diol (X[5]) (35 mg.), oil, $\nu_{max.}$ 1740 (AcO), and 3500 (OH) cm.$^{-1}$

τ 3.7-5.3 (m, $HC=CH_2$, 2AcOCH), 7.96 (s, OAc), 8.15 (s,AcO), and 9.32 (s,18-Me) (see Discussion for mass spectrum).

A solution of the diol (X[5]) (30 mg.) in t.butanol (3 ml.) was treated with lead tetraacetate in acetic acid (0.065M, 4 ml.) and the mixture kept at 45° for 4 hr. The mixture was poured into water, extracted with ether, the ether extract washed with sodium hydroxide (1% solution), water and dried. Evaporation of the solvent gave the diketone (X[6]) (20 mg.) oil, $\nu_{max.}$ 1720 (C=O) and 1740 (AcO) $cm.^{-1}$, τ 4.6-5.0 (m, 2AcOCH), 8.05 (s, AcO), 8.12 (s, AcO), and 9.05 (s, 18-Me) (see Discussion for mass spectrum).

Epoxidation of (X[1c]).-A solution of the diene (X[1c]) (100 mg.) in dry ether (2 ml.) was treated with monoperphthalic acid (1 ml., 0.65N) and the mixture stirred at room temperature for 12 hr. The usual work up gave 3β,6β-diacetoxy-9α, 10-epoxy-5-ethenyl-19-nor-5β,10α-cholestane (X[8]) (80 mg.) m.p. 98-100° (from methanol) $[\alpha]_D$+ 22° (c, 0.7), τ 4.0-5.3 (m, $HC=CH_2$,2AcOCH), 8.1 (s, 2AcO), and 9.25 (s,18-Me) (Found: C, 74.57; H, 9.78 $C_{32}H_{50}O_5$ requires C, 74.67; H, 9.79%).

3β,19-Diacetoxy-19-methylcholest-5-ene (XI[1b]).- To lithium (300 mg.) in dry ether (30 ml.) was added methyl iodide (4.0 g.) and the mixture stirred until all the lithium had reacted. A solution of (IX[1d]) (600 mg.) in dry ether (30 ml.) was added and the mixture refluxed for 2 hr. The excess methyl lithium was destroyed by addition of methanol and the resulting

mixture poured into water, extracted with ether and the ether extract dried. Evaporation gave the crude diol (XI[1a]) (500 mg.)

Acetylation of the crude diol with acetic anhydride and pyridine gave (XI[1b]) (550 mg.) oil, $[\alpha]_D$- 0.5) τ 4.3-4.9 (m, HC=C, AcOCH), 5.3-5.8 (m, AcOCH), 8.05 (s, 2AcO), and 9.28 (s, 18-Me) (Found: C, 76.69; H, 10.35 $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.47%).

19-Acetoxy-19-methylcholest-5-en-3β-ol (XI[1c]).- A solution of the diacetate (XI[1b]) (550 mg.) in methanol (25 ml.) was treated with sodium carbonate (500 mg.) and the mixture refluxed for 1 hr. The mixture was poured into water, extracted with ether and the organic layer dried. Evaporation of the solvent gave (XI[1c]) (456 mg.) oil, $[\alpha]_D$ - 43° (c, 0.5) (Found: C, 78.88; H, 11.45 $C_{30}H_{50}O_3$ requires C, 78.55; H, 10.99%).

19-Acetoxy-3β-methoxy-19-methylcholest-5-ene(XI[1d]).- A solution of (XI[1c]) (456 mg.) in trimethylorthoformate (10 ml.) was treated with perchloric acid (0.6 ml.) and the mixture allowed to stand at room temperature for 15 min. The mixture was poured into water and extracted with ether. The ether extract was washed with sodium bicarbonate solution, water, and dried. Evaporation gave (XI[1d]) (405 mg.) m.p. 169-70° (from methanol) $[\alpha]_D$- 49° (c, 0.5), τ 4.4-4.85 (m, HC=C, AcOCH), 6.78 (s,OMe), 6.8-7.3 (m,CHO), 8.05 (s,AcO), and 9.29 (s, 18-Me) (Found: C, 78.64; H, 10.95

$C_{31}H_{52}O_3$ requires C, 78.76; H, 11.09%).

3β-Methoxy-19-methylcholest-5-en-19-ol (XI[1e]).- A solution of (XI[1d]) (400 mg.) in 1% methanolic potassium hydroxide (20 ml.) was heated under reflux overnight. The mixture was poured into water, extracted with ether and the ether extract dired. Evaporation gave (XI[1e]) (330 mg.) m.p. 103-4° (from methanol), $[\alpha]_D$ - 5° (c, 0.15), τ 4.4-4.6 (m, HC=C), 5.8-6.2 (m, AcOCH), 6.8 (s, MeO), 6.85-7.2 (m, OCH), and 9.3 (s, 18-Me) (Found: C, 80.86; H, 11.9 $C_{29}H_{50}O_2$ requires C, 80.87; H, 11.70%).

