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REACTIONS OF EPOXIDES—XVII[1]

"BACKBONE REARRANGEMENTS" OF CHOLEST-5-ENE AND 5,6α-EPOXY-5α-CHOLESTANE

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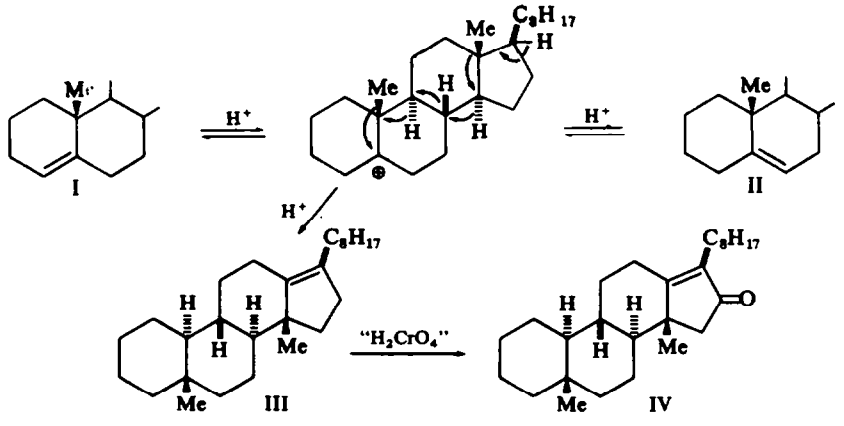
Abstract—The "backbone rearrangement" leading to 13(17)-enes (e.g. III) occurs when cholest-5-ene is heated with toluene-*p*-sulphonic acid in acetic acid, and also when 5,6α-epoxy-5α-cholestane (VII) is treated with boron trifluoride.

TURNER *et al.*[2] described the equilibration of cholest-4-ene (I) and cholest-5-ene (II) with toluene-*p*-sulphonic acid/acetic acid at 80°, and showed that further isomerization occurred when the reaction was performed under anhydrous conditions at the boiling point of acetic acid. We have now identified the major component (ca. 70%) of the oily product formed under the latter reaction conditions as the "backbone-rearranged" $\Delta^{13(17)}$-olefin (III). The structure of the olefin follows from NMR evidence[3] (21-CH_3; δ = 0·95 ppm, doublet, J = 6 c/s, decoupled by a superimposed frequency 88 c/s downfield), and was confirmed by its allylic oxidation to give the $\Delta^{13(17)}$-16-ketone (IV), and by its formation from other related rearranged systems, as described below.

GLC showed that the $\Delta^{13(17)}$-olefin, prepared by Turner's method, was contaminated by ca. 20% of another olefinic compound, and traces of at least two more, but cholest-4-ene and -5-ene were absent. The minor products have not been identified.



Treatment of the crude $\Delta^{13(17)}$-olefin (III) with sodium dichromate–acetic acid, followed by chromatography, gave the conjugated ketone (IV), as the major product. The UV absorption (λ_{max} 245 nm) resembled that reported for a similar compound with a 17-isopropyl group (λ_{max} 243 nm, ε = 13,200), prepared in the same way from a derivative of hydroxyhopanone.[4] The NMR spectrum of the 16-ketone exhibited a sharp singlet (δ = 2·02 ppm) due to the two $C_{(15)}$ protons, in accordance with the location of the angular ($C_{(18)}$) Me group at $C_{(14)}$. Moreover its ORD curve (a = −58) confirmed the 14β-configuration of the Me group. It may be seen by inverting the diagram (IV) that the unsaturated ketone is equivalent in structure and stereochemistry to a D-homo-A-nor-androst-3-en-2-one, substituted at $C_{(3)}$ by the cholestane side chain. The A-nor-3-en-2-one system is reported as giving a negative Cotton effect.[5]

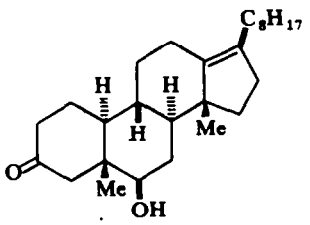
We reported previously[6] that the 6β-hydroxy-13(17)-en-3-one (V) was among the products derived by rearrangement of 5,6β-epoxy-3,3-ethylenedioxy-5β-cholestane with boron trifluoride. Huang-Minlon reduction of the product (V) gave the 6β-hydroxy-13(17)-ene structure (VIa). Oxidation of (VIa) with chromic acid, followed by further Huang-Minlon reduction of the 6-ketone (VIb) gave the $\Delta^{13(17)}$-olefin (III), identical (IR, NMR, and UV spectra, and GLC retention time) with the major olefinic component of the material derived from cholest-5-ene.

