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REACTIONS OF EPOXIDES—XIV*

THE PREPARATION AND SOME REACTIONS OF THE 12,12′-EPOXY-DERIVATIVES OF 12-METHYLENE-TIGOGENIN

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Abstract—Contrary to earlier reports, the reaction between methylmagnesium bromide and hecogenin gives predominantly the 12α-hydroxy-12β-methyl derivative, and epoxidation of 12-methylenetigogenin gives the 12α,12′- and 12β,12′-epoxides in ratio 2:1. The reactions of these epoxides with both boron trifloride and aqueous perchloric acid have been studied.

BLADON and McMeekin[1] reported the preparation of a 12,12′-epoxide by treatment of 12-methylene-tigogenin (I) with perbenzoic acid. The β-configuration assigned to this epoxide was based upon the identity of the derived 12-hydroxy-12-methyl compound (by $LiAlH_4$ reduction) and the tertiary alcohol obtained by the action of methyl lithium on hecogenin. The latter reaction was presumed to involve α-face attack on the 12-ketone. Levine and Wall[2] prepared the two epimeric 12-hydroxy-12-methyl derivatives of tigogenin. These authors hydroxylated 12-methylene-tigogenin with osmium tetroxide, and assumed the resulting diol to be the 12α-hydroxy-12β-hydroxymethyl compound (II) formed by preferential attack of the reagent from the α-face. The 12′-tosylate of the diol (II) was reduced to give a tertiary alcohol formulated as 12α-hydroxy-12β-methyltigogenin (V). This compound differed from the tertiary alcohol obtained as the major product by treating hecogenin with methylmagnesium bromide, which was accordingly assigned the 12β-hydroxy-12α-methyl structure (VI). We now find that all the foregoing configurational assignments must be reversed, as was suggested by Just and Nagarajan[3] following their finding that the Grignard methylation of 3α,20β-diacetoxy-5β-pregnan-12-one gave 12β-methyl-5β-pregnan-3α,12α,20β-triol as the major product.

As part of our study of epoxide rearrangements we required the two epimeric 12,12′-epoxy-derivatives of 12-methylenetigogenin. We therefore re-examined the epoxidation of 12-methylenetigogenin acetate (I). Reaction with monoperphthalic acid gave a mixture, separated by chromatography to give the 12α,12′-epoxide (III; m.p. 242–243°, $[\alpha]_D$ −10°) and the 12β,12′-epoxide (IV; m.p. 172–173°, $[\alpha]_D$ −62°), in ratio 2:1. Bladon and McMeekin[1] characterized only one of the 12,12′-epoxides (m.p. 240–242°, $[\alpha]_D$ −24°), which evidently corresponds to our major product, the α-epoxide.

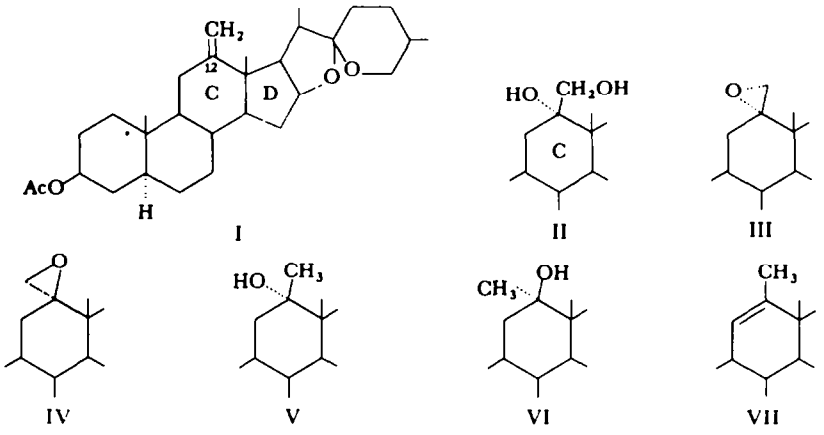
* Part XIII: J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **23**, 1811 (1967).

† Present address: Department of Chemistry, Westfield College, London, N.W.3.

[1] P. Bladon and W. McMeekin, *J. Chem. Soc.* 2191 (1960).

[2] S. G. Levine and M. E. Wall, *J. Am. Chem. Soc.* **82**, 3391 (1960).

[3] G. Just and R. Nagarajan, *Canad. J. Chem.* **39**, 548 and 1274 (1961); **40**, 377 (1962).



