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REACTIONS OF EPOXIDES—XVIII[1]

THE PREPARATION AND SOME REACTIONS OF 11,12-EPOXY DERIVATIVES OF 12-METHYL-TIGOGENIN AND TIGOGENIN

J. M. COXON and M. P. HARTSHORN
Department of Chemistry, University of Canterbury, Christchurch, New Zealand

and

D. N. KIRK
Department of Chemistry, Westfield College, London, N.W.3

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Abstract—The 11α,12α-epoxy-, 11β,12β-epoxy- and 12β-methyl-11α, 12α-epoxy- derivatives of tigogenin acetate rearrange on treatment with BF_3-etherate to give products among which are C-nor-D-homo compounds.

HECOGENIN acetate reacts with methyl magnesium bromide to give largely the 12α-hydroxy-12β-methyl compound (I; ca. 87%) contaminated with other products including a trace of the $C_{(12)}$ epimer (II). Dehydration of the 12α-hydroxy-12β-methyl compound (I) with thionyl chloride-pyridine gave the Δ^{11}-olefin (III) resulting from the favourable *anti*-elimination. The Δ^{11}-olefin was identified by comparison of its physical constants with the literature data, and from its NMR spectrum which revealed the structural features $\diagdown C{=}C{-}CH_3$ (δ = 1·61 ppm) and $-CH{=}C\diagup$ (δ = 5·12 ppm).

Reaction of 12-methyl-Δ^{11}-tigogenin acetate with monoperoxyphthalic acid gave the 11α,12α-epoxy-12β-methyl compound (IV) (ca. 70% yield). There was no evidence for the formation of any isomeric 11β,12β-epoxide. The configuration of epoxide (IV) was established by its reduction to the known 12α-hydroxy-12β-methyl compound (I). The reduction of the epoxide was not complete even after heating under reflux with $LiAlH_4$ in ether for 10 hr. This is consistent with the known steric hindrance to attack at $C_{(11)}$ of the steroid nucleus. The epoxide configuration was confirmed from the NMR spectrum, which showed the 11β-hydrogen as a sharp singlet at δ = 2·68. A Dreiding model shows the dihedral angle between the 9αH and 11βH to be ca. 90°, consistent with a coupling constant near to zero.

The unsubstituted 11α,12α-epoxide was prepared by epoxidation of the known Δ^{11}-olefin (V) with monoperoxyphthalic acid. The reaction gave only the known 11α,12α-epoxide (VI). The 11β and 12β protons of the α-epoxide showed an AB quartet (δ_A 2·93, δ_B 2·86, J_{AB} = 4 c/s). As with the 12β-methyl-11α,12α-epoxide there was no coupling of the 11β-H with the 9α-H, consistent with a dihedral angle of ca. 90° in a Dreiding model of the epoxide (VI).

The 11β,12β-epoxide (VII) was kindly provided by Glaxo Research Limited.