Rearrangement of 5,6α-epoxy-5α-cholestane. Henbest and Wrigley[7] reported the isolation of 5β-cholestan-6-one (VIII; 30%) and two unidentified hydroxy compounds from the rearrangement of 5,6α-epoxy-5α-cholestane (VII) with boron trifluoride etherate. We have re-examined this reaction, in collaboration with Dr. J. M. Coxon and Mr. W. J. Rae, University of Canterbury, and have obtained 5β-cholestan-6-one (56%), the 6α-hydroxy-$\Delta^{13(17)}$-olefin (VIc; 18%), cholesta-3,5-diene (5%), and two further compounds tentatively assigned the 5-formyl-B-nor-5α-cholestane (IX; 5%) and the 6α-hydroxy-$\Delta^{8(9)}$-olefin (X; 5%) structures. The last two compounds were incompletely characterized; the proposed structures are based upon mechanistic considerations and spectroscopic data (Experimental).

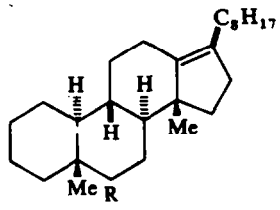
The location of the olefinic bond in the $\Delta^{13(17)}$ compound (VIc) was established from its NMR spectrum, which showed the typical low-field signal (δ = 2·42 ppm) due to the allylic $C_{(20)}$ proton: double-irradiation experiments confirmed the spin–spin coupling with the $C_{(21)}$ Me group (doublet, J = 6 c/s, δ = 0·95 ppm), characteristic of $\Delta^{13(17)}$-unsaturated "backbone rearranged" cholestenes.[3] The NMR spectrum also showed the 6α-OH group to be axial (6β-H signal; δ = 3·30 ppm, $W_{\frac{1}{2}}$ = 5·5 c/s[8]). The derived ketone (VIb) was identical in all respects with the sample obtained from the 6β-hydroxy compound (VIc) as described above, and afforded another sample of the $\Delta^{13(17)}$-olefin (III) on Huang-Minlon reduction.

Henbest and Wrigley have attributed the relatively slow and inefficient hydride shift in the 5α,6α-epoxide (VII) to the unfavourable 5β-configuration of the product (VIII).[7] The 4α,5α-epoxide (XI) was reported to react easily, although also affording a strained 5β-compound.* The greater flexibility of ring A was offered[7] in explanation of the higher reactivity of the 4α,5α-epoxide. We believe the difference can be interpreted more precisely in terms of conformational features of the respective

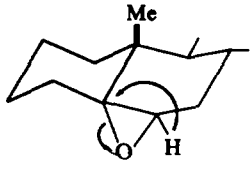
* We are grateful to Dr. J. R. Hanson for drawing our attention to this apparent anomaly.



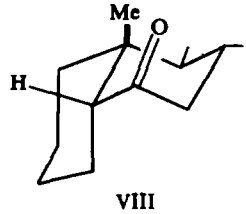
V



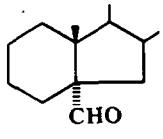
VI a: R = β-OH
b: R = :O
c: R = α-OH



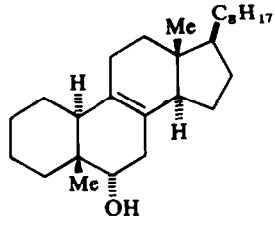
VII



VIII

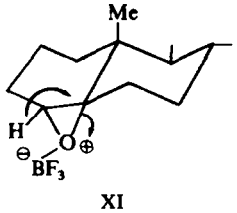


IX

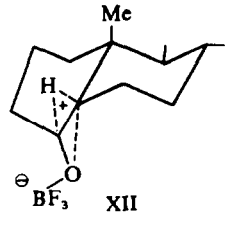


X

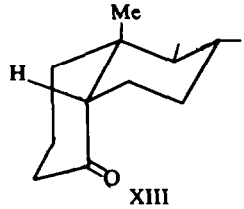
transition states for hydride migration. In the 4α,5α-epoxide (XI) a transition state (XII) involves only a modest change in geometry of ring A, and no strain in ring B. The subsequent adjustment of ring A to the stable chair conformation in the 5β-4-ketone (XIII) needs relatively little activation energy, and would occur rapidly *after* the rate-determining hydride shift. In the 5α,6α-epoxide (VII), however, the hydride group needs to move through a greater distance, and the transition state (XIV)



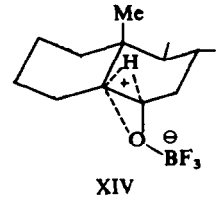
XI



XII



XIII



XIV

requires considerable and simultaneous distortion of both rings A and B, with correspondingly greater energy requirements. Competition from alternative reactions is therefore more effective in the 5α,6α-epoxide, and migration of the *anti* $C_{(19)}$-Me group ensues to give a $C_{(10)}$-carbonium ion, as the primary step in the "backbone rearrangement".

Although we cannot yet explain why some epoxides undergo the complete "backbone rearrangement" while others give "Westphalen" ($\Delta^{9(10)}$) type products,[3] the cholestene isomerizations[9] