Tetrahedron, 1965, Vol. 21, pp. 2489 to 2499. Pergamon Press Ltd. Printed in Northern Ireland

REACTIONS OF EPOXIDES—VII*

ACID-CATALYSED REACTIONS OF 13,17a-EPOXY-AND 17a,18-EPOXY-C-NOR-D-HOMO-SPIROSTANS

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(*Received* 24 *March* 1965; *in revised form* 29 *April* 1965)

Abstract—New preparative routes to the 13α,17aα-epoxide (II) and the 13β,17aβ-epoxide (III) are described. Boron trifluoride in benzene converts the α-epoxide (II) into a mixture from which five products were isolated, but the β-epoxide (III) gives only the 17aβ-hydroxy-$\Delta^{8(14)}$-olefin (VIII). Both epoxides give fluorohydrins with boron trifluoride in ether. The 17aα,18-epoxide (X) reacts with either boron trifluoride or perchloric acid to give mainly the 18-aldehyde (XII). The 17aβ,18-epoxide gives a variety of products under different reaction conditions.

EPOXIDATION[1] of the C-nor-D-homo-$\Delta^{13(17a)}$-olefin (I)[2] gives a mixture of the α- and β-epoxides (II and III respectively) which are separable by careful chromatography. We now find that the α-epoxide can also be prepared by treating the olefin (I) with aqueous hypobromous acid followed by mild alkaline hydrolysis of the resulting bromohydrin, which we therefore formulate as the 17aβ-bromo-13α-hydroxy compound (IVa) derived by a stereospecific *trans*-addition. The NMR spectrum confirms the 17a location of the bromine atom, for the 18-methyl signal appears as a sharp peak at τ 8·18. Attempts to reconvert the α-epoxide into the bromohydrin were unsuccessful. The epoxide was stable to hydrobromic acid under mild conditions, and prolonged treatment caused rupture of the spiroketal system.

The β-epoxide (III) which is the minor component of the mixed epoxides, may be prepared from the 13α,17aβ-diol (IVb) by the action of thionyl chloride–pyridine. Presumably a chlorosulphite ester is first formed at 13α. Abstraction of the 17aβ-hydroxyl proton by pyridine would then allow closure of the β-epoxide ring with elimination of the 13α-ester group. As the diol is easily obtained by acid-catalysed hydrolysis of the mixed epoxides,[1b] the chromatographic separation can be avoided.

The ready availability of these tetra-substituted epoxides prompted us to include them in our studies of boron trifluoride-catalysed rearrangements. We have already reported[2] that the α-epoxide (II) afforded hecogenin acetate as one of a number of products, an observation which helped to confirm the $\Delta^{13(17a)}$-structure of the parent olefin. Chromatographic separation of the other products gave a conjugated diene (V), a carbonyl fraction, and the fluorohydrin (IVc). The $\Delta^{8(14),13(17a)}$-structure is assigned to the diene on the basis of its UV absorption (λ_{max} 259 mμ) and its NMR spectrum. This showed the absence of olefinic protons, but a peak at τ 8·25 (three protons) is assigned to the 18-methyl group at the end of the conjugated system,[3]

* Part VI, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **21**, 1547 (1965).

[1(a)] J. Elks, G. H. Phillipps, D. A. H. Taylor and L. J. Wyman, *J. Chem. Soc.* 1739 (1954); [(b)] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Austr. J. Chem.* **18**, 759 (1965).

[2] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* No. 2, 119 (1965).

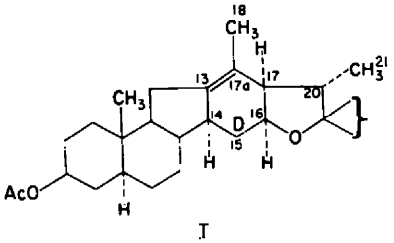
[3] J. B. Davis, L. M. Jackman, P. T. Siddons and B. C. L. Weedon, *Proc. Chem. Soc.* 261 (1961).

and the 19-methyl signal showed an up-field shift to τ 9·43, compared with its normal position at ca. τ 9·2 in related compounds in this series. This shift is attributed to shielding by the unsaturated system, and indicates a $\Delta^{8(14)}$ component[4] of the diene. The carbonyl fraction was a gum, apparently homogeneous by thin-layer chromatography, but the NMR spectrum indicated that it was a mixture of two compounds in unequal amounts. The major component (ca. 85% of the material) was assigned the 13-acetyl-C-nor structure (VI). The acetyl group was revealed by the IR spectrum (ν_{max} 1365 cm^{-1}) and by a peak equivalent to three protons at τ 7·85 in the NMR spectrum. This peak was quite distinct from the acetoxy methyl signal (τ 7·98) which disappeared after alkaline hydrolysis of a sample. The minor carbonyl component was isolated in impure condition by treating the mixture with benzaldehyde in alkaline solution to convert the acetyl compound into its benzylidene derivative. Chromatography then gave the minor product which was distinctly different from hecogenin. On the basis of the discussion below we believe this product to be the C-nor-D-homo-17a-ketone (VII). This structure is supported by its failure to form a benzylidene derivative, and by the IR absorption at 1722 cm^{-1}. The ORD curve showed a negative Cotton effect, but a Dreiding model shows ring D to be distorted and flexible in structure (VII), preventing a clear application of the octant rule.

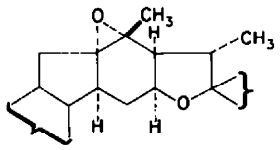
The fluorohydrin (IVc) gave back the α-epoxide on alkaline hydrolysis. The chemical shift of the 18-methyl signal (τ 8·42) in the NMR spectrum supports the 17a-fluoro structure, which was expected from the results of treating the epoxide with other nucleophilic reagents.[2] This fluorohydrin was the sole product when the reaction between the epoxide and boron trifluoride was carried out in ether solution. As in earlier work,[5] we were able to demonstrate the possible intermediacy of the fluorohydrin in the formation of the other reaction products by treating the fluorohydrin with boron trifluoride in benzene. A mixture of V, VI, VII and hecogenin acetate was obtained. However, this reaction was slow compared with the direct formation of these compounds from the epoxide in benzene, so it seems that a major part of the product mixture must be derived directly from the epoxide, only a minor proportion arising through the fluorohydrin in this case.

The β-epoxide (III) was converted smoothly into a single unsaturated hydroxy compound (VIII) by boron trifluoride in benzene (96% yield). The location of the unsaturation at the 8(14)-position was revealed by the NMR spectrum, which showed no olefinic proton, but the C-19 methyl signal was a sharp singlet at τ 9·30, characteristic of $\Delta^{8(14)}$-olefins (Zürcher[4] gives τ 9·29 for 19-Me in 3β-acetoxy-5α-ergost-8(14)-ene). The hydroxyl group is clearly at the 17a-position, for the C-18 methyl signal was a sharp singlet at τ 8·92. The NMR and IR spectra were normal in the regions characteristic of the spiroketal system. The UV absorption exhibited the profile characteristic of a $\Delta^{8(14)}$-olefin,[6] and was quite different from the spectrum which would be expected from a $\Delta^{13(14)}$-olefin (this should show some resemblance to a $\Delta^{8(9)}$-olefin[6]). Dehydration of compound (VIII) with thionyl chloride–pyridine gave the diene (V) in good yield, an observation which supports the (*trans*-) 13α,17aβ-configuration of VIII (see below).

[4] R. F. Zürcher, *Helv. Chim. Acta* **46**, 2054 (1963).
[5] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **21**, 559 (1965).
[6] D. W. Turner, *J. Chem. Soc.* 30 (1959); P. S. Ellington and G. D. Meakins, *Ibid.* 697 (1960), and Refs cited.



I



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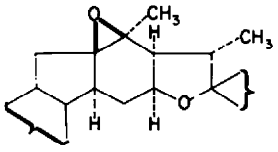
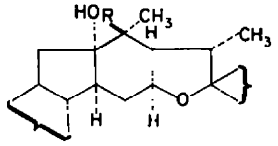
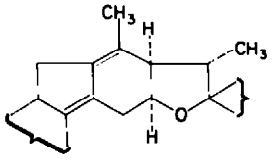


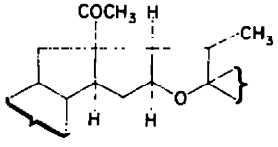
III



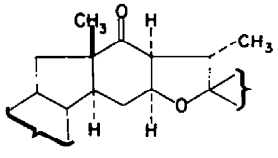
IV (a) R, Br
(b) R, OH
(c) R, F
(d) R, H



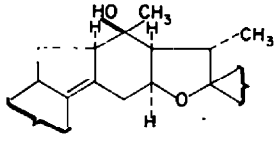
V



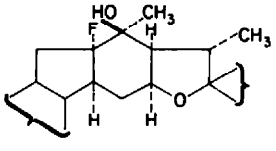
VI



VII



VIII



IX

The reaction between the β-epoxide and boron trifluoride in ether gave only the fluorohydrin (IX) and unreacted epoxide. This fluorohydrin does not appear to be an intermediate in the reaction in benzene solution leading to the $\Delta^{8(14)}$-olefin (VIII), for reaction conditions similar to those employed for rearrangement of the epoxide (Experimental) caused only slow degeneration of the fluorohydrin to give no identifiable products.

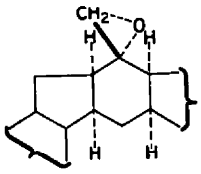
Having available from earlier work[1b] a quantity of each of the 17a,18-epoxides

(X and XI), we examined their behaviour with boron trifluoride, and also with aqueous perchloric acid, the latter in the hope of being able to assign a configuration to the *cis*-diol obtained previously[16] by the action of osmic acid on the $\Delta^{17\alpha(18)}$-olefin. In this we were disappointed, for no diols were obtained.

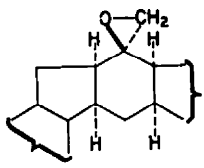
The α-epoxide (X) gave one major product (60% yield) to which we assign the 17aα-18-oxo structure (XII) on the basis of the IR (ν_{max} 2703 and 1721 cm^{-1}) and NMR spectra (doublet at τ 0·21, J = 7 c/s, due to aldehydic proton coupled with the 17aβ-proton, which appeared as a doublet at τ 7·32, J = 7 c/s). The compound was not epimerized by base, confirming the α-configuration of the —CHO group (pseudo-equatorial conformation in a boat-like ring D). Two minor products isolated from the reaction had suffered rupture of the spiroketal system, and their structures are unknown. The 17aα,18-epoxide was not affected by treatment with boron trifluoride in ether solution for 1 hr. The aldehyde (XII) was obtained in higher yield (83%) when the α-epoxide was treated with perchloric acid in aqueous dioxan. The remainder of the product from this reaction was the 18-hydroxy-$\Delta^{13(17a)}$-olefin (XIIIa), the structure of which followed from the reduction of its acetate (XIIIb) by lithium–ethylamine to give the endocyclic olefin (I). The two C-18 protons in compound (XIIIa) appeared as a doublet at τ 5·82, but in other respects the NMR spectrum was very similar to that of the olefin (I).

The behaviour of the 17aβ,18-epoxide (XI) with boron trifluoride was quite unusual. The reaction in benzene solution gave a mixture which afforded three products by chromatography. The least polar, and major product, was a compound isomeric with the epoxide, but having neither hydroxyl nor carbonyl groups, and no unsaturation, as revealed by its spectra and chemical properties. However, the spectra (IR and NMR) gave indications of ether linkages additional to those in the spiroketal system, and on the basis of the evidence available we suggest the 14β,18-cyclic ether structure (XIV) for the compound. The NMR spectrum had a doublet equivalent to two protons at τ 6·23 (J = 4 c/s), which we attribute to the $CH_2{\cdot}O$ moiety at C-18, and the absence of any other signal (except those due to the 16α- and C-26 protons) in this region showed the other point of attachment of the ether oxygen to be a tertiary centre. The stability of the ether to prolonged treatment with lithium–NH_3 or with LAH is consistent with the 5-membered ether ring structure, and together with the chemical shift of the C-18 protons eliminate the possibility of a 4-membered ring involving C-13. Acidic reagents (HBr in acetic acid or BF_3–Ac_2O) rapidly attacked both the ether bridge and the spiroketal system giving no recognizable products. This can be rationalized on the basis of structure XIV, for protonation of the ether bridge with rupture of the C_{14}—O bond would lead to unsaturation at 8(14) or 14(15). The resulting activation of the C_{18}—O bond would allow collapse of the spiroketal. A possible mechanism leading to the ether (XIV) is outlined below.

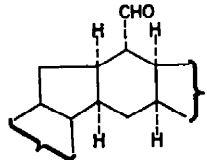
The second product from the epoxide–boron trifluoride reaction was a fluoro-alcohol, probably the 17aα-fluoro compound (XVa). This structure was supported by its smooth conversion to the 18-acetate, which showed IR absorption at the unusually high frequency of 1760 cm^{-1}, probably resulting from the proximity of the fluorine atom. The fluoro-alcohol was, however, completely stable to vigorous alkaline treatment. This may be due to steric difficulties in assuming the *trans*-conformation required for epoxide formation at 17aβ,18, but leaves room for slight



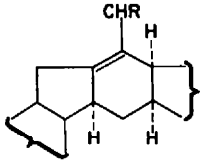
X



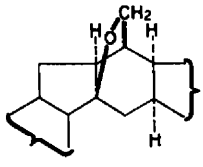
XI



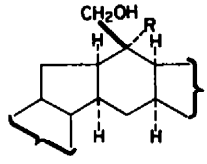
XII



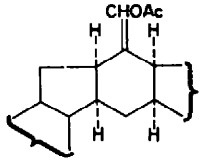
XIII (a) R; H, OH
(b) R; H, OAc
(c) R; O



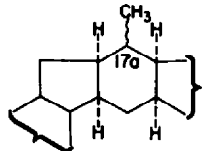
XIV



XV (a) R, F
(b) R, OH



XVI



XVII (a) 17aα-CH_3
(b) 17aβ-CH_3

uncertainty as to structure XV. The presence of a trace (ca. 20%) of the 18-hydroxy-$\Delta^{13(17a)}$-olefin (XIIIa) in the hydroxylic fraction was demonstrated by oxidation of the residues (using 2,3-dichloro-5,6-dicyanobenzoquinone) after crystallization of part of the fluoro-alcohol. The unsaturated alcohol was oxidized selectively to give the unsaturated aldehyde (XIIIc) which was separated from unreacted fluoro-alcohol by chromatography.

Boron trifluoride in ether converted the β-epoxide (XI) into a mixture of the cyclic ether and the 18-hydroxy-olefin. The absence of any fluoro-alcohol in the product is another remarkable feature of this epoxide, and is not understood. Perchloric acid converted the epoxide into the 18-hydroxy-olefin in high yield.

Although the foregoing results shed no light upon the configuration of the 17a,18-diol mentioned earlier, this was finally decided from a study of the diol itself. Acetylation of the diol at C-18, followed by treatment with thionyl chloride–pyridine, gave a product consisting essentially of the enol acetate (XVI) of the 18-aldehyde (XII). The enol acetate was a gum, and splitting of several peaks in the NMR spectrum suggested that it was probably a mixture of geometrical isomers at C-18 in ratio ca. 2:1. The mixture was easily hydrolysed by mild alkaline treatment to give the 18-aldehyde. The formation of the exocyclic rather than the endocyclic olefin from the diol 18-acetate is regarded as establishing the 17aα-configuration of the hydroxyl group (cf. Part III[1b]), and shows that osmium tetroxide attacks the exocyclic $\Delta^{17a,18}$-olefin from the α-face.

DISCUSSION

Examination of Dreiding models suggests that the reactions of these epoxides will be dominated by the tendency of ring D to assume a boat-like or skew conformation as a result of its mode of fusion to rings C and E. The strong steric interaction in a boat-like ring D between the 15β-H and any 17aβ-substituent can be relieved by elimination reactions leading to a $\Delta^{13(17a)}$-olefin, although it is not clear why this elimination is preferred over the formation of the $\Delta^{17(17a)}$-isomer. While we could not have predicted the reaction paths taken by the epoxides, we offer a rationalization of some of the observed results.

The 13,17a-epoxides are prevented by their attachment to the adjoining rings from undergoing a purely "axial" cleavage (see Part VI) for ring D cannot easily assume a chair form. The two carbonium ions accessible from the 13α,17aα-epoxide are illustrated in Fig. 1 (which shows ring D only). The 17a-carbonium ion (a) is favourably oriented for migration of the 13,14-bond, giving hecogenin acetate. The 13-carbonium ion (b), which can give the diene (V) by elimination reactions initiated by loss of the 14α-proton, may also rearrange to give two ketonic products (VI and VII) by migration of the 17,17a-bond or the 18-methyl group respectively. The low yield of the product of methyl migration may be due to the 15β-H/18-methyl interaction in the transition state. Inspection of the model (b) shows that migration of the 17,17a-bond can occur most easily *trans* to the epoxide-oxygen atom, and that the resulting 13-acetyl group should have the α-configuration.