Our stereochemical assignments for the epoxides are based upon the course of dehydration of the corresponding tertiary alcohols (V and VI) obtained by reducing the epoxides (III and IV) with lithium aluminum hydride, and re-acetylating the 3β-hydroxy functions. The tertiary nature of both C-12 alcohols (V and VI) followed from non-acetylation of the 12-hydroxyl groups by acetic anhydride–pyridine and the presence in their NMR spectra of sharp, three proton singlets (ca. $\delta = 1{\cdot}2$ ppm) assigned to the 12-methyl groups. Dehydration of the 12α-hydroxy-12β-methyl compound (V) with thionyl chloride–pyridine gave the Δ^{11}-olefin (VII) (80% yield) resulting from the favourable trans-diaxial elimination. The Δ^{11}-olefin (VII) was identified by comparison of its physical constants with the literature data and from its NMR spectrum which revealed the structural features C=C—$\underline{CH}_3$ ($\delta = 1{\cdot}61$ ppm) and —$\underline{CH}$=C ($\delta = 5{\cdot}12$ ppm). The isomeric 12β-hydroxy-12α-methyl compound (VI) with an equatorial hydroxyl group, underwent the expected[4] smooth elimination to give 12-methylenetigogenin (I) in high yield. The results stand in sharp contrast to those reported by Levine and Wall[2], who studied the dehydration of their 12-hydroxy-12-methyl compounds with thionyl chloride–pyridine, and reported that both isomers gave mixtures of the two olefins in similar proportions, in addition to chlorinated material which was not characterized. It is difficult to explain these results except on the presumption that the supposed C-12 epimeric alcohols[2] were actually mixtures. The pure epimers obtained in our present work are very similar in properties, and exhibit almost identical IR spectra, the only significant difference being a band at 830 cm^{-1} in the spectrum of the 12α-hydroxy-12β-methyl epimer. We found that the epimers can be distinguished by thin-layer chromatography on silica gel and each of the samples used in our dehydration studies was free from contamination by the other. These results clearly require a reversal of configurations assigned by the previous workers to all their C-12 derivatives of tigogenin. Moreover, Bladon and McMeekin[1] prepared a 12-chloro derivative to which they assigned the 12α-chloro-12β-methyl configuration on the supposition that the precursor of the chloro compound was the 12β-hydroxy-epimer, and that the reaction with phosphorus pentachloride would proceed in the normal manner

[4] D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956).

with inversion of configuration.[5] These authors found, however, that the chloro compound was converted into the exocyclic olefin, 12-methylene-tigogenin (I), by dehydrochlorination with sodium methoxide, an observation which clearly requires that the chloro-substituent should have the equatorial (12β)-configuration. This result can now be re-interpreted in terms of the formation of the 12β-chloro compound from the 12α-hydroxy isomer, with inversion of configuration in the reaction with phosphorus pentachloride.

There seems to be no reason to doubt the validity in the present case of the generalization[4] that the elimination of an axial substituent from a 1-methyl-cyclohexyl system proceeds with loss of the *trans*-coplanar proton to give the endocyclic olefin, while elimination of the corresponding equatorial substituent involves preferentially a *trans*-coplanar proton of the methyl group to give an exocyclic methylene derivative. Ring C is held rigidly in a chair conformation by its *trans* attachment to the adjacent rings, and it is clear from study of Dreiding models that the conformational integrity of the groups at C-12 is unlikely to be disturbed by any ring distortion. Moreover there are no large steric interactions, comparable with those which lead to the abnormal stability of an exocyclic methylene group at C_{11},[6] which might affect C_{12} and conceivably *reverse* the usual preferences for *trans*-coplanar elimination by a base-catalysed E2-type mechanism. The Canadian workers[3] found, however, that *acid-catalysed* dehydration of either of their C-12 epimeric pregnane derivatives gave predominantly the 12-exocyclic methylene pregnane derivative, suggesting that this is more stable than its 12-methyl-Δ^{11}-isomer. Steroidal Δ^{11}-olefins are known to be highly strained.

Repetition of the reaction of hecogenin acetate with methyl magnesium bromide under the conditions described by Levine and Wall[2] gave a product consisting largely (ca. 87%) of the 12α-hydroxy-12β-methyl compound (V) contaminated with other products including the C_{12} epimer (VI). It is clear that the assumption of a "propensity of steroids to 'rear attack' "[1] as a criterion for assigning configurations to steroid derivatives must be made with caution. Grignard reactions, in particular, tend to give the tertiary alcohol with an equatorial methyl group from a steroid ketone.[7] This is thought to be a consequence of unfavourable 1,3-diaxial interactions in the transition state leading to the axial-methyl product. Equatorial (12β) approach of the $—CH_3$ group to the 12-ketone appears to be especially favourable in the case of hecogenin. It is now well established that the behaviour of 12-ketones towards nucleophilic addition is remarkably influenced by the nature of the C-17 side chain. Equilibration experiments and reduction of ketones under conditions known to lead to the thermodynamically stable products, have shown that 12α-derivatives are the more stable in the cholane series, where a 12β-substituent interferes with the side chain in its stable conformation. In hecogenin, in contrast, the rigid spiroketal system removes the 21-methyl group from the vicinity of a 12β-substituent, which in this case represents the more stable epimer. It is therefore not surprising that approach of a methyl group should occur almost exclusively towards the 12β-position of hecogenin giving the equatorial-methyl product, and with somewhat reduced stereo-

[5] R. J. Bridgewater and C. W. Shoppee, *J. Chem. Soc.* 1709 (1953).

[6] J. Elks, *J. Chem. Soc.* 3333 (1960); D. N. Kirk and V. Petrow, *ibid.*, 2091 (1961).

[7] A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron* **18**, 705 (1962), and Refs therein.

specificity in the pregnane series.[3] Inspection of a Dreiding model shows that a 12α-methyl group will be in a state of steric compression with the 17α-H as well as with the two hydrogen atoms at the 9α- and 14α-positions, while the only comparable interference to β-attack comes from the 18-methyl group.

The above considerations do not necessarily apply to per-acid attack upon the 12-exo-methylene group, which should proceed by electrophilic attack upon the double bond leading, according to Markownikov (cf. Ref. 1), to greater bond development to the unsubstituted 12'-carbon atom in the step which is probably rate-determining. The subsequent closure of the epoxide-ring does not introduce any notable steric strains, so that the observed modest preference for 12α,12'-epoxide formation is reasonable. It is also in accordance with the reported observation[9] that epoxidation of 4*t*-butyl methylenecyclohexane gave predominantly the *cis*-epoxy derivative with a *pseudo*-axial C—O bond. The implication from the present results that osmium tetroxide attacks the exocyclic olefinic bond from the β-direction, in contrast to the earlier report[2], also agrees with the mode of attack on 4-*tert*-butyl methylenecyclohexane.[9]

ACID CATALYSED REARRANGEMENTS OF EPOXIDES

(a) *Boron trifluoride*

During earlier studies we became interested in boron trifluoride-catalysed rearrangements of epoxides derived from steroids containing an exo-methylene function. In particular, the formation among other products of a five membered cyclic ether (IX) from the C-nor-D-homo-epoxide (VIII)[10] prompted us to examine the reactions of the epoxides derived from 12-methylenetigogenin.

Brief reaction (1 min) of the 12β,12'-epoxide (IV) with boron trifluoride etherate in benzene gave a mixture of products. Chromatographic separation gave an olefin (29%) which was identified (m.p. and m.m.p., IR and NMR spectra) as the known C-nor-D-homo-$\Delta^{13(17a)}$-olefin (X).[11] This material was followed by the 12β-aldehyde (XI) (41%). The aldehyde function was revealed by the IR (2717 and 1739 cm^{-1}) and NMR (δ = 9·60 ppm; J = 2 c/s) spectra. The equatorial (12β) nature of the aldehyde was assigned on the basis of the probable stereochemistry of the rearrangement process, and from the position of the —CHO proton in the NMR spectrum (see below). The final product from the β-epoxide (IV) rearrangement was an unsaturated alcohol (19%) the structure of which is unknown (see Experimental).

The rearrangement of the β-epoxide (IV) with BF_3 in ether solution gave similar yields of the $\Delta^{13(17a)}$-C-nor-D-homo-olefin (X) and the 12β-aldehyde (XI), and also a new compound which appeared to be a primary/teriary diol. Only one of the hydroxyl groups could be acetylated, and the NMR spectrum of the diol contained a two-proton singlet (δ = 4·02 ppm), indicating a —CH_2OH group. The diol resisted cleavage with periodic acid or lead tetraacetate, and so seems unlikely to be a 12,12'-diol. Its structure remains obscure.

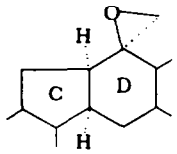
Reaction of the α-epoxide (III) with boron trifluoride etherate in benzene solution

[8] J. W. Huffman, D. M. Alabran, T. W. Bethea and A. C. Ruggles, *J. Org. Chem.* **29**, 2963 (1964); M. Alauddin and M. Martin-Smith, *ibid.*, **28**, 886 (1963).

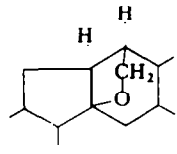
[9] H. B. Henbest, *Proc. Chem. Soc.* 159 (1963).

[10] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **21**, 2489 (1965).

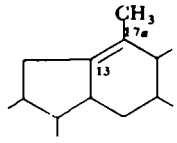
[11] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* 119 (1965).



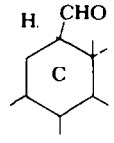
VIII



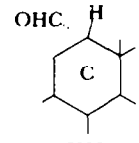
IX



X



XI



XII

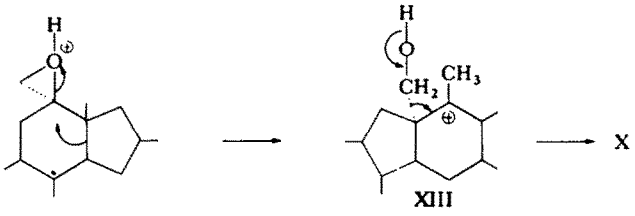
gave a mixture of products from which the 12α-aldehyde (XII) was obtained directly by crystallization. The NMR spectrum of the residue from the crystallization exhibited NMR signals due to both the 12α-aldehyde (XII) and the 12β-aldehyde (XI). Comparison of the integrals of the aldehydic proton signals, followed by a product analysis to determine the total aldehydes present, allowed the estimation of separate yields of the aldehydes as: 12α-aldehyde (XII; 53%); 12β-aldehyde (XI; 13%). The failure of the 12α-aldehyde (XII) to undergo epimerization at C-12 on treatment with boron trifluoride in benzene (control experiment), requires that the 12β-aldehyde isolated from this reaction be regarded as a primary product of the rearrangement of the α-epoxide. Chromatography of the residues from the above crystallization gave well-defined fractions consisting of the $\Delta^{13(17a)}$-olefin (X; 18%), and the thermodynamically more stable 12β-aldehyde (XII). The epimerization of the axial 12α-aldehyde during chromatography was demonstrated in a separate experiment, and supports the above structural assignments. The aldehyde configurations are also indicated by the respective chemical shifts of their CHO protons (12α-CHO; $\delta = 9{\cdot}85$ ppm: 12β-CHO; 9·60 ppm) which differ in the same sense as data reported[12] for a limited number of natural products and their derivatives, of known configuration.

Reaction of the α-epoxide (III) with BF_3 in ether solution resulted in the formation of relatively more $\Delta^{13(17a)}$-olefin (X) (20%), with a corresponding reduction in the yields of the 12-aldehydes (XI and XII).

The formation of the C-nor-D-homo-$\Delta^{13(17a)}$-olefin (X) by loss of the C-12′ carbon atom from both epoxides is envisaged as proceeding through cleavage of the C_{12}—O bond and migration of the electron pair of the C_{13}—C_{14} bond to give the intermediate (XIII), fragmentation of which could give rise to the rearranged olefin (X) with loss of formaldehyde. While the electron shifts involved in the transformation of the 12β,12′-epoxide into the intermediate (XIII) and the 12β-aldehyde could be concerted with the cleavage of the C_{12}—O bond, the formation of both the 12β-aldehyde and the $\Delta^{13(17a)}$-olefin in modest proportions from the 12α,12′-epoxide (III) requires the intermediacy of a discrete C-12 carbonium ion, since the stereochemical requirements for a synchronous rearrangement are not fulfilled in this

[12] T. J. King and J. P. Yardley, *J. Chem. Soc.* 4308 (1961); E. Wenkert, P. W. Jeffs and J. R. Mahajan, *J. Amer. Chem. Soc.* 86, 2218 (1964); W. R. Chan, C. Willis, M. P. Cava and R. P. Stein, *Chem. & Ind.* 495 (1963).

case. The product of concerted hydride migration in the 12α,12'-epoxide would be the 12α-aldehyde, the less stable epimer. We therefore conclude that the reaction pathway involving a carbonium ion intermediate can compete effectively with the concerted rearrangement when the latter leads to the less stable isomer.



XIII

(b) Aqueous perchloric acid

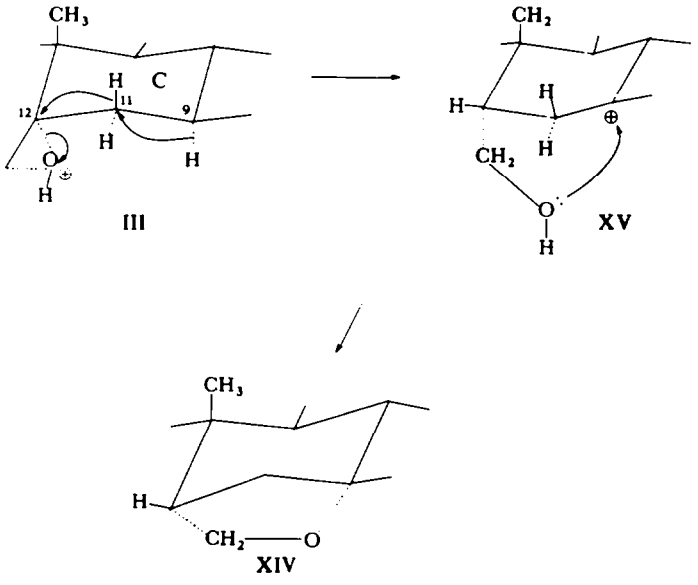
Treatment of the β-epoxide (IV) with 60% perchloric acid in acetone gave largely the $\Delta^{13(17a)}$-olefin (X; 81%), accompanied by a minor product (18%) to which the cyclic ether structure (XIV) is tentatively assigned. The spectra and chemical properties of the ether (XIV) indicate the absence of either hydroxyl groups, ketone or aldehyde functions, or unsaturation. Both the IR and NMR spectra indicate the presence of ether linkages in addition to those in the spiroketal ring system. The NMR spectrum shows a doublet equivalent to two protons at $\delta = 3{\cdot}95$ ppm ($J = 3$ c/s) which we assign to the methylene group in the $\rangle CH—CH_2—O—$ moiety. The absence of any other signals (apart from those associated with the 16α and C_{26} protons) in this region suggested a tertiary centre as the other point of attachment of the ether bridge. The signal due to the C-19 methyl protons showed a paramagnetic shift to $\delta = 0{\cdot}97$ ppm, compared with values ca. $\delta = 0{\cdot}85$ ppm, for related compounds substituted only at C-12. This suggests C-9 as the probable site of attachment of the oxygen atom (Zurcher[13] lists an additional chemical shift of 0·14 ppm for 9α-OH). The rest of the spectrum showed no unusual features which might have indicated substitution in ring D or elsewhere. A Dreiding molecular model shows that the 9α,12α-O—CH_2— bridge can be constructed without excessive strain.

The α-epoxide (III) reacted with perchloric acid to give the cyclic ether (XIV) (65%) as the major product, accompanied by the 12β-aldehyde (XI; 10%) and a new unsaturated compound (19%) the structure of which is unknown. A possible mode of formation of the cyclic ether (XIV) from the α-epoxide (III) is shown in diagram XV. Formation of the ether (XIV) from the β-epoxide (IV) could not proceed *via* the same favourable (*anti*-) hydride shifts concerted with C_{12}—O cleavage and would require the intermediacy of a C-12-carbonium ion. The markedly lower yield of cyclic ether from the β-epoxide is therefore very reasonable.

Attempts to cleave the cyclic ether with acetic anhydride and various acidic catalysts gave complex mixtures of products (with partial rupture of the spiroketal system) which afforded no additional evidence concerning the structure of the ether.

The product ratios observed for the present epoxy systems imply that the free energy of activation for "carbonium ion" processes is only very slightly greater (perhaps 1–1·5 kcal/mol, after allowing for conformational effects) than for con-

[13] R. F. Zurcher, *Helv. Chim. Acta* **46**, 2054 (1963).



III XV XIV

certed hydride migration leading to aldehydes. This conclusion is supported by experimental evidence from other epoxy-steroid systems which we are examining.

NMR SPECTRA

NMR data* for the compounds described above are listed in the accompanying Tables. The spectra of the C-12 tertiary alcohols (V and VI) (Table 1) support their revised formulations. Published data[14] for the epimeric 17a-hydroxy-17a-methyl-D-homoandrostanes are also included in the Table. They provide reference values for chemical shifts of the methyl substituent at the site of the tertiary hydroxyl group, and of the C-18 angular methyl group, in immediate environments almost enantiomeric with the C-12 tertiary alcohols. The *actual* chemical shifts differ somewhat between the two series because of the differing structural features of adjoining rings, but the *relative* chemical shifts, and the numerical differences in δ-values within each epimeric pair of compounds, are clearly consistent with our revised configurations at C-12.

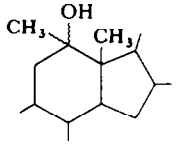
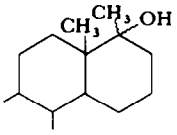
EXPERIMENTAL

Rotations were measured for $CHCl_3$ solutions at room temperature. IR spectra were recorded for CS_2 solutions, and 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. Solvents used for BF_3 reactions were dried over Na. Light petroleum refers to the fraction b.p. 50–70°.

* Determined at 60 mc/s in $CDCl_3$ relative to TMS.

[14] S. N. Ananchenko, V. N. Leonov, V. I. Zaretskii, N. S. Wulfson and I. V. Torgov, *Tetrahedron* **20**, 1279 (1964).

TABLE 1. CHEMICAL SHIFTS OF METHYL-GROUP RESONANCES IN TERTIARY ALCOHOLS

Spirostan series Compound	D-homo-androstane-series Chemical shifts (δ, ppm)			
	12- or 17a-CH_3		18-CH_3	
12α-OH, 12β-CH_3 (V)	1·15	$\Delta\delta$ = 0·12	0·82	$\Delta\delta$ = 0·08
12β-OH, 12α-CH_3 (VI)	1·27		0·90	
17aα-OH, 17aβ-CH_3 [14]	1·12	$\Delta\delta$ = 0·13	0·92	$\Delta\delta$ = 0·08
17aβ-OH, 17aα-CH_3	1·25		1·00	

TABLE 2. CHEMICAL SHIFTS OF PROTONS AT C-19, C-18 AND C-12′ IN NMR SPECTRA OF SPIROSTAN DERIVATIVES

Compound	Chemical shifts (δ, ppm) C-19	C-18	C-12′
12,12′-exocylic olefin (I)	0·90	0·87	4·55
12α,12′-epoxide (III)	0·83	0·92	2·52
12β,12′-epoxide (IV)	0·85	0·97	2·97 (4)*
12-methyl-Δ^{11}-olefin (VII)	0·78	0·87	1·61
12β-aldehyde (XI)	0·87	0·75	9·60 (2)
12α-aldehyde (XII)	0·83	0·92	9·85 (3)
9α,12′-cyclic ether (XIV)	0·97	0·87	3·95 (3)

* Figures in parentheses are approximate J-values.

Preparation of the 12,12′-*epoxides* (III *and* IV)

12-Methylenetigogenin acetate (21·5 g) in dry benzene (2000 ml) was treated with an ethereal solution of monoperphthalic acid (0·7 M; 200 ml) and the resulting solution kept at 20° for 12 hr. The steroidal material, isolated by means of ether, was absorbed onto alumina (1 kg). Elution with light petroleum–benzene (3:7) and crystallization from acetone gave the 12β,12′-*epoxide* (IV) as needles (6·2 g), m.p. 172–173°, $[\alpha]_D$ −62° (*c* 1·17), ν_{max} 1742 and 1242 cm^{-1}. (Found: C, 74·2; H, 9·7. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%.) Elution with benzene and benzene–ether (10:1) gave, after crystallization from methanol, the 12α,12′-*epoxide* (III) as needles (10·8 g), m.p. 242–243°, $[\alpha]_D$ −10° (*c* 0·93), ν_{max} 1742 and 1242 cm^{-1}. (Found: C, 74·2; H, 9·5. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%.)

Lithium aluminium hydride reduction of 12,12′-*epoxides*

(a) 12β,12′-*epoxide* (*IV*). To a solution of the epoxide (500 mg) in dry tetrahydrofuran (50 ml) was added lithium aluminium hydride (500 mg), and the resulting suspension was heated under reflux for 4 hr. Isolation of the steroid by use of ether and crystallization from light petroleum–methanol gave 12β-*hydroxy*-12α-*methyl-tigogenin* (VI; 3β-OH) as needles (350 mg), m.p. 200–201°, $[\alpha]_D$ −40° (*c* 1·05), ν_{max} 3610 cm^{-1}. (Found: C, 74·7, H, 10·4. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%.) A solution of this diol (280 mg) in pyridine (6 ml) and acetic anhydride (1·2 ml) was kept at 20° for 12 hr. Isolation by use of ether and crystallization from light petroleum gave 3β-*acetoxy*-12β-*hydroxy*-12α-*methyltigogenin* (VI; 3β-OAc) as flakes (241 mg), m.p. 226–227°, $[\alpha]_D$ −50° (*c* 1·0), ν_{max} 3610, 1742 and 1242 cm^{-1}. (Found: C, 74·0; H, 10·2. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%.)

(b) 12α,12′-*epoxide* (III). Reduction of the epoxide (750 mg) as above gave the diol (V; 3β-OH) as fine needles (from light petroleum) (660 mg), m.p. 210°, $[\alpha]_D$ −33° (*c* 0·91), ν_{max} 3610 cm^{-1}. (Found: C, 74·9; H, 10·6. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%.) Acetylation of the diol (550 mg), as above, gave 3β-*acetoxy*-12α-*hydroxy*-12β-*methyltigogenin* (V; 3β-OAc) as flakes (from light petroleum) (500 mg), m.p. 222–223°, $[\alpha]_D$ −35° (*c* 1·06), ν_{max} 3610, 1742, 1242 and 830 cm^{-1}. (Found: C, 73·6; H, 10·0. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%.)

Dehydration of 12-*hydroxy*-12-*methyltigogenin acetate*

(a) 12β-*Hydroxy*-12α-*methyltigogenin acetate* (VI). A solution of the 12β-alcohol (190 mg) in pyridine (6 ml) and thionyl chloride (0·09 ml) (purified by distillation, first from linseed oil then from quinoline) was kept at −20° for 30 min. Isolation by use of pentane and crystallization from acetone gave 12-methylenetigogenin acetate (146 mg), m.p. and mixed m.p. 178–180°, $[\alpha]_D$ −17° (*c* 1·01); IR and NMR spectra identical with an authentic sample.

(b) 12α-*Hydroxy*-12β-*methyltigogenin acetate* (*V*). Dehydration of the 12α-alcohol (400 mg), as above, and crystallization from methanol gave 12-methyl-Δ^{11}-tigogenin acetate (VII) as fine needles (340 mg), m.p. 156–157°, $[\alpha]_D$ −47° (*c* 0·85), ν_{max} 1742, 1242 cm^{-1}. (Found: C, 76·5; H, 10·0. Calc. for $C_{30}H_{46}O_4$ C, 76·5; H, 9·9%.) (Lit.[2] m.p. 162·5–164·5°, $[\alpha]_D$ −45°.) The IR spectrum of the material in the mother liquors (15%) showed the presence of a small proportion of exocyclic olefin (I).

Reaction of hecogenin acetate with methyl magnesium bromide

A solution of hecogenin acetate (4·0 g) in dry benzene (40 ml) was added with stirring over 30 min. to an ethereal solution of methyl magnesium bromide (1·5 M; 26 ml). After a further 3 hr the steroidal material was isolated by means of ether, and reacetylated at C_3 by treatment with acetic anhydride–pyridine (1:10) at 100° for 45 min. The crude product, on crystallization from light petroleum, gave the 3β-acetoxy-12α-hydroxy-12β-methyl compound (V) as flakes (2·8 g), m.p. and mixed m.p. 222–223°, $[\alpha]_D$ −35° (*c* 1·03). In another experiment, 10 g hecogenin acetate gave 8·7 g of product (V) by crystallization followed by chromatography of mother-liquors.

Reaction of the 12β,12′-*epoxide* (IV) *with* BF_3 *in benzene*

A solution of the 12β,12′-epoxide (1·8 g) in anhydrous benzene (180 ml) was treated with boron trifluoride etherate (1·8 ml) at 20° for 1 min. The crude product, isolated by means of ether, was adsorbed onto alumina (100 g). Elution with light petroleum–benzene (10:1) gave the C-nor-D-homo-$\Delta^{13(17a)}$-olefin (X) (521 mg) as cubes from ethanol, m.p. and mixed m.p. 140–141°, $[\alpha]_D$ −49° (*c* 1·235); IR and NMR spectra indistinguishable from those of an authentic sample. (Found: C, 76·5; H, 9·8. Calc. for $C_{29}H_{44}O_4$, C, 76·3; H, 9·7%.)

Elution with light petroleum–benzene (1:1) and crystallization from light petroleum gave the 12β-*aldehyde* (XI) (735 mg) as needles, m.p. 178–179°, $[\alpha]_D$ −106° (*c* 1·14), ν_{max} 2717 cm^{-1} (—CHO), 1739 and 1242 cm^{-1}. (Found: C, 73·9; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%.)

Finally elution with ether and crystallization from methanol gave an unsaturated alcohol (350 mg) as needles, m.p. 219–222°, $[\alpha]_D$ −47° (*c* 0·74). ν_{max} 3571 (OH), 1742 (OAc), 1639 (C=C) and 1242 cm^{-1}, UV; ε_{220} = 840, ε_{215} = 1170, ε_{210} = 2080, ε_{205} = 4170. NMR: One proton signal at δ = 5·22 ppm (*H*C=C) The hydroxyl group was stable to acetylation or oxidation under normal conditions.

