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REACTIONS OF EPOXIDES—XIII*

THE BACKBONE REARRANGEMENT OF 3α-ACETOXY-4α,5-EPOXY-5α-CHOLESTANES WITH LEWIS ACID

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Abstract—3α-Acetoxy-4α,5-epoxy-4β-methyl-5α-cholestane (Ia) undergoes a "backbone rearrangement" with BF_3-etherate to give the (enantio) 5β,14β-dimethyl-18,19-bisnorcholest-13(17)-ene derivative (IIa). One of the products obtained from reaction of 3α-acetoxy-4α,5-epoxy-5α-cholestane (Ib) with a Grignard reagent is now shown to be the related 13(17)-olefin (IIb). The epoxide Ib also undergoes a backbone rearrangement on treatment with BF_3-etherate.

IN THE course of our earlier study[1] of the rearrangement of 3-substituted 4,5-epoxy-4-methylcholestanes with BF_3-etherate, the 3α-acetoxy-4α,5α-epoxide (Ia) was found to yield only (ca. 90%) an unidentified unsaturated hydroxy-acetate (IIa). In view of our recent reports[2–6] that cholestane derivatives which could give rise to a C-5 carbonium ion may undergo a backbone rearrangement, we re-examined the hydroxyacetate IIa obtained earlier. Evidence detailed below indicates the backbone rearranged 4α-hydroxy-$\Delta^{13(17)}$-olefin structure (IIa) for the hydroxyacetate.

The tentative assignments of signals in the NMR spectrum of the hydroxyacetate IIa (determined at 100 Mc for a CCl_4 solution) are given in Table 1. The absence of

TABLE 1. NMR DATA (IN PPM) FOR $\Delta^{13(17)}$-DERIVATIVES AT 60 Mc

Compound (Solvent)	5β-CH_3	14β-CH_3	21-CH_3	26,27-CH_3	3-H ($W_{1/2}$)	4-H
IIa*(CCl_4)	0·89	0·89	0·89, 0·945	0·80, 0·87	ca. 4·85(~16)	(4β-CH_3 1·00)
IIb(CCl_4)	0·825	0·92	0·90, 1·00	0·80, 0·88	3·85(15)	3·20(J = 2·5 c/s)
IIc(CCl_4)	0·90	0·90	0·90, 1·00	0·80, 0·90	5·05(20)	3·35(J = 3 c/s)
VIIa(CCl_4)	0·93	0·90	0·90, 1·00	0·80, 0·90	4·03(15)	4·73(J = 3 c/s)
VIIb(CCl_4)	1·00	0·90	0·90, 1·00	0·79, 0·88	5·05(15)	4·78(J = 2·5 c/s)

* Run at 100 Mc.

a signal in the NMR spectrum below 0·8 ppm suggested that the C/D ring system had been modified, probably by the presence of the tetrasubstituted (NMR data) double bond resulting in the shift of the C-18 Me resonance to lower field. A signal (ca. 1½ protons) at 0·945 ppm was assigned to one component of a doublet due to the 21-Me

* Part XII M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters*, 3913 (1966).

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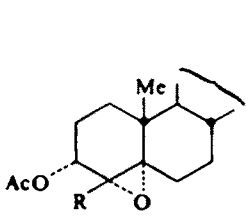
[1] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron*, **20**, 2531 (1964).

[2] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Chem. Comm.* 160 (1966).

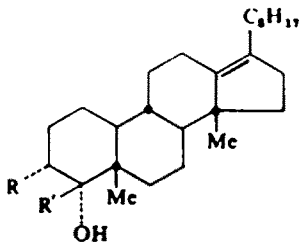
[3] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters*, 2125 (1966).

[4] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **22**, 3195 (1966).

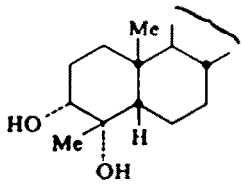
[5] M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters*, 3913 (1966).



Ia R, Me
b R, H.



IIa R, OAc; R', Me
b R, OH; R', H.
c R, OAc; R', H.



III.

group, the other half of the doublet being concealed under a strong peak (ca. 7½ protons) at 0·89 ppm. This latter peak is thought also to comprise signals due to the 5β- and 14β-Me groups. Double irradiation with a frequency of −148 c/s removed the 0·945 ppm signal and reduced the magnitude of the peak at 0·89 ppm with the appearance of a new singlet (21-Me group) at 0·92 ppm. From these data the methine proton at C-20 in the hydroxyacetate IIa could be located at 2·40 ppm, corresponding to a one-proton multiplet which was evident in the spectrum. This value should be compared with the locations for the C-20 methine proton for analogous backbone rearranged systems reported earlier[3-5] which occur in the range 2·40–2·45 ppm.

The rearrangement of the epoxide Ia on treatment with BF_3-etherate may be rationalized in terms of cleavage of the C_5—O bond of the epoxide followed by migration of the 19-Me group to the β-face at C-5. Subsequent 1,2-shifts and loss of the 17α-proton would give rise to the observed product. Migration of the 19-Me group would be favoured in this instance by the consequent shift of the 3-acetate group from an axial to an equatorial configuration.

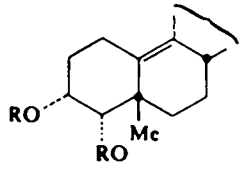
Hall and Just[6] reported the isolation of 4β-methyl-5β-cholestane-3α,4α-diol (III; 32%) and 5β-methyl-19-norcholest-9-ene-3α,4α-diol (IVa; 20%) from the reaction of 3α-acetoxy-4α,5-epoxy-5α-cholestane (Ib) with MeMgI. In view of our results for the reaction of the corresponding 4-methylepoxide (Ia) with a Lewis acid (the presumed[6] mode of formation of IVa) we re-examined the reaction reported by Hall and Just. Chromatography of the crude product from the reaction of MeMgI with the epoxide Ib gave in our hands the 4-methyl-3α,4α-diol (35%; III), mixed fractions (31%) and a further diol (30%), m.p. 110–111°, to which we assign the rearranged structure IIb. The NMR spectrum (60 Mc; CCl_4) of the diol IIb was consistent with the structure assigned (see Table 1). In particular, double irradiation with a frequency −88 c/s reduced the magnitude of the 0·90 ppm signal and removed the signal at 1·00 ppm with the appearance of a singlet at 0·95 ppm. The methine proton at C-20 could be located at 2·41 ppm consistent with an 18-nor-14β-methyl-$\Delta^{13(17)}$-structure. The nature of ring A was confirmed as follows. The NMR spectrum exhibited a broad multiplet equivalent to one proton at 3·85 ppm ($W_{1/2}$ 15 c/s) assigned to the axial 3β-H and a poorly resolved doublet (1 proton) at 3·20 ppm (J = 2·5 c/s) assigned to the 4β-H split by only one adjacent proton (3). These data are consistent[7] with the

[6] N. D. Hall and R. B. Just, *Steroids*, 111 (1965).
[7] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*, p. 42. Holden-Day (1964).

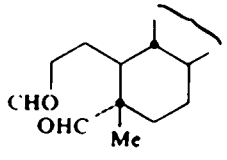
assignment as a 3α,4α-diol with a 5β,10α-A/B ring junction. The location of the Me group at C-5 in the diol IIb was confirmed by examination of the NMR spectrum (60 Mc in CCl_4) of the di-aldehyde V formed on reaction of the diol IIb with lead tetraacetate. A sharp singlet at 9·23 ppm was assigned to the aldehyde attached to the tertiary C-5, while a triplet (J = 1·3 c/s) at 9·58 ppm was assigned to the aldehyde derived from the C-3 alcohol function.

Acetylation of the diol IIb with acetic anhydride–pyridine at 20° for 3 days gave a diacetate (VIIb) as a gum, shown to be pure by TLC. The structure assigned was supported by the NMR spectrum (Table 1) which clearly pointed to the presence of an axial 3β-proton and a backbone rearranged skeleton as would be implied by its genesis from diol IIb. At no time were samples of a diol or a diacetate isolated to correspond to the physical constants reported for compounds assigned by Hall and Just[6] the structure IVa (m.p. 141–142°) and IVb (m.p. 110–111°).

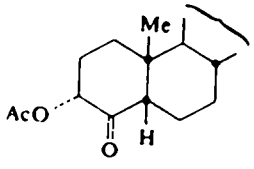
In view of the arrangement of the epoxide Ib by a Grignard reagent it was clearly of interest to investigate the reaction of the epoxide Ib with BF_3-etherate in benzene. Chromatography of the crude product gave first an acetoxy-ketone (25%) to which structure VI was assigned on the basis of spectroscopic data. The equatorial nature of the acetoxy group follows from the NMR signal of the 3β-H (4·97 ppm; $W_{1/2}$ 14 c/s) and the wavelength of the extrema in the ORD curve (303 and 276 mμ[8]). The acetoxy ketone should therefore exhibit a Cotton effect closely resembling the corresponding ketone. The observed Cotton effect (a + 10) allows assignment of the 3α-acetoxy-5β-4-keto structure (VI) [cf. 5β-4-ketone, a + 3 and 5α-4-ketone, a − 94[9]]. This is the expected product from rearrangement of a 4α,5α-epoxy compound, and is epimeric with the 3β-acetoxy-5β-cholestan-4-one described previously.[10]



IVa R, H
b R, Ac.



V



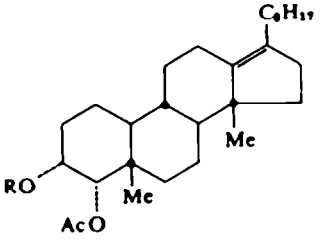
VI

Elution with solvents ranging from light petroleum–benzene to ether–benzene gave a series of gums (total 58% yield). The early fractions consisted largely of a compound to which the 3α-acetoxy-4α-hydroxy backbone rearranged structure (IIc) was assigned on the basis of its NMR spectrum. Double irradiation with −88 c/s collapsed a doublet assigned to the 21-Me group (1·00 ppm and 0·90 ppm, the latter obscured under the combined signals of the 14-Me, 5-Me and one component of the side chain doublet, 0·90 and 0·80 ppm) to a singlet at 0·95 ppm. This data and the lack of an 18-Me resonance in the normal position about 0·66 ppm pointed to the presence of an 18-nor-14β-methyl-$\Delta^{13(17)}$-structure. Further, the resonance for the 3β-H at 5·05 ppm ($W_{1/2}$ 20 c/s), being split by two adjacent protons at C_2 and one at C_4, is consistent with its assignment as geminal to an acetate group and in an axial configuration.

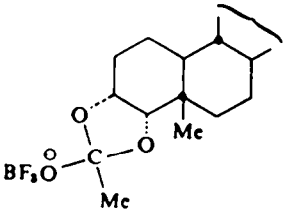
[8] C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta.* **41**, 250 (1958).
[9] C. Djerassi and W. Klyne, *J. Chem. Soc.* 2390 (1963).
[10] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* 2547 (1964).

This data supported the 5β-methyl-10α-structure proposed. Finally, the signals due to the 4β-H, a doublet centred at 3·35 ppm (J = 3 c/s) are consistent with its assigned position, equatorial and flanked to one side by a quaternary carbon and on the other by a single axial proton.

The later fractions consisted largely of a compound to which the structure VIIa was assigned on the basis of the NMR spectrum. Decoupling experiments on the 21-Me signals confirmed the presence of the 18-nor-14β-methyl-$\Delta^{13(17)}$-structure. The nature of ring A followed from the signals assigned to the 3β-H (4·03 ppm; $W_{1/2}$ 15 c/s) and 4β-H (doublet centred at 4·73 ppm; J = 3 c/s). These data are consistent with the 19-nor-5β-methyl-4α-acetoxy-3α-alcohol structure. In confirmation of structure both hydroxyacetates (IIc and VIIa) gave the diol IIb on brief treatment with LAH. The ratio of the two hydroxyacetates (IIc and VIIa) obtained from the column was estimated (TLC) as ca. 1:2.



VIIa R, H.
b R, Ac.



VIII.

The isolation of the 4α-acetoxy-3α-alcohol (VIIa) in high yield was of interest in that it was conceivable that the 3α-acetoxy group might have been drawn into the rearrangement to form the BF_3 complex of the ortho ester (VIII). Subsequent cleavage on quenching with water could then lead to a mixture of the 3α-acetoxy-4α-alcohol (IIc) and the 4α-acetoxy-3α-alcohol (VIIa). Independent experiments (TLC on silica), however, clearly demonstrated that the 4α-acetoxy-3α-alcohol (VIIa) was not formed during the BF_3 reaction but it was generated during chromatography on alumina.

The exclusive formation of the rearranged hydroxyacetate (IIa) from the epoxide Ia compared with the formation of significant quantities of the acetoxy-ketone VI in addition to rearranged material (IIc and VIIa) from epoxide Ib may be explained in terms of the greater migratory aptitude of hydrogen as compared with Me (viz. ref. 11). The unfavourable Me migration to form a 5β-methyl-3-acetoxy-4-ketone would allow the backbone rearrangement reaction to compete more favourably than in the 4-hydrogen series (Ib) where facile hydrogen migration may occur.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solns at room temp. IR spectra were recorded on a Perkin–Elmer 337 spectrometer. Alumina used for chromatography was P. Spence, Grade H, deactivated by the addition of 5% of 10% AcOH. Light petroleum refers to the fraction of b.p. 50–70°. ORD curves were determined at Westfield College, London, by kind permission of Professor W. Klyne.