The β-epoxide (III) presumably rearranges with loss of the 8β-proton in the sterically favourable process illustrated in Fig. 2. This would result in the product having the 13α-configuration, the usual 15/17a *trans*-annular interaction being avoided by considerable flattening of ring D by the olefinic bond. It is not clear why ketone-formation fails to compete with this reaction.

The smooth formation of the 18-aldehyde (XII) from the 17aα,18-epoxide is represented in Fig. 3. The simultaneous formation of the 18-hydroxy-olefin (XIIIa) requires a *cis*-elimination, and presumably involves full development of the carbonium ion at C-17a. The energy requirement for formation of this tertiary carbonium ion cannot be much greater than the energy of the concerted reaction leading to the aldehyde, where complete formation of the carbonium ion need not necessarily occur.

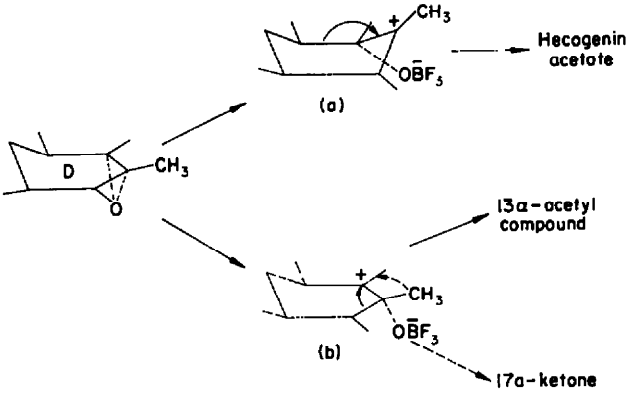


FIG. 1.

FIG. 2.

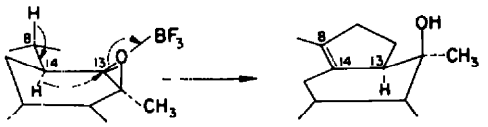


FIG. 3.

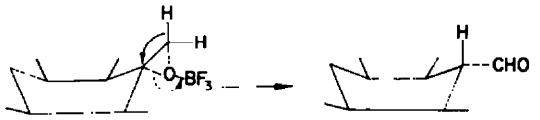
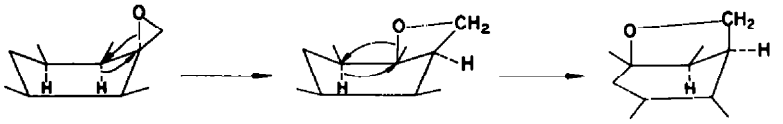


FIG. 4.



The cyclic ether (XIV) is visualized as arising by a two-step process (Fig. 4) involving the 4-membered ring as an unstable intermediate, with the alternative loss of the 13α-proton leading to the 18-hydroxy-olefin (XIIIa) The relative importance of these reactions cannot be explained, for the *trans*-elimination process appears to be highly favourable.

NMR spectra

The signals attributed to the protons at C-18, C-19, and C-21 in the present series of compounds including compounds in Part III[1b] are listed in Table 1. The "parent" compounds with the 17aα- and 17aβ-methyl groups and no other substituents in ring D are included for reference purposes. The 17aα-methyl compound (XVIIa) was prepared by a Huang-Minlon reduction of the 18-aldehyde (XII), and the 17aβ-methyl compound (XVIIb) was obtained by hydrogenation of the 17a(18)-olefin as described previously. The 18-methyl signals in these compounds are split into doublets by spin-spin coupling with the 17a-proton, and appear in a region of the spectrum already containing the 19-methyl and 27-methyl signals, so that the τ-values given in the table must be regarded as tentative, being based upon analysis of integrals in this region.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solutions at room temp. IR spectra were in CS_2, and UV spectra in MeOH. Alumina used for chromatography was P. Spence Grade "H", deactivated by the addition of 5% of 10% acetic acid. Boron trifluoride diethyl etherate was freshly distilled before use. Solvents used for BF_3 reactions were dried over Na. Light petroleum refers to the fraction b.p. 50–70°. ORD curves (in MeOH) were kindly determined by Professor W. Klyne.

Preparation of 13α,17aα-epoxide (II). A solution of I (500 mg) in dioxan (80 ml) was treated with 0·1 M HOBr aq (14 ml) at room temp for 40 min. Water was added, and the product was crystallized from light petroleum to give the *17aβ-bromo-13α-hydroxy-compound* (IVa; 480 mg) m.p. 130–131°, $[\alpha]_D$ −36° (*c*, 0·5), ν_{max} 3600, 1726 and 1247 cm^{-1} (Found: C, 63·3; H, 8·4; Br, 14·3. $C_{28}H_{45}O_6Br$ requires: C, 62·9; H, 8·2; Br, 14·4%).

The bromohydrin (135 mg) in EtOH (10 ml) was treated with KOH (150 mg) for 18 hr at 20°, giving the 3β-hydroxy-13α,17aα-epoxide (80 mg) m.p. 215–218°. Acetylation with acetic anhydride–pyridine (1:10) overnight gave the 3β-acetoxy-13α,17aα-epoxide, m.p. 194–196°, undepressed when mixed with an authentic sample.

Preparation of 13β,17aβ-*epoxide* (III). Compound IVb (3 g) in pyridine (25 ml) was treated dropwise at 0° with $SOCl_2$ (2·5 ml). The product, isolated by addition of water and extraction with

TABLE 1. CHEMICAL SHIFTS OF PROTONS AT C-18, C-19 AND C-21 IN NMR SPECTRA* OF C-NOR-D-HOMO-SPIROSTANS (τ VALUES)

Compound	C-18 protons	19-Me	21-Me
17aα-Methyl series			
Parent compound (XVIIa)	9·19 (5 c/s)†	9·18	9·03 (6 c/s)
17aβ-OH	8·85	9·19	8·92 (6)
17aβ-OH-$\Delta^{8(14)}$ (VIII)	8·92	9·30	8·92 (6·5)
13α-OH (IVd)	8·90 (4)	9·25	8·90 (4)
13α,17aβ-$(OH)_2$ (IVb)	8·77	9·20	8·91 (6)
13α-OH,17aβ-F (IVc)	8·42	9·20	8·86 (7)
13α-OH,17aβ-Br (IVa)	8·18	9·13	8·77 (7)
13α-F,17aβ-OH (IX)	8·73	9·20	8·89 (7)
17aβ-Methyl series			
Parent compound (XVIIb)	9·12 (4)†	9·18	9·03 (6)
17aα-OH	8·85	9·18	8·91 (5)
$\Delta^{13(17a)}$-series			
Parent compound (I)	8·33	9·22	8·87 (6·5)
8(14),13(17a)-diene (V)	8·25	9·43	8·88 (6·5)
18-Hydroxy (XIIIa)	5·82 (4)	9·22	8·80 (6)
18-Acetoxy (XIIIb)	5·45	9·22	8·92 (6)
Epoxides			
13β,17aβ (III)	8·65	9·17	8·87 (6)
13α,17aα (II)	8·68	9·20	8·87 (6·5)
17aβ,18 (XI)	7·58	9·23	9·03 (6)
17aα,18 (X)	7·27	9·22	9·07 (7)
Miscellaneous			
$\Delta^{17a(18)}$-olefin	5·15 (6)	9·20	8·92 (6·5)
18-Aldehyde (XIIIc)	0·21 (7)	9·25	9·02 (7)
Cyclic ether (XIV?)	6·23	9·16	8·98 (6)
13α-Acetyl-compound (VI)	7·85	9·15	8·98 (5·5)
17α-Ketone (VII)	8·80	9·22	8·97 (6·5)
17aα,18-diol (XVb)	6·42 (3·5)	9·22	8·95 (6·5)
Enol acetate (XVI)	3·13, 3·02	9·22	9·05 (6·5)

* Determined at 60 mc in $CDCl_3$, with $CHCl_3$ and $(CH_3)_4Si$ as internal standards.
† Tentative assignment only (see Discussion).

ether, was the 13β,17aβ-epoxide (2·2 g), m.p. 187·5–189°, identical in all respects with an authentic sample.

Reaction of α-epoxide (II) *with* BF_3 *in benzene.* The α-epoxide (1 g) in anhydrous benzene (100 ml) was treated with BF_3–etherate (1 ml) for 30 sec, then ether was added and the solution was washed with $NaHCO_3$ aq. and water, the solvents were removed, and the product was adsorbed onto alumina (80 g). Elution with light petroleum–benzene (8:1) gave the 8(14),13(17a)-*diene* (333 mg), which crystallized first from pentane then from MeOH as cubes, m.p. 160–162°, $[\alpha]_D$ −62° (*c*, 1·17), λ_{max} 259 mμ (ε 23,100). ν_{max} 1726, 1234 cm^{-1} (Found: C, 76·3; H, 9·35. $C_{28}H_{42}O_4$ requires: C, 76·6; H, 9·3%.) A gum (300 mg), eluted by light petroleum–benzene (1:1) consisted mainly of the 13-*acetyl-C-nor-compound* (VI), $[\alpha]_D$ −53° (*c*, 1·33), ν_{max} 1726, 1234 (OAc), 1696, 1356 cm^{-1} (CO·Me), but was contaminated with the C-nor -D-homo-17a-ketone (see below). ORD (of crude material) $[\phi]_{400}$ −405°; $[\phi]_{310}$ −1720°; $[\phi]_{270}$ +430°. Elution with benzene gave hecogenin acetate (180 mg), m.p. 250–252° from MeOH, $[\alpha]_D$ −7°, identical in all respects with an authentic sample. Final

elution with ether gave the *fluorohydrin* (IVc; 128 mg) needles, m.p. 176–177° (from hexane), $[\alpha]_D$ −62° (*c*, 0·73), ν_{max} 3602, 1726 and 1238 cm^{-1}. (Found: C, 70·5; H, 9·3; F, 3·6. $C_{29}H_{45}O_5F$ requires: C, 70·7; H, 9·2; F, 3·9%.)

A portion (175 mg) of the material (above) consisting of the 13-acetyl compound contaminated with the C-nor-D-homo-17a-ketone (VII) was treated with benzaldehyde (0·5 ml) in EtOH (10 ml) containing KOH (60 mg) at room temp for 18 hr. The product, isolated by means of ether, was adsorbed unto alumina (20 g). Elution with benzene gave the benzylidene derivative of the 13-acetyl compound (143 mg) as a gum, $[\alpha]_D$ −38° (*c*, 0·93), ν_{max} 3584 and 1695 cm^{-1}, λ_{max} 221 (ε 11,000), 226 (ε 11,000) and 290 mμ (ε 19,600). Elution with ether gave the *3β-hydroxy-C-nor-D-homo-17a-ketone* (29 mg) as a gum, $[\alpha]_D$ −42° (*c*, 1·12), ν_{max} 3597 and 1722 cm^{-1}, ORD $[\phi]_{600}$ −195°; $[\phi]_{305}$ −2140°; $[\phi]_{288}$ +3600°; $[\phi]_{321}$ +1950°.