Reaction of the 12β,12′-*epoxide* (IV) *with* BF_3 *in ether*

A solution of the 12β,12′-epoxide (1·6 g) in anhydrous ether (160 ml) was treated with boron trifluoride etherate (1·6 ml) at 20° for 3 min. The crude product, isolated by means of ether, was adsorbed on alumina (100 g). Elution with light petroleum–benzene mixtures (3:1) and (1:1) gave the $\Delta^{13(17a)}$-olefin (X) (504 mg) and the 12β-aldehyde (XI) (706 mg) respectively. Finally elution with ether and crystallization from light petroleum gave a *diol* of unknown structure, as needles (175 mg), m.p. 165–166°, $[\alpha]_D$ −46° (*c* 0·97), ν_{max} 3610, 3496, 1745 and 1242 cm^{-1}. (Found: C, 71·1; H, 9·5. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·6%.)

Reaction of the 12α,12′-*epoxide* (III) *with* BF_3 *in benzene*

A solution of the epoxide (1·6 g) in anhydrous benzene (160 ml) was treated with boron trifluoride etherate (1·6 ml) and kept at 20° for 5 min. The crude product, isolated by means of ether, crystallized from methanol to give the 12α-*aldehyde* (XII; 490 mg) as needles, m.p. 190–193°, $[\alpha]_D$ −30° (*c* 0·94), ν_{max} 2725 cm^{-1} (CHO), 1742 and 1242 cm^{-1}. (Found: C, 73·7; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%.) After

removal of methanol from the mother liquors the residue was adsorbed onto alumina (80 g). Elution with light petroleum–benzene (3:1) gave the $\Delta^{13(17a)}$-olefin (X) (300 mg), m.p. and mixed m.p. 140–141°. Elution with benzene and crystallization from light petroleum gave the 12β-aldehyde (550 mg), m.p. and mixed m.p. 178–179°, $[\alpha]_D$ −106° (*c* 0·95). Finally elution with ether gave an oil (195 mg) which was not characterized.

Epimerization of the 12α-*aldehyde* (XII) *into the* 12β-*aldehyde* (XI)

The 12α-aldehyde (180 mg) and KOH (200 mg) in aqueous ethanol (90%, 20 ml) were kept at room temperature for 18 hr. Re-acetylation of the crude product (acetic anhydride–pyridine, 18 hr at room temperature) gave the 3β-acetoxy-12β-aldehyde, m.p. 178–179°. A similar epimerization occurred when a benzene solution of the 12α-aldehyde was passed through an alumina column.

Reaction of the 12α,12′-*epoxide* (III) *with* BF_3 *in ether*

The epoxide (1·65 g) in anhydrous ether (165 ml) was allowed to react with BF_3-etherate (1·6 ml) for 35 min, and the products were separated as described above, giving the 12α-aldehyde (450 mg), the $\Delta^{13(17a)}$-olefin (327 mg), and the 12β-aldehyde (314 mg).

Epoxide rearrangements in aqueous perchloric acid

12β,12′-*epoxide* (IV). A solution of the epoxide (1 g) in dichloromethane (30 ml) and acetone (60 ml) was treated with aqueous perchloric acid (1·5 M; 1·0 ml). After 20 min the mixture was diluted with water. The crude product isolated from the organic phase was chromatographed on alumina (80 g). Elution with light petroleum–benzene (9:1) gave the $\Delta^{13(17a)}$-olefin (X; 809 mg), m.p. 140–141°. Elution with benzene gave the 9α,12′-*cyclic ether* (XIV; 180 mg), m.p. 210–211°, $[\alpha]_D$ −35° (*c* 0·90), ν_{max} 1742 and 1242 cm^{-1}, no significant UV absorption. (Found: C, 73·7; H, 9·4. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%.)

12α,12′-*epoxide* (III). The epoxide (1 g) in dichloromethane (10 ml) and acetone (50 ml) was allowed to react with perchloric acid (1·5 M; 4·0 ml) for 18 hr. The crude product afforded the 9α,12′-cyclic ether (XIV; 370 mg) by direct crystallization from methanol. Chromatography of the residue and elution with light petroleum gave an unsaturated compound (190 mg) of unknown structure, needles from pentane, m.p. 196–198°, $[\alpha]_D$ −69° (*c* 0·96), ν_{max} 1742 and 1242 cm^{-1}. Elution with light petroleum–benzene (2:1) gave the 12β-aldehyde (XI; 100 mg), m.p. 176–176°, and final elution with benzene gave a further 250 mg of the cyclic ether (XIV) m.p. 220–222°.

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