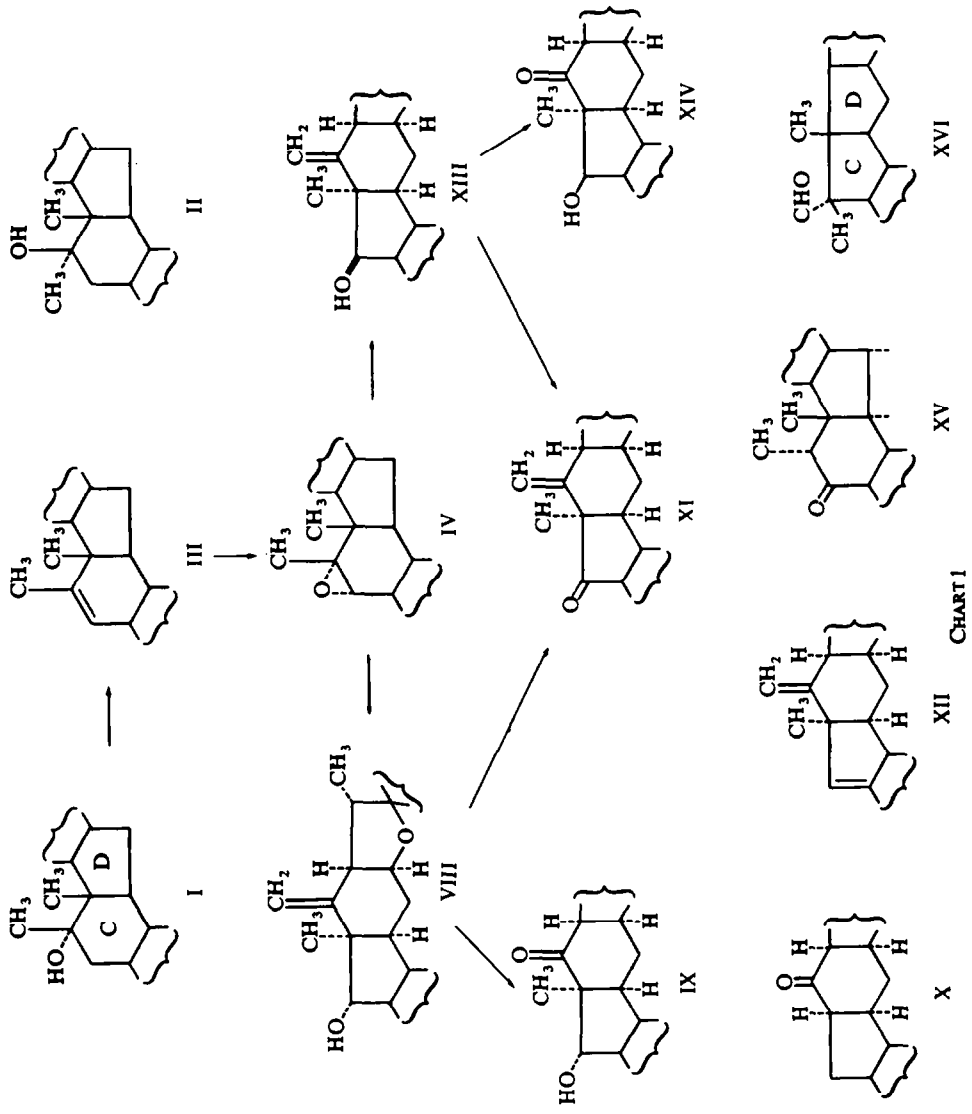

CHART I

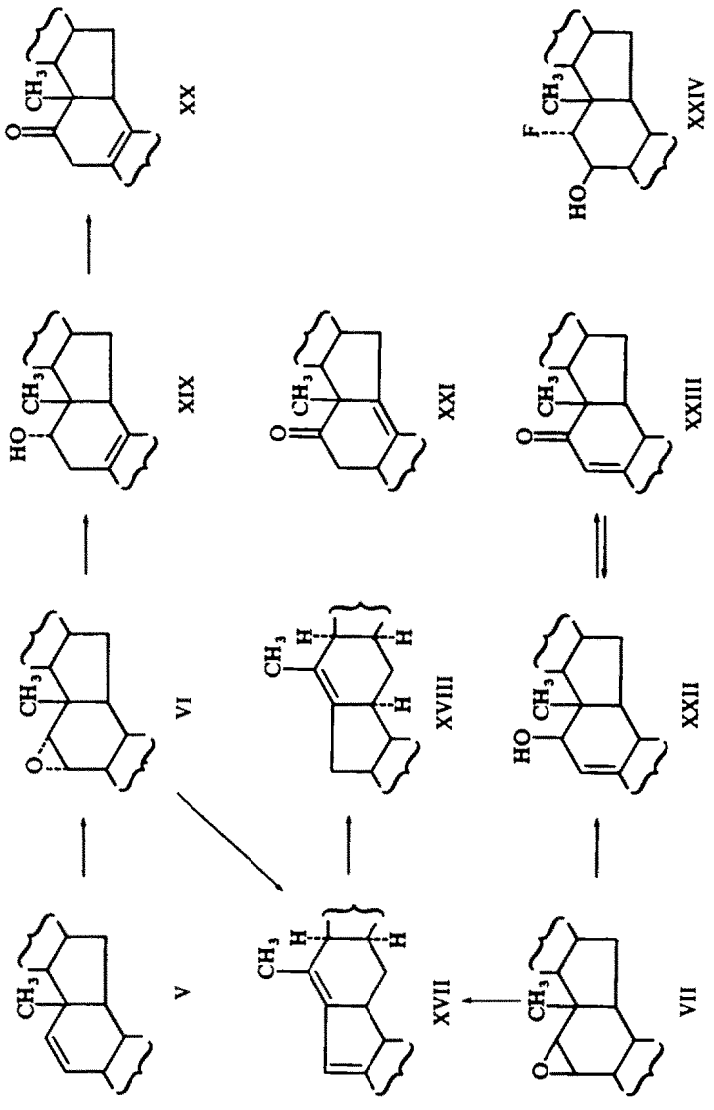

CHART 2

TABLE 1. NMR SPECTRA* (δ, PPM; "APPARENT" J-VALUES IN PARENTHESES)

Compound	Methyl groups				Other protons
	$C_{(18)}$	$C_{(19)}$	$C_{(21)}$	$C_{(27)}$	
11-ene (V)	0·79	0·79	0·96 (6·5)		
12-methyl-11-ene (III)	0·87	0·77	1·06 (7)	0·79 (5)	12-CH_3, 1·61; 11-H, 5·12 (s)
11α,12α-epoxide (VI)	0·90†	0·87†	1·00 (6·5)	0·75 (5·5)	
12β-methyl-11α,12α-epoxide (IV)	0·85	0·85	1·03 (6)	0·74 (5)	12-CH_3, 1·20; 11-H, 2·68 (s)
12α-methyl-11-ketone (XV)	0·80	1·07	0·94 (7)		12α-CH_3, 1·17 (6)
11-methyl-C-nor-aldehyde (XVI)	0·79	0·87	1·01 (7)	0·79 (5)	11-CH_3, 0·87; 11-CHO, 9·72 (1·5)
13α-H, C-nor-D-homo-17a(18)-ene	—	0·80	1·09 (7)	0·81 (5)	18-CH_2, 4·85
11α-OH, 13α-Me, C-nor-D-homo-17a(18)-ene (VIII)	—	0·93	1·12 (6·5)	0·83 (5)	13α-CH_3, 1·07; 18-CH_2, δ_A 4·88, δ_B 5·06, J_{AB} = 2
11α-OAc, 13α-Me, C-nor-D-homo-17a(18)-ene (VIII; 11α-OAc)	—	0·93	1·10 (6)	0·81 (5)	13α-CH_3, 1·11; 18-CH_2, δ_A 4·82, δ_B 5·19, J_{AB} = 2; 11β-H, 5·45 (10)
11-oxo, 13α-Me, C-nor-D-homo-17a(18)-ene (XI; 3β-OH)	—	0·87	1·03 (7)	0·76 (5)	13α-CH_3, 1·22; 18-CH_2, 4·87
13α-Me, C-nor-D-homo-9(11), 17a(18)-diene (XII)	—	0·97	1·07 (7)	0·80 (5)	13α-CH_3, 1·16; 18-CH_2; 4·75 (2); 11-H, 5·10
11β-OH,13α-Me, C-nor-D-homo-17a(18)-ene (XIII)	—	1·03†	1·12 (7)	0·79 (5·5)	13α-CH_3, 1·07†; 18-CH_2, δ_A 4·94, δ_B 5·08, J_{AB} = 2·5; 11β-H, 4·11 (2)
12α-hydroxy-8-ene (XIXa)	0·84	1·03	0·93 (7)	0·78 (5)	12β-H, 3·47
12α-acetoxy-8-ene (XIXb)	0·90	1·03	0·88 (6)	0·79 (5)	12β-H, 4·83
8-en-12-one (XX)	1·23	1·07	1·11 (7)	0·78 (5)	11-CH_2, 2·36 (s)
C-nor-D-homo-9(11), 13(17a)-diene (XVII)	—	1·00	1·14 (7)	0·78 (5)	17a-CH_3, 1·78; 11-H, 5·87 (3·5)
12β-hydroxy-9(11)-ene (XXII)	0·70	1·00	1·03 (6)	0·78 (5·5)	11-H, 5·17 ($W_{\frac{1}{2}}$ = 4); 12α-H, 3·99 ($W_{\frac{1}{2}}$ = 5)

* Determined at 60 mc/s in $CDCl_3$ relative to TMS. Spectra are for 3β-OAc derivatives unless otherwise indicated.