Hydrolysis of fluorohydrin (IVc). The fluorohydrin (100 mg) and KOH (100 mg) was heated in aq. EtOH (90%; 25 ml) under reflux for ¾ hr to give the 3β-hydroxy-13α,17aα-epoxide, m.p. 215–218°, which was acetylated in acetic anhydride–pyridine (18 hr at 20°) to give the 3β-acetoxy-13α,17aα-epoxide, m.p. and m.m.p. 194–196°, IR spectrum identical.

Reaction of α-epoxide (II) *with* BF_3 *in ether*. The epoxide (800 mg) and BF_3-etherate (0·8 ml) were allowed to react in anhydrous ether (80 ml) for 1 hr. The product was IVc (646 mg), m.p. and m.m.p. 176–177°.

Reaction of fluorohydrin (IVc) *with* BF_3 *in benzene*. The fluorohydrin (140 mg) and BF_3-etherate (0·16 ml) were dissolved in benzene (16 ml) for 22 min, then the products were isolated as above. The UV spectrum of the crude product (λ_{max} 251 mμ, ε 3200) indicated the presence of 14% of diene (V). Crystallization from MeOH gave hecogenin acetate (20 mg), m.p. 246–248°, and chromatography of the residues on alumina gave a ketonic fraction (53 mg) consisting mainly of the 13α-acetyl compound (VI), and unreacted fluorohydrin (43 mg).

BF_3*-catalysed rearrangement of the β-epoxide* (III) *in benzene*. The epoxide (500 mg) in dry benzene (50 ml) was treated with BF_3-etherate (0·5 ml) for 3 min. Isolation of the steroid as above gave the *17aβ-hydroxy-17aα-methyl-*$\Delta^{8(14)}$*-olefin* (VIII), m.p. 170–171° (prisms from MeOH), $[\alpha]_D$ −94° (*c*, 1·03), λ_{max} 207 mμ (ε 11,500), ν_{max} 3640, 1729 and 1237 cm^{-1} (Found: C, 73·2; H, 9·4. $C_{29}H_{44}O_5$ requires: C, 73·7; H, 9·4%). The compound gave a deep yellow colouration with tetranitromethane.

Dehydration of the hydroxy-olefin (VIII) *to give the diene* (V). Thionyl chloride (0·045 ml) was added to a solution of VIII (100 mg) in pyridine (1·5 ml) at −30°. The solution was allowed to come to room temp over 15 min and the product was isolated by use of ether and purified by chromatography on alumina. The diene (60 mg) formed cubes, m.p. and m.m.p. 160–162°, identical IR and UV spectra.

Reaction of β-epoxide (III) *with* BF_3 *in ether*. The epoxide (500 mg) and BF_3-etherate (0·5 ml) were allowed to react in ether (50 ml) for 1 hr then the steroids were isolated as above. Crystallization from light petroleum gave IX (195 mg), m.p. 130–137° (dec), $[\alpha]_D$ −50° (*c*, 0·96), ν_{max} 3608, 1726 and 1235 cm^{-1}. (Found: C, 70·5; H, 9·3; F, 3·6. $C_{29}H_{45}O_5F$ requires: C, 70·7; H, 9·2; F, 3·9%.) The residue crystallized from MeOH to give unreacted epoxide (250 mg).

Hydrolysis of IX (50 mg) with KOH (50 mg) in refluxing EtOH (20 ml) for 4 hr gave the 3β-hydroxy-13β,17aβ-epoxy, m.p. 128–140°, $[\alpha]_D$ −60·5, which was acetylated by acetic anhydride–pyridine (18 hr at 20°) to give the 3β-acetoxy-13β,17aβ-epoxide, m.p. and m.m.p. 187–189°, identical IR spectrum.

Rearrangement of the 17aα,18*-epoxide* (X) *with* BF_3 *in benzene*. The epoxide (1·3 g) and BF_3-etherate (1·3 ml) were allowed to react in benzene (130 ml) for 15 min and the products were isolated as above. Crystallization from light petroleum gave the 18-*aldehyde* (XII; 250 mg), m.p. 186–188°, $[\alpha]_D$ −63° (*c*, 0·92), ν_{max} 2703 and 1721 (CHO), 1736 and 1241 cm^{-1} (OAc). (Found: C, 73·9; H, 9·8. $C_{29}H_{44}O_5$ requires: C, 73·7; H, 9·4%.)

Chromatography of the residues on deactivated alumina (75 g) gave two products of unknown structure, both lacking the spectral features of the spiroketal system. The first compound (210 mg), eluted by light petroleum–benzene (10:1) crystallized from pentane, m.p. 167–173°, $[\alpha]_D$ −46° (*c*, 1·22), ν_{max} 1731, 1672, 1242 and 1029 cm^{-1}. UV: ε_{220} 4580, ε_{310} 4920. (Found: C, 75·45; H, 9·0%.) The second compound, eluted by light petroleum–benzene (20:3) gave needles (210 mg) from MeOH, m.p. 187–190°, $[\alpha]_D$ −9° (*c*, 1·0), ν_{max} 1742, 1242, 1028 cm^{-1}. UV: ε_{220} 4160, ε_{310} 7450. (Found: C, 76·0; H, 9·0%.) A further quantity (330 mg) of the 18-aldehyde was eluted by the same solvent. Examination of intermediate fractions by thin-layer chromatography showed them to consist essentially of the same three compounds.