10-Acetyl-3β-methoxylcholest-5-ene (XI[2a]).-A solution of (XI[1e]) (320 mg.) in acetone (30 ml.) was treated with Jones reagent[33] (0.6 ml.) and the mixture stirred at room temperature for 4 min.. The solution was poured into water and the usual work up gave (IX[2a]) (300 mg.) m.p. 119-20° (from methanol), $[\alpha]_D$- 120° (c,0.5), $\nu_{max.}$ 1710 (C=O) cm.$^{-1}$, τ 4.2-4.45 (m, HC=C), 6.8 (s,OMe), 7.95 (s,CH_3CO), and 9.38 (s,18-Me) (Found: C, 81.55; H, 11.12 $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.29%).

10-Acetylcholest-5-en-3β-ol (XI[2b]).- A solution of (XI[1c]) in dry chloroform (40 ml.) was heated on a steam bath with exclusion of moisture until 50% of the solvent was distilled off. The solution was cooled and dihydropyran (1 ml.) and p-toluene sulphonic acid (10 mg.) were added and the mixture stirred at room temperature for 20 hrs. The solution was then washed with sodium bicarbonate solution, water, and then dried. Removal of the solvent gave the 3-tetrahydropyranyl

ether derivative[86]. A solution of the crude product in dry ether (20 ml.) was treated with lithium aluminium hydride (500 mg.) and the mixture heated under reflux for 10 hr. The excess lithium aluminium hydride was decomposed by addition of methanol and the resulting mixture was poured into water, extracted with ether and dried. Evaporation gave the crude alcohol, which was dissolved in pyridine (7 ml.) and treated with chromium trioxide (500 mg.) in pyridine (2 ml.). The mixture was stirred for 4 hr., and poured into water, extracted with ether and the ether layer dried. Evaporation gave the 10-acetyl derivative which was dissolved in methanol (10 ml.) containing 2N hydrochloric acid solution (1 ml.) and the mixture left at room temperature for 1 hr.. Addition of water gave (XI[2b]) (250 mg.) m.p. 148-9° $[\alpha]_D$- 112° (c, 0.2), τ 4.2-4.4 (m, HC=C), 6.3-6.8 (m, OCH) 7.88 (s, CH_3CO), and 9.4 (s, 18-Me) (Found: C, 80.94; H, 11.22 $C_{28}H_{46}O_2$ requires C, 81.10; H, 11.18%).

19-Phenylcholest-5-en-3β,19R-diol (XI[3]) and 19-phenylcholest-5-en-3β,19S-diol (XI[4]).- To lithium (300 mg.) in dry ether (20 ml.) was added bromo benzene (3.2 g.) and the mixture stirred until all the lithium had reacted. A solution of (IX[1d]) (500 mg.) in dry ether (20 ml.) was added and the mixture refluxed for 2 hr. The excess phenyl lithium was destroyed by adding methanol and the resulting mixture was poured into water, extracted with ether and the ether layer dried. Evaporation of the solvent gave an oil. Preparative t.l.c.

[elution (x3) with benzene-ethylacetate (3:1)] gave (XI [3]) (300 mg.) an oil, $[\alpha]_D$ - 81° (c, 0.8), $\nu_{max.}$ 3640 (-OH hydrogen bonded) cm.$^{-1}$ τ 2.5-2.95 (broad singlet, phenyl). 4.4-4.6 (m, HC=C), 5.1-5.15 (m, $W_{\frac{1}{2}}$ ca. 5 Hz. Ø CHO), 6.4-6.9 (m, OCH), and 9.45 (s, 18-Me) (Found: C, 82.29; H, 10.36 $C_{33}H_{50}O_2$ requires C, 82.79; H, 10.53%) and (XI[4]) (150 mg.) an oil $[\alpha]_D$ - 104° (c, 0.3), $\nu_{max.}$ 3640 (-OH broad) cm.$^{-1}$ τ 2.5-3.1 (m, phenyl), 4.4-4.7 (m, HC=CH), 4.8-5.05 (m, ØCHO), and 9.7 (s, 18-Me) (Found: C, 82.8; H, 11.0 $C_{33}H_{50}O_2$ requires C, 82.79; H, 10.53%).

19-Benzoylcholest-5-en-3β-ol (XI[7b]).- A solution of (XI[3]) and (XI[4]) (500 mg.) in pyridine (15 ml.) was treated with acetic anhydride (2 ml.) and the mixture allowed to stand at room temperature overnight. The usual work up gave a mixture of mon-acetate (XI[6] and diacetate (XI[5]). The mixture was dissolved in acetone (20 ml.) and treated with Jones reagent (0.6 ml.) for 3 min. The usual work up gave a mixture of (XI[5].) and (XI[7a]). The mixture was then treated with 1% methanolic potassium hydroxide solution (20 ml.). The usual work up gave an oil. Preparative t.l.c. [elution with benzene: ethylacetate (3:1)] gave (XI[7b]) (250 mg.) oil. $[\alpha]_D$ - 217° (c, 0.3), $\nu_{max.}$ 1670 and 1680 (d, PhC=O) and 3640 (broad OH) cm.$^{-1}$ τ 2.05-2.3 (m, 2 ortho protons PhCO), 2.5-2.8 (m, 3 meta-para protons PhC=O), 4.2-4.4 (m, HC=C) 6.4-6.9 (m, OCH), and 9.9 (s, 18-Me) (Found: C, 83.14; H, 10.23 $C_{33}H_{48}O_2$ requires C, 83.14; H, 10.15%).

Mass Spectral Data

	Base Peak	Molecular Ion		Other Ions			Metastable peaks	
	m/e	m/e	Formula (Calculated mass)	Relative abundance %	m/e	Formula (Calculated mass)	Relative abundance %	m/e	transition
III[2]	43	397		33.3	382		4.7	368	397 - 382
					369		3.6	344	397 - 369
					284		4.7	87	397 - 186
					186		10.7	74.5	397 - 172
					172		36		
III[6]	384	399		68	371		5.35	369.5	399 - 384
								345	399 - 371
III[7]	127	446		1.8	418		89	391	446-418
					386		3.2	367	418-386
					328		6.4	282	418-328
					114		1.7		
IV[7b]	43	506		17.2	488		26.5	471	506-488
					415		15.5	340	506-415
					398		53	313	506-398
					380		28	362	398-380
					344		50	297	398-344

Mass Spectral Data

	Base Peak	Molecular Ion			Other Ions			Metastable peaks	
	m/e	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	transition
V [2]	57				488.3638	$C_{34}H_{48}O_2$	31.8	337	366-351
					474	(488.3654)	2.28		
					386		6.8		
					384		9.1		
					366.3272		41		
					351		13.7		
					325		18		
V[3a]	105	534		10	519		5	505	534-519
					458		15	404	519-458
					421		20	332	534-421
					429		7.5	345	534-429
V[3b]	69	490.3843	$C_{34}H_{50}O_2$ (490.3811)	-	337				
V[5]		486			426.3498	$C_{29}H_{46}O_2$ (426.3498)			

Mass Spectral Data

	Base Peak	Molecular Ion			Other Ions			Metastable peaks	
	m/e	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	transition
V[7]	43	490.3814	$C_{34}H_{50}O_2$ (490.3811)	47	399 384 382		43.5 36.4 31.0	325 301 298	490-339 490-384 490-382
VII[3b]	28	430		0.1	412.3705 397	$C_{29}H_{48}O$ (412.3705)	13.5 11.3	383	412-397
VII[4d]	327	500		16	485 440 387		4 7.5 10	460 387 300 276	500-485 500-440 500-387 387-327
VII[2b]	43	412.3337	$C_{28}H_{44}O_2$ (412.341)	32.8					

Mass Spectral Data

	Base Peak	Molecular Ion			Other Ions			Metastable peaks	
	m/e	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	transition
VII[4c]	313	426		25	411		8.3	230	426-313
VII[5]		426.3499	$C_{29}H_{46}O_2$ (426.3498)						
lactone (structure not assigned)	43	426.3502	$C_{29}H_{46}O_2$ (426.3498)	18.8	271		12.5	172	426-271
IX[2h]	43	518		11.5	458 39.8 385 367		38.5 11 3.8 15.4	406 347	518-458 458-398
X[1c]	378				438.3496 398 363 351	$C_{30}H_{46}O_2$ (438.3498)	61 17.4 13 6.5	426	438-378

Mass Spectral Data

	Base Peak	Molecular Ion			Other Ions			Metastable peaks	
	m/e	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	Formula (Calculated Mass)	Relative abundance %	m/e	transition
X [5]	43				472 412 384 264		47.5 43 59.5 100%	360	(472-412 (412-384
X[6]	43	530.3597	$C_{32}H_{50}O_6$ (530.3607)	0.5	470 428 410		1.25 4.5 1.2	358	470-410

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