Reaction of 3α-*acetoxy*-4α,5-*epoxy*-5α-*cholestane* (Ib) *with methyl magnesium iodide*

The epoxide (1·5 g, prepared as in Ref. 6) in benzene (22 ml) was added to an ether soln of MeMgI formed from Mg (1·0 g) and MeI (3·5 ml) in ether. The soln was distilled until the temp reached 66°,

[11] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* 1421 (1966).

and then refluxed for 5 hr. The reaction was worked up by pouring it into sat NH_4Cl_{aq} and extraction with ether. Adsorption of the isolated products on to alumina (100 g) in light petroleum followed by elution with light petroleum–benzene (1:2) afforded III (35%), crystallized from acetone, m.p. 154·5–155·5°. (lit.[6] m.p. 154–155°).

Benzene eluted mixed fractions (31%) and ether–benzene (1:3) eluted the 3α,4α-diol IIb (30%), crystallized acetone, m.p. 110–111°, $[\alpha]_D$ +15° (*c* 0·97), ν_{max} (CS_2) 3500 cm^{-1}, λ(EtOH) 206 mμ (*e* 8700), 210 mμ (7200), 215 mμ (4600) and 220 mμ (2300). (Found: C, 79·9; H, 11·5. $C_{37}H_{60}O_3$ requires: C, 80·5; H, 11·5%.)

Reaction of diol IIb with pyridine–Ac_2O for 3 days at 20° gave VIIb* as a gum, pure by TLC, $[\alpha]_D$ +32° (*c* 2·13), ν_{max} (liquid film) 1745, 1250 cm^{-1}.

Reaction of IIb (60 mg) in pyridine (10 ml) with $Pb(OAc)_4$ (200 mg) for 35 min at 20° gave, after work up, the dialdehyde V as a gum, ν_{max} (liquid film) 1732, 2712 cm^{-1}, NMR: 9·58 (t, J = 1·3 c/s) (C^3—H), 9·23 (s): (C^4—H).

Reaction of 3α-*acetoxy*-4α,5-*epoxy*-5α-*cholestane* (Ib) *with* BF_3-*etherate*

The epoxide (1·45 g) in benzene (35 ml) was allowed to react with BF_3-etherate (1·3 ml) for 20 sec at 20°. The reaction was quenched by the addition of sat $NaHCO_3$ aq, and the isolated products were adsorbed on to alumina (110 g) in light petroleum. Benzene–light petroleum (3:17) eluted VI (25%), crystallized from acetone, m; 165–167°, $[\alpha]_D$ +100 (*c* 0·91), ν_{max} (liquid film) 1712, 1750, 1255 cm^{-1}, ORD (MeOH–dioxan (2:1)) a_{376}^{804} +10, NMR 4·97 ($W_{1/2}$, 14 c/s) (C^3—H), 2·06 (OAc), 1·10 ($C^{19}H_3$), 0·90, 0·81 (C^{26}—H_3, C^{27}—H_3, C^{21}—H_3), 0·63 ppm ($C^{18}H_3$). (Found: C, 78·7; H, 11·0; $C_{35}H_{60}O_3$ requires: C, 78·4; H, 10·8%.) Elution with solvent mixtures ranging from benzene–light petroleum (1:1) to ether–benzene (1:40) gave a series of fractions (58%) as gums, of which the earlier fractions were shown (TLC) to consist almost exclusively of IIc $[\alpha]_D$ +30° (*c* 1·16), ν_{max} (liquid film) 3500, 1736, 1720, 1246 cm^{-1}. The later fractions were similarly shown to consist mainly of VIIa, $[\alpha]_D$ +33° (*c* 0·7) ν_{max} (liquid film) 3450, 1742, 1718, 1240 cm^{-1}. From a consideration of the intensities of the spots obtained on TLC for each of the fractions, the ratio of IIc to VIIa was estimated as ca. 1:2. Each of the hydroxy acetates IIc and VIIa gave, on reaction with LAH in ether followed by crystallization from n-hexane, the diol IIb, mp and mmp 105–109°.

Acknowledgements—We thank the Research Committee of the New Zealand Universities Grants Committee for financial support, and for fellowships (J. W. B. and J. M. C.).

* The monoacetates IIc and VIIb were never isolated completely free from each other; while the analysis figures of these materials, IIc contaminated with traces of VIIb and *vice versa*, would have agreed with the expected values it was pointless to include such data. In addition, the monoacetates and the diacetate IVb are related directly to the well characterized diol IIb.