Rearrangement of the 17aα,18-*epoxide* (X) *with perchloric acid.* A solution of the epoxide (1·2 g) in CH_2Cl_2 (60 ml) and acetone (120 ml) was treated with aq. perchloric acid (1·5M; 1·2 ml). After 10 min at 20° the solution was diluted with water and the organic phase was washed neutral and the solvent removed. The product was adsorbed onto alumina (50 g). Elution with benzene gave XII (1·009 g), m.p. and m.m.p. 186–188°, identical in all respects with the product obtained from the BF_3 reaction above. Elution of the column with ether gave the 18-*hydroxy*-$\Delta^{18(17a)}$-*olefin* (XIIIa; 150 mg) which crystallized from light petroleum as needles, m.p. 204–206°, $[\alpha]_D$ −64° (*c*, 1·28), ν_{max} 3597, 1745 and 1241 cm^{-1}. (Found: C, 73·3; H, 9·6. $C_{30}H_{44}O_5$ requires: C, 73·7; H, 9·4%.)

Alkaline hydrolysis of the 18-*aldehyde* (XII). The aldehyde (100 mg) and KOH (100 mg) were dissolved in aq. EtOH (90%; 10 ml) for 18 hr. The product, which crystallized from light petroleum, was the 3β-*hydroxy*-18-*aldehyde* (70 mg), m.p. 168–170°, $[\alpha]_D$ −47° (*c*, 0·95), ν_{max} 2703, 1736 cm^{-1} (CHO), (Found: C, 74·8; H, 9·8. $C_{27}H_{42}O_4$ requires: C, 75·3; H, 9·8%.) Re-acetylation of the hydroxy-aldehyde with acetic anhydride–pyridine gave back the acetoxy-aldehyde (XII), m.p. and m.m.p. 186–188°.

BF_3-*catalysed rearrangement of the* 17aβ,18-*epoxide* (XI) *in benzene.* The epoxide (2·3 g) in benzene (230 ml) was treated with BF_3-etherate (2·3 ml) for 30 sec then the product was isolated as above, and adsorbed onto alumina (80 g). Elution with light petroleum–benzene (1:1) gave a gum (1·5 g) which crystallized from MeOH to give the *cyclic ether* (XIV?) as needles m.p. 209–210°, $[\alpha]_D$ −62·5° (*c*, 0·83), ν_{max} 1742, 1242 (OAc), 1081, 1055, 1031, 1023, 957 and 943 cm^{-1}. No UV absorption down to 202 mμ. (Found: C, 73·45; H, 9·2. $C_{30}H_{44}O_5$ requires: C, 73·7; H, 9·4%.) Benzene eluted the *fluorohydrin* (XVa) which crystallized from MeOH as needles (340 mg), m.p. 206–209°, $[\alpha]_D$ −64° (*c*, 1·0), ν_{max} 3610, 3484 (OH), 1745 and 1241 cm^{-1} (OAc). (Found: C, 70·4; H, 9·4; F, 3·9. $C_{29}H_{45}O_5F$ requires: C, 70·7; H, 9·2; F, 3·9%.) The residues (398 mg) from the fraction which afforded the fluorohydrin were dissolved in dioxan (5 ml) and treated with 2,3-dichloro-5,6-dicyano-benzoquinone (400 mg) for 18 hr at 20°. The resulting solution was poured into ether and washed with NaOH aq. The product was adsorbed onto alumina (40 g), from which benzene–ether eluted the $\Delta^{18(17a)}$-*aldehyde* (XIIIc; 90 mg), which crystallized from MeOH m.p. 197–199°, $[\alpha]_D$ −41° (*c*, 0·98), ν_{max} 2740 (CHO), 1742, 1241 (OAc), and 1689 cm^{-1} (C:C·CHO), λ_{max} 257 mμ (ε 12,650). (Found: C, 73·6; H, 8·9. $C_{30}H_{42}O_5$ requires: C, 74·0; H, 9·0%.) A further quantity of XVa was eluted from the column by means of ether (total yield 590 mg).

The 3,18-*diacetate* was prepared from XVa by reaction with acetic anhydride–pyridine at 20° for 18 hr. It was an oil, $[\alpha]_D$ −55° (*c*, 1·18) ν_{max} 1760, 1745 and 1235 cm^{-1}.

The 3-*acetate*-18-*benzoate*, prepared by reaction of the fluorohydrin with benzoyl chloride–pyridine, was also an oil, $[\alpha]_D$ −52° (*c*, 0·87) ν_{max} 1733, 1269, and 1242 cm^{-1}.

Alkaline hydrolysis of fluorohydrin (XVa). The fluorohydrin (50 mg), KOH (50 mg) and aq. EtOH (10 ml) were heated under reflux for 2 hr, giving the 3β-*hydroxy-fluorohydrin* which crystallized from MeOH as needles, m.p. 258–259°, $[\alpha]_D$ −63° (*c*, 0·77), ν_{max} (CH_2Cl_2) 3610 cm^{-1}. (Found: C, 71·6; H, 9·2; F, 4·0. $C_{27}H_{43}O_4F$ requires: C, 72·0; H, 9·6; F, 4·2%.)

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

Reaction of the 17aβ,18-*epoxide* (XI) *with* BF_3 *in ether.* The epoxide (1·97 g) in ether (200 ml) was treated with BF_3-etherate (2 ml) for 90 min, then the product was isolated and separated by chromatography as above to give the cyclic ether (XIV?; 769 mg), m.p. and m.m.p. 209–211°, and the 18-hydroxy-$\Delta^{18(17a)}$-olefin (XIIIa; 1·17 g), m.p. and m.m.p. 204–206°.

Rearrangement of 17aβ,18-*epoxide* (XI) *with perchloric acid.* The epoxide (500 mg) in CH_2Cl_2 (16 ml) and acetone (32 mg) was treated with aq. perchloric acid (1·5 M; 0·5 ml) for 10 min at 20°. The product, which crystallized from light petroleum, was the 18-hydroxy-$\Delta^{18(17a)}$-olefin (XIIIa; 332 mg), m.p. and m.m.p. 202–206°, identical in all respects with the sample obtained from the α-epoxide (above).