† These methyl-group assignments are tentative, and may need to be interchanged.

BORON TRIFLUORIDE-CATALYSED REARRANGEMENT OF THE EPOXIDES

12β-Methyl-11α,12α-epoxide

Reaction of the 12β-methyl-11α,12α-epoxide (IV) with BF_3-etherate in benzene was complete in 1 hr (t.l.c.). Crystallization of the reaction mixture gave a hydroxy-olefin, identified on the following evidence as 3β-acetoxy-11α-hydroxy-13α-methyl-C-nor-D-homo-5α,25D-spirost-17a (18)-ene(VIII). The presence of a five-membered ring alcohol was demonstrated by oxidation with "Jones reagent", and subsequent hydrolysis of the 3-acetate, to give a five-membered ring ketone (XI), ν_{max} 1740 cm^{-1}. Acetylation of the alcohol (VIII) was effected by heating for 5 hr at 100° with acetic anhydride-pyridine. The $C_{(3)}$-OAc and $C_{(11)}$-OAc gave a six-proton peak at $\delta = 2{\cdot}0$ ppm in the NMR spectrum. The presence of an exocyclic double bond in the hydroxy-olefin was indicated by the UV spectrum ($\varepsilon_{205} = 2960$), the IR spectrum (ν_{max} 1640 cm^{-1}), and by a 2–H multiplet in the NMR spectrum (δ_A 4·88, δ_B 5·06 $J = |2|$). Hydrolysis of the 3β-acetate in compound (VIII) followed by ozonolysis and cleavage of the ozonide with zinc-acetic acid gave a six membered ring ketone (IX), ν_{max} 1710 cm^{-1}. The Cotton curve ($a = +38{\cdot}5$) for this ketone supports the 13α-CH_3 configuration of the hydroxy-olefin (VIII). We earlier reported the Cotton curve ($a = -29$) for the 13α-H-C-nor-D-homo-ketone (X).[3] Examination of a Dreiding model indicates a major positive contribution to the Cotton effect from the *pseudo*-axial 13α-CH_3 (Fig. 1), in agreement with the observed increment of +67. The ORD

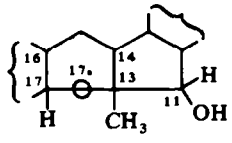

FIG. 1

curve for the 11-oxo-$\Delta^{17a(18)}$-olefin (XI) ($a = -5$) is more difficult to interpret since little is known about βγ-unsaturated ketones when the olefin and ketone are in a *cis*-relationship.

Dehydration of the hydroxy-olefin (VIII) with thionyl-chloride/pyridine gave a non-conjugated diene (UV spectrum) assigned the structure (XII). The NMR spectrum of the diene showed the structural features —CH=C< ($\delta = 5{\cdot}10$ ppm) and >C=CH_2 (δ 4·65; $J_{AB} = |2|$).

Spin-decoupling experiments on the NMR spectrum of the hydroxy olefin (VIII) added support to the structure. The 11β-H signal ($\delta = 4{\cdot}07$ ppm, doublet, $J = 8$ c/s) collapsed to a singlet on irradiating the 9α-H at $\delta = 1{\cdot}165$ ppm. The allylic 17α-H appeared as a triplet centred at δ 2·82 ppm. This signal was decoupled by irradiation at −78 c/s (i.e. the 16α-H, centred at $\delta = 4{\cdot}12$ ppm) and at +62 c/s (the 20β-H, centred at δ 1·78 ppm), in each case giving a doublet, $J = 10$ c/s. The $C_{(21)}$-methyl doublet, centred at $\delta = 1{\cdot}115$, also collapsed, on irradiation of 20β-H, to give a singlet. Only one allylic proton could be found in the spectrum, confirming that the exocyclic double bond is adjacent to one secondary position.

The mother liquors after crystallization of compound (VIII) were chromatographed on alumina, and gave four compounds. The first compound eluted is believed to be 3β-acetoxy-11β-hydroxy-13α-methyl-C-nor-D-homo-5α,25D-spirost-17a,(18)-ene (XIII) (i.e. the $C_{(11)}$-epimer of VIII). When the secondary alcohol was oxidised with "Jones reagent", the resulting ketone was identical in all respects with the ketone (XI) derived from the 11α-hydroxy isomer (VIII). It did not prove possible to effect more than partial acetylation of the 11β-hydroxyl group; vigorous reaction conditions (reflux with acetic anhydride-pyridine) ruptured the spiroketal side chain. The presence of a double bond ($\rangle C{:}CH_2$), exocyclic to a six-membered ring, was shown by the IR spectrum (ν_{max} 1622 cm^{-1}) and by a 2-H multiplet in the NMR spectra (δ_A 4·94, δ_B 5·08, $J = |2{\cdot}5|$). After hydrolysis of the 3-acetoxy group, ozonolysis of compound (XIII), and cleavage of the ozonide with zinc-acetic acid gave a six-membered ring ketone (XIV), ν_{max} 1721 cm^{-1}. The Cotton curve for this compound ($a = +50$) was similar to that obtained for the 11α-hydroxy-17a-ketone (IX). The 11β-assignment was confirmed from the 11α-H signal ($\delta = 4{\cdot}11$ ppm, doublet, $J = 2$ c/s) in the NMR spectrum of (XIII). This was decoupled to a singlet by irradiating the 9α-H ($\delta = 1{\cdot}29$ ppm).