Conversion of the 18-*hydroxy-olefin* (XIIIa) *into the* $\Delta^{18(17a)}$-*olefin* (I). The 18-hydroxy-olefin (200 mg) in acetic anhydride (0·4 ml) and pyridine (4 ml) was kept at 20° for 18 hr, and the product was isolated by use of ether. Crystallization from light petroleum gave the 3β,18-*diacetoxy*-$\Delta^{18(17a)}$-olefin (XIIIb) as needles, m.p. 159–163°, $[\alpha]_D$ −48° (*c*, 0·87), ν_{max} 1745 and 1239 cm^{-1}. (Found: C, 72·3; H, 9·3. $C_{31}H_{46}O_6$ requires: C, 72·3; H, 9·0%.)

The 3,18-diacetate (60 mg) in ethylamine (20 ml) was stirred during the addition of small pieces of Li until there was a permanent blue colour in the solution (45 min). After a further 30 min

stirring solid NH_4Cl was added followed by ether and water, and the residue, after washing and evaporating the ether, was treated with acetic anhydride–pyridine for 18 hr. The product, isolated by use of ether, was the $\Delta^{18(17\alpha)}$-olefin (35 mg), m.p. 141–145° after crystallization from MeOH. The identity was confirmed by m.m.p. and comparison of IR spectra.

Hydroxylation of the 17a,18-*olefin with osmic acid.* A solution containing the exocyclic olefin (0·5 g), osmium tetroxide (0·5 g), pyridine (0·3 ml), benzene (12·5 ml) and dioxan (20 ml) was left at room temp for 6 days, then stirred during the addition of $Na_2S_2O_5$ (2 g) in water (30 ml) and pyridine (35 ml). The clear orange solution obtained after 1 hr was diluted with water and the product was extracted by use of $CHCl_3$ and adsorbed onto alumina (20 g). Elution with light petroleum–benzene (1:1) gave unreacted olefin (80 mg). Ether then eluted the 3β-*acetoxy*-17aα,18-*diol* (410 mg), m.p. 126–128° (needles from hexane), $[\alpha]_D$ −33° (*c*, 1·132), ν_{max} 3558, 3448, 1742, and 1244 cm^{-1}. (Found: C, 70·8; H, 9·4. $C_{29}H_{46}O_6$ requires: C, 71·0; H, 9·45%.)

Acetylation of the 17aα,18-*diol* (XVb). The diol (300 mg) in pyridine (2 ml) was treated with acetic anhydride (0·3 ml) at 20° for 18 hr and the product was isolated by use of ether. Crystallization from MeOH gave the 3β,18-*diacetate* as needles, m.p. 218–219°, $[\alpha]_D$ −22° (*c*, 0·90), ν_{max} 3584, 1742 and 1242 cm^{-1}, (Found: C, 70·1; H, 9·3. $C_{31}H_{48}O_7$ requires: C, 69·9; H, 9·1%.)

The 18-acetate (200 mg) in pyridine (10 ml) was treated at −40° with $SOCl_2$ (0·2 ml). The solution was allowed to come to room temp over 15 min then poured into water and the product extracted with pentane. Chromatography of the product on deactivated alumina and elution with light petroleum–benzene (2:1) gave the *enol acetate* (XVI) of the 18-aldehyde as an oil (158 mg), $[\alpha]_D$ −60° (*c*, 1·54), ν_{max} 1763, 1742, 1242 and 1219 cm^{-1}.

Hydrolysis of this enol acetate (80 mg) in aq. EtOH (10 ml) with KOH (300 mg) gave XI (60 mg), m.p. and m.m.p. 168–167°, $[\alpha]_D$ −47·5° (*c*, 1·03), IR spectrum identical with previous sample.

Reduction of the 18-*aldehyde to give the* 17aα-*methyl derivative* (XVIIa). The 18-aldehyde (250 mg) and hydrazine hydrate (60%; 1·5 ml) were heated in ethane diol (10 ml) at 120° for 1 hr, then KOH (1 g) was added and the solution was heated up to 200° in a slow stream of N_2 and kept at 200° for 2 hr. The product, isolated by use of ether, was treated with acetic anhydride (0·2 ml) in pyridine (10 ml) at 100° for 30 min. The product crystallized from MeOH to give the 17aα-*methyl compound* (180 mg) as needles, m.p. 154–155°, $[\alpha]_D$ −60° (*c*, 0·85), ν_{max} 1742 and 1242 cm^{-1}, (Found: C, 75·6; H, 10·3. $C_{29}H_{46}O_4$ requires: C, 75·9; H, 10·1%.)

Preparation of the 17aβ-*methyl isomer* (XVIIb). The $\Delta^{17a(18)}$-olefin (250 mg) in acetic acid (10 ml) was hydrogenated at atm. press. over a Pd–C catalyst (10%:150 mg) for 7 hr. The filtered solution was evaporated to dryness at 20 mm and the residue crystallized from MeOH to give the 17aβ-methyl compound (222 mg) m.p. 175–176°, $[\alpha]_D$ −49·5° (*c*, 1·07), ν_{max} 1742 and 1242 cm^{-1} (Lit:[7] m.p. 179–181°, $[\alpha]_D$ −112°). (Found: C, 75·5; H, 10·1. $C_{29}H_{46}O_4$ requires: C, 75·9; H, 10·1%.)

Acknowledgements—The authors thank Glaxo Laboratories Ltd for a generous gift of hecogenin acetate. Acknowledgement is made to the Research Committee of the New Zealand Universities Grants Committee for grants and for a Research Fund Fellowship to one of us (J. M. C.).

[7] W. F. Johns, *J. Org. Chem.* **29**, 2545 (1964).