A Dreiding model of the hydroxy-olefin (XIII) shows that the 9α,11α dihedral angle is ca. 50°, explaining the small J-value. This is in contrast with the 11α-epimer (VIII) where the dihedral angle is ca. 170°, giving the larger coupling of 8 c/s. The 11β-compound (XIII), like the 11α-isomer, showed only one allylic proton at $C_{(17)}$, as a triplet centred at $\delta = 2{\cdot}62$ ($J = 10$, $J' = 10$). The 17α-H signal was reduced to a doublet by irradiating either the 16α-proton, centred at 3·96 ppm, or the 20β-H, centred at ca. 1·85 ppm.

Dehydration of the 11β-hydroxy olefin (XIII) was inefficient. Thionyl chloride/pyridine gave a mixture, with an NMR spectrum showing the following structural features: $\rangle C{=}C(H)\langle$ ($\delta = 5{\cdot}14$ ppm), $\rangle C{=}CH_2$ (δ 4·72 ppm). The methyl region of the spectrum suggested a mixture of compounds.

Further chromatography of the mixture derived from the epoxide (IV) gave the 12α-methyl-11-ketone (XV), thought to be derived via a stereospecific hydride shift from $C_{(11)}$ to $C_{(12)}$. The presence of the 6-membered ring ketone was shown by the IR spectrum (ν_{max} 1712 cm^{-1}). The axial conformation of the 12α-methyl group was demonstrated by the NMR spectrum, which showed a shift of the $C_{(12)}$-CH_3 from

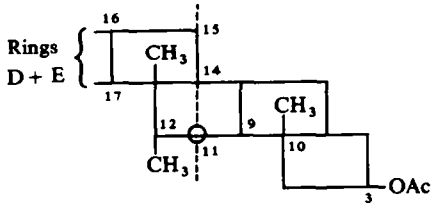

FIG. 2

δ = 1·17 ppm (J = 6 c/s) in $CDCl_3$ to δ = 1·015 ppm (J = 6 c/s) in benzene.[4] The ketone gave a negative Cotton curve (a = −21). The increment of −55 for the introduction of the 12α-methyl into 11-oxo-tigogenin 3-acetate (a + 34) confirms the 12α-methyl configuration (Fig. 2).

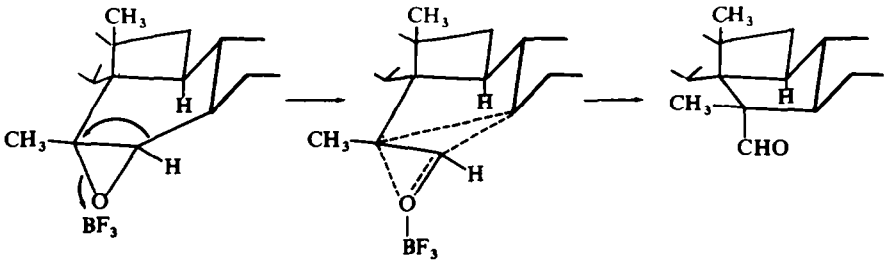

FIG. 3

The final product from the epoxide rearrangement was a C-nor-aldehyde (XVI). The aldehyde was identified from its IR (ν_{max} 2720 cm^{-1}) and NMR spectra (δ = 9·72 ppm; J = 1·5 c/s). It was not possible to establish unequivocally the configuration of the —CHO group. If it is formed by concerted attack of the 9(11) bond upon $C_{(12)}$, involving inversion at $C_{(12)}$ with rupture of the $C_{(12)}$—O bond (cf. Fig. 3), the —CHO group would have the α-configuration (XVI). The tertiary aldehyde proton exhibiting J = 1·5 indicates that there is a preferred conformation of the —CHO group, allowing long range coupling. The Cotton effect (a = −40) is too small to interpret.

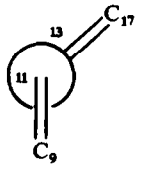

FIG. 4

11α,12α-*Epoxide* (VI)

Reaction of the 11α,12α-epoxide with boron trifluoride etherate in dry benzene was complete (TLC) in 1 hr. The reaction mixture consisted of two compounds, which were separated by chromatography on alumina. The least polar compound was the C-nor-D-homo $\Delta^{9(11),13(17a)}$-diene (XVII) (ca. 40%). The UV spectrum showed it to be a conjugated diene (λ_{max} 253 nm). The NMR spectrum revealed the structural features —C=CH— (δ = 5·87 ppm; $W_{\frac{1}{2}}$ = 3·5 c/s) and —C=C—C=C—CH_3 (δ = 1·78). The 16α-proton gave a multiplet (δ = 4·26 ppm; $W_{\frac{1}{2}}$ = 30 c/s), the width agreeing with data for the corresponding $\Delta^{13(17a)}$-olefin (XVIII), where spin–spin coupling has been demonstrated with the 15α-, 15β- and 17α-protons.[5] Three allylic protons (9α, 14α and 17α) account for the spectrum integral between δ = 2·25 and 3·00 ppm. The ORD curve showed a strong negative Cotton effect, (a, −540) consistent with a diene skewed in the sense of Fig. 4.[6]

A Dreiding model confirms the direction of twist of the diene. Catalytic hydrogenation of the diene, over a palladium-calcium carbonate catalyst, caused absorption of only one molar proportion of hydrogen, and gave the known $\Delta^{13(17a)}$-unsaturated compound (XVIII).

The second compound (53%) from the rearrangement of the 11α,12α-epoxide (VI) has been assigned the 12α-hydroxy-$\Delta^{8(9)}$ olefinic structure (XIX) on the following evidence. The compound contained a hydroxyl group (IR) and gave a positive test for double bond character with tetranitromethane. The end-absorption in the UV (ε_{196nm} = 12,050) and absence of olefinic protons in the NMR spectrum indicated a tetra-substituted double bond. The NMR spectrum also showed three protons in the region δ = 4·0–5·0 ppm (3α,16α and 12β-protons) and five in the region δ = 2·1–3·0 ppm (7α,β,11α,β and 14α-protons). The alcohol could be acetylated. Oxidation gave a compound (XX) having UV absorption characteristic of a β,γ-unsaturated ketone[7] (ε_{300nm} = 303; ε_{210} = 4000) and the Cotton curve (a = +80) is consistent with the $\Delta^{8(9)}$-structure but not with the alternative $\Delta^{8(14)}$-isomer (XXI).

The NMR spectrum of this enone showed the $C_{(11)}$-methylene as a sharp singlet at δ = 2·36 ppm.

11β,12β-*Epoxide.* The reaction between the 11β,12β-epoxide (VII) and BF_3-etherate in benzene was followed polarimetrically. The $[\alpha]_D$ value changed from ca. −35° to ca. −120° in 15 min, then decreased over 1 hr to −70°. A reaction mixture worked up after 15 min, followed by chromatography, gave the C-nor-D-homo-$\Delta^{9(11),13(17a)}$-diene (XVII; 57%), and the 12β-hydroxy-9(11)-ene (XXII) (ca. 20%) as major products. The structure of the latter compound followed from its oxidation to give the known 9(11)-en-12-one[8] (XXIII). It was regenerated by reduction of the ketone (XXIII) with sodium borohydride.

The residues after isolation of the two compounds (XVII) and (XXII) were rechromatographed, and gave a second hydroxy compound (ca. 5%). The mass spectrum indicated mol.wt. 492, corresponding to a fluorohydrin, so the compound is tentatively formulated as 12α-fluoro-11β-hydroxytigogenin acetate (XXIV). Oxidation gave a ketone, ν_{max} 1721 cm^{-1} after hydrolysis of the 3-acetate. The compound was not examined further. A third hydroxy-compound evident on TLC plates between the fluorohydrin and the 12β-hydroxy-9(11)-ene could not be obtained pure.

DISCUSSION

The rearrangement products from the 12β-methyl-11α,12α-epoxide (IV) all result from the cleavage of the tertiary $C_{(12)}$—O bond. The major product, the 13α-methyl-C-nor-D-homo-olefin (VIII), being formed with retention of configuration at $C_{(12)}$, must arise by the rearrangement of the discrete carbonium ion (Fig. 5). The formation of the 11β-hydroxy isomer (XIII) represents inversion at $C_{(11)}$, and is, to the best of

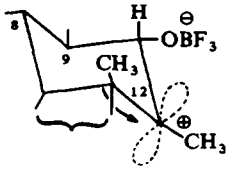

FIG. 5

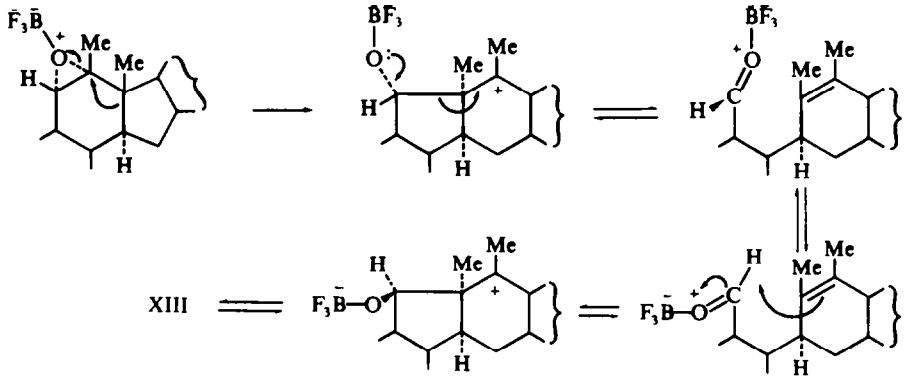

FIG. 6

our knowledge, unprecedented. We can only speculate at present upon the mechanism of inversion. One possibility involves rupture and re-closure of the $C_{(11)}$–$C_{(13)}$ bond (Fig. 6), which would be dependent upon the intermediacy of a species with the carbonium ion centre and the —OBF_3^- group in a 1,3-relationship. Experiments are in progress to test this hypothesis, and perhaps find other examples of hydroxyl inversion in similar situations. A separate experiment confirmed that the 11β-OH compound (XIII) largely reverts to the 11α-OH isomer in the presence of BF_3, suggesting that the C-seco intermediate may represent the principle pathway for rearrangement of the epoxide.

The major products from the rearrangements of the 11α,12α- (VI) and 11β, 12β-epoxides (VII) clearly arise by mechanisms involving "axial cleavage",[9] that is, cleavage of the $C_{(11)}$-O bond for (VI) and the $C_{(12)}$-O bond for (VII). An apparent exception is the formation of the C-nor-D-homo-diene (XVII) from the 11α,12α-epoxide (VI), probably *via* rearrangement of a $C_{(12)}$-carbonium ion as the key step.

The 12α-hydroxy-8(9)-ene seems likely to arise from the 11α,12α-epoxide by a "1,3" hydride shift (8β → 11β) of the type demonstrated for a 9β,11β-epoxide, which gave the 11β-hydroxy-8(14)-ene.[10] The concerted hydride shift is stereoelectronically favourable (Fig. 7), whereas loss of the *cis*-9α-H would require a fully-developed carbonium ion at $C_{(11)}$. The 11α,12α-epoxy derivative of oleanolic acid has been reported as giving the 12-ketone[11]: here the 8β-CH_3 precludes a hydride shift from 8β → 11β.

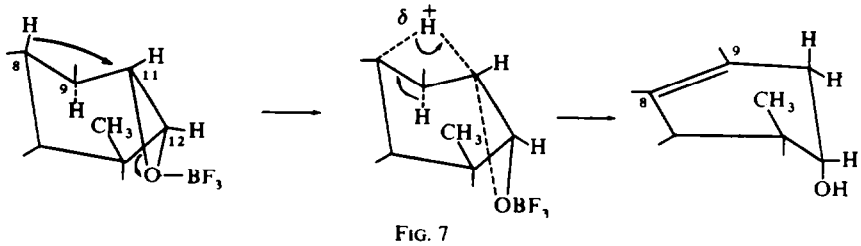

FIG. 7

The *trans* relationship of the 9α-H to the 11β,12β-epoxide permits elimination to give the 12β-hydroxy-9(11)-ene, even though this minor product represents "equatorial cleavage" of the epoxide.

EXPERIMENTAL

Rotations were measured in $CHCl_3$ solutions at room temperature. IR spectra were recorded for CS_2 solutions, and the UV spectra for methanol solutions. 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. Light petroleum refers to the fraction b.p. 40–60° or 50–70°. ORD curves (in MeOH) were kindly determined by Professor W. Klyne.

Preparation of the 12-*methyl*-11α,12α-*epoxide* (IV)

3β-Acetoxy-12-methyl-5α,25D-spirost-11,12-ene (24 g) in dry chloroform (800 ml) was treated with an ethereal solution of monoperphthalic acid (0·65M: 450 ml) and the resulting solution was kept at 20° for 12 hr. The steroidal material isolated by means of ether was crystallised from methanol to give the 12β-*methyl*-11α,12α-*epoxide* as needles (17 g), m.p. 204–205°; $[\alpha]_D$ −52° (*c*, 1·0), ν_{max} 1742 and 1242 cm^{-1} (Found: C, 73·6; H, 9·5; $C_{30}H_{46}O_5$ requires: C, 74·0; H, 9·5%).

Preparation of the 11α,12α-*epoxide* (VI)

The 11(12)-dehydro-derivative of tigogenin acetate (2 g) in dry ether (25 ml) was treated with an ethereal solution of monoperphthalic acid (0·60M; 50 ml) at 20° for 24 hr. The steroidal material isolated by means of ether was crystallized from methanol to give the 11α,12α-epoxide as plates (1·6 g), m.p. 221–223°, $[\alpha]_D$ −39° (*c*, 0·61) (Lit.[12] m.p. 221–225, $[\alpha]_D$ −49·5°).

Reaction of the 12β-*methyl*-11α.12α-*epoxide* (IV) *with* BF_3

A solution of the 12-methyl-11α,12α-epoxide (2 g) in anhydrous benzene (200 ml) was treated with BF_3-etherate (2 ml) at 20° for 1 hr. The crude product, isolated by means of ether, crystallized from light petroleum to give the 11α-*hydroxy*-13α-*methyl*-C-*nor*-D-*homo*-17a(18)-*ene* (VIII) as needles, (240 mg), m.p. 223–224°, $[\alpha]_D$ −54° (*c*, 1·06), ν_{max} 3520, 1720, 1640 and 1270 cm^{-1} (Nujol mull), UV: ε_{205} = 2960. (Found: C, 73·8; H, 9·5 $C_{30}H_{46}O_5$ requires: C, 74·0; H, 9·5%).

The residue was adsorbed on alumina (150 g). Elution with light-petroleum–benzene mixtures (10:1) gave the 11β-*hydroxy*-13α-*methyl*-C-*nor*-D-*homo*-17a(18)-*ene*(XIII) (280 mg) which crystallized from acetone as needles, m.p. 162–163°, [α] −50° (*c*, 0·89), ν_{max} 3587, 1740, 1622 and 1245 cm^{-1}; ε_{200} = 6445, ε_{205} = 4143; ε_{210} = 1565; ε_{220} 184 (Found: C, 74·0; H, 9·4. $C_{30}H_{46}O_5$ requires: C, 74·0; H, 9·5%).

Elution with light petroleum–benzene (1:1) gave the 12α-*methyl*-11-*ketone* (XV), (320 mg) needles from methanol, m.p. 194–195°, $[\alpha]_D$ −49° (*c*, 0·88), ν_{max} 1742, 1242, and 1712 cm^{-1} (six membered ring ketone). ORD: $[\phi]_{312}$ −1110°, $[\phi]_{276}$ +950°, $[\phi]_{222}$ ±0°. (Found: C, 74·0; H, 9·7. $C_{30}H_{46}O_5$ requires: C, 74·0; H, 9·5%).

Further elution with light petroleum–benzene (1:1) gave the 11β-*methyl*-11α-*formyl*-C-*nor* compound (XVI) (420 mg), which crystallized from methanol as needles m.p. 178–180°, $[\alpha]_D$ −85° (*c*, 0·70), ν_{max} 2735 (CHO), 1730 and 1245 cm^{-1}. ORD: $[\phi]_{326}$ −3150°, $[\phi]_{279}$ +860°, $[\phi]_{213}$ −1560°. (Found: C, 73·9; H, 9·4. $C_{30}H_{46}O_5$ requires: C, 74·0; H, 9·5%).

Further elution with benzene and benzene–ether mixtures gave a further sample of the 11α-*hydroxy*-13α-*methyl*-C-*nor*-D-*homo*-17a(18)-*ene* (VIII) (440 mg), m.p. 223–224°.

ORD data for 11-*oxotigogenin*. $[\phi]_{317}$ +390°, $[\phi]_{273}$ −1310°, $[\phi]_{214}$ ±0°; 11-Oxo-tigogenin acetate: $[\phi]_{316}$ +720°, $[\phi]_{268}$ −2700°, $[\phi]_{250}$ −2300°.

Reactions of the 11α-*hydroxy*-13α-*methyl*-C-*nor*-D-*homo*-17a(18)-*ene* (VIII)

(1) *Acetylation*. A solution of hydroxy-olefin (VIII) (20 mg) in acetic anhydride (0·1 ml) and pyridine (1 ml) was heated at 100° for 3 hr. Isolation of the steroidal material gave gum, ν_{max} 1740, 1250 cm^{-1} (no absorption at 3500 cm^{-1}); TLC showed none of the 11α-hydroxy compound.

(2) *Oxidation*. To a solution of the hydroxy-olefin (VIII) (200 mg) in acetone (10 ml) was added Jones Reagent, and the solution was kept at room temperature for 20 min. Isolation of the steroidal material in the usual manner gave the 11-ketone (XI) as an oil (179 mg) ν_{max} 1740, 1250 cm^{-1} (no absorption at 3500 cm^{-1}). Hydrolysis of this material with sodium hydroxide (200 mg) in 95% methanol (20 ml) at room temperature for 18 hr, and isolation in the usual manner, and crystallization from aq. methanol gave the 3β-*hydroxy*-13α-*methyl*-C-*nor*-D-*homo*-17a(18)-*en*-11-*one* (XI), (105 mg) as chunky crystals, m.p. 115–116°, $[\alpha]_D$ −51° (*c*, 0·92), ν_{max} 3640, 1740 cm^{-1} (five-membered ring ketone). UV: λ_{max} 300 nm (ε 71·4). ε_{196} = 7129, ε_{200} = 5347, ε_{205} = 3279, ε_{210} = 2139, ε_{215} = 1141, ε_{220} = 570. ORD: $[\phi]_{328}$ −3060°, $[\phi]_{289}$ +2360°, $[\phi]_{240}$ ±0°. (Found: C, 76·0; H, 9·6. $C_{28}H_{42}O_4$ requires: C, 76·0; H, 9·6%).

(3) *Hydrolysis and ozonolysis*. The hydroxy-olefin (VIII) (50 mg) in methanol (5 ml) was treated with

aqueous sodium hydroxide (50 mg NaOH, 1 ml H_2O) at room temperature overnight. The unsaturated diol, isolated in the usual manner, was dissolved in chloroform (10 ml) and a stream of ozone was passed through the solution for 30 min. The solution was evaporated to dryness under reduced pressure at room temperature, and the resulting ozonide was stirred with zinc powder (A.R., 100 mg) in acetic acid (5 ml) for 24 hr. Isolation of the steroidal material gave an oil (32 mg), ν_{max} 3610, 3460 (OH), 1710 cm^{-1} (six-membered ring ketone). ORD: $[\phi]_{310}$ +550°, $[\phi]_{270}$ −3300°, $[\phi]_{251}$ −1650°, $[\phi]_{222}$ −4500°.

(4) *Dehydration.* A solution of hydroxy-olefin (VIII) (200 mg) and thionyl chloride (0·5 ml) in pyridine (10 ml) was kept at room temperature for 18 hr. Isolation of the steroidal material in the usual manner gave the diene (XII) (130 mg) m.p. 193–195°, $[\alpha]_D$ −84° (*c*, 0·44), ν_{max} 1740, 1640 and 1240 cm^{-1}. UV: ε_{205} = 9560, ε_{210} = 4500, ε_{215} = 1690. ORD: $[\phi]_{262}$ −3080°, $[\phi]_{222}$ −10,380°! (no extremum). (Found: C, 77·0; H, 9·5. $C_{30}H_{44}O_4$ requires: C, 76·9; H, 9·5%).

Reactions of the 11β-*hydroxy*-13α-*methyl*-C-*nor*-D-*homo*-17a(18)-*ene* (XIII)

(1) *Acetylation.* A solution of the hydroxy-olefin (XIII) (200 mg) in pyridine (10 ml) and acetic anhydride (3 ml) was heated on a steam bath for 8 hr. The isolated steroidal material was unchanged (IR, NMR, and TLC). A similar mixture heated under reflux for 24 hr gave an oil, shown by TLC to consist of starting material and a more polar fraction, probably resulting from rupture of the spiroketal side-chain.

(2) *Oxidation.* The hydroxy-olefin (XIII) (200 mg) in acetone (10 ml) was oxidized with "Jones reagent" at room temperature for 20 min, to give the keto-olefin (180 mg), as an oil. Alkaline hydrolysis to remove the 3-acetate afforded the 3β-*hydroxy keto-olefin* (XI), as needles from methanol (110 mg), m.p. 114–116°, identical with the sample described above.

(3) *Hydrolysis and ozonolysis.* A solution of the hydroxy-olefin (XIII) (200 mg) and potassium hydroxide (100 mg) in aqueous methanol (20 ml) was kept at room temperature for 16 hr. Isolation of the steroidal material and crystallization from methanol gave 3β,11β-*dihydroxy compound* as chunky crystals (145 mg), m.p. 246–248°, $[\alpha]_D$ −36° (*c*, 0·92), ν_{max} 3500 cm^{-1} (broad). (Found: C, 75·5; H, 9·8; $C_{28}H_{44}O_4$ requires: C, 75·6; H, 9·97%).

Ozone was bubbled through a solution of this compound (50 mg) in chloroform (10 ml) for 30 min. The solution was evaporated to dryness under vacuum at room temperature and the resulting ozonide was stirred with zinc powder (100 mg) in acetic acid (5 ml) for 24 hr. Isolation of the steroidal material gave an oil (XIV) (41 mg); ν_{max} 1710 cm^{-1} (Nujol mull) (six-membered ring ketone). ORD: $[\phi]_{325}$ +385°, $[\phi]_{282}$ −4630°, $[\phi]_{225}$ −1460°, $[\phi]_{208}$ −3600°!

Rearrangement of 3β-*acetoxy*-11α,12α-*epoxy*-5α,25D-*spirostan* (VI) *with* BF_3

A solution of 3β-acetoxy-11α,12α-epoxy-5α,25D-spirostan (1 g) in anhydrous benzene (100 ml) was treated with BF_3-etherate (0·5 ml) for 1 hr. The steroidal material was isolated in the usual manner, and chromatographed on alumina. Elution with light petroleum–benzene (10:1) gave the C-*nor*-D-*homo*-9(11),13(17a)-*diene* (380 mg) (XVII), which crystallized from methanol, followed by ethanol, to give needles, m.p. 150–151°. $[\alpha]_D$ −191° (*c*, 0·6), ν_{max} 1744, 1250 cm^{-1}, λ_{max} 253 nm (ε 16,300). ORD: $[\phi]_{252}$ −22,600, $[\phi]_{221}$ +31,600°. (Found: C, 76·8; H, 9·4. $C_{29}H_{42}O_4$ requires: C, 76·6; H, 9·3%).

Further elution with petroleum–ether–benzene (1:1) gave 3β-*acetoxy*-12α-*hydroxy*-5α,25D-*spirost*-8(9)-*ene* (530 mg) (XIX), which crystallized from methanol as needles, m.p. 172–173°, $[\alpha]_D$ −125° (*c*, 0·89), ν_{max} 3500, 1740, 1250 cm^{-1}. UV: ε_{240} = 558; λ_{max} 196 nm (ε 12,050). (Found: C, 74·0; H, 9·35. $C_{29}H_{44}O_5$ requires: C, 73·7; H, 9·4%).

Oxidation of 3β-*acetoxy* 12α-*hydroxy*-5α,25D-*spirost*-8(9)-*ene*

A solution of 3β-acetoxy-12α-hydroxy-5α, 25D-spirost-8(9)-ene (20 mg) in acetone (2 ml) was oxidised with Jones reagent to give 3β-acetoxy-5α,25D-spirost-8(9)-en-12-one (XX), crystallized as needles from methanol, m.p. 194–195°, ν_{max} 1740, 1704 (six-membered ring ketone), 1250 cm^{-1}, λ_{max} 300 nm (ε = 303), ε_{210} = 3980. ORD: $[\phi]_{313}$ +1110°, $[\phi]_{260}$ −6880°, $[\phi]_{235}$ −5400°, $[\phi]_{220}$ −6020°!

Acetylation of 3β-*acetoxy*-12α-*hydroxy*-5α,25D-*spirost*-8(9)-*ene*

A solution of hydroxy olefin (XIX) (10 mg) in acetic anhydride (0·1 ml) and pyridine (1 ml) was kept at 100° for 6 hr. Isolation of the steroidal material in the usual manner gave a gum, ν_{max} 1740, 1250 cm^{-1} (no absorption at 3500 cm^{-1}). 6-H singlet at δ 2·0 ppm in the NMR spectrum (two OAc groups).

Reaction of the 11β,12β-*epoxide* (VII) *with* BF_3

The epoxide (580 mg) in benzene (58 ml) was allowed to react with BF_3-etherate (0·58 ml) for 15 min, then the product was isolated in the usual way and chromatographed in alumina (30 g).

Light petroleum–benzene (5:1) eluted the C-nor-D-homo-9(11), 13(17a)-diene (XVII) (317 mg), identical (m.p., IR, UV, NMR, GLC) with the diene from the 11α,12α-epoxide. Further elution with light petroleum–benzene mixtures, followed by benzene and benzene–ether (20:1) gave mixtures of more polar products (ca. 80 mg) which were re-chromatographed (see below).

Benzene–ether (5:1) finally eluted the 12β-*hydroxy*-9(11)-*ene* (XXII) (crude wt. 113 mg) m.p. 210–215°. Repeated crystallizations from methanol gave flakes, m.p. 235–237°, $[\alpha]_D$ −55° (*c*, 1·0), ν_{max} 3540, 1735, 1238 cm^{-1}. (Found: C, 73·6; H, 9·2. $C_{29}H_{44}O_5$ requires: C, 73·7; H, 9·4%).

Re-chromatography of the intermediate fractions above gave a compound thought to be the fluorohydrin (XXIV) (23 mg) m.p. 230–232° from acetone–hexane. $[\alpha]_D$ −31° (*c*, 0·4), ν_{max} 3520, 3460, 1735, and 1238 cm^{-1}. Mass spectrum: $M^+ = 492$ ($C_{29}H_{45}FO_5$ requires 492).

Hydrogenation of the 9(11),13(17a)-*diene* (XVII)

The diene (45 mg) in ethanol (20 ml) was hydrogenated over a 5% $Pd/CaCO_3$ catalyst. Absorption of hydrogen became very slow after the first molar proportion and was stopped at ca. 1·2 mole to give the known 13(17a)-ene (XVIII) m.p. 140–142° from methanol (Lit.[12] m.p. 142–145°). The identity was confirmed by IR spectrum and GLC retention time.

Oxidation of the 12β-*hydroxy*-9(11)-*ene* (XXII)

Jones' reagent in acetone oxidised the 12β-hydroxy-9(11)-ene to give the 9(11)-en-12-one (XXIII), m.p. 218–221° (Lit.[6] m.p. 219·5–221·5°) identical (UV, IR) with a sample prepared by dehydrogenation of hecogenin acetate with selenium dioxide.[8] The 9(11)-en-12-one (50 mg) was reduced by stirring for 5 hr with sodium borohydride, (20 mg) in methanol (5 ml) and ether (5 ml). The product appeared to be a mixture of the 3β-acetoxy-12β-hydroxy-9(11)-ene (XXII) with a little of the 3β,12β-diol (TLC), with no evidence for any significant amount of 12α-isomer. Crystallization from methanol gave the pure 12β-hydroxy compound, m.p. 235–237°, identical (IR, NMR, mass spect.) with the product derived from the 11β,12β-epoxide.

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REFERENCES

[1] Part XVII, J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **25**, 149 (1969).
[2] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* 4469 (1965); J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **23**, 3511 (1967).
[3] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Aust. J. Chem.* **18**, 759 (1965).
[4] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*, p. 165. Holden-Day, San Francisco (1964).
[5] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* 119 (1965); J. M. Coxon, M. P. Hartshorn, D. N. Kirk and M. A. Wilson, *Tetrahedon* in press.
[6] E. Charney, H. Ziffer and U. Weiss, *Ibid.* **21**, 3121 (1965).
[7] R. C. Cookson and S. MacKenzie, *Proc. Chem. Soc.* 423 (1961).
[8] R. Hirschmann, C. S. Snoddy and N. L. Wendler, *J. Am Chem. Soc.* **75**, 3252 (1953).
[9] M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **21**, 1547 (1965).
[10] J. Fried and E. F. Sabo, *J. Am. Chem. Soc.* **79**, 1130 (1957); N. L. Wendler, R. P. Graber, C. S. Snoddy and F. W. Bollinger, *Ibid.*, p. 4476.
[11] I. Kitagawa, K. Kitazawa and I. Yosioka, *Tetrahedron Letters* 509 (1968).
[12] J. Elks, G. H. Phillipps, D. A. H. Taylor and L. J. Wyman, *J. Chem. Soc.* 1739 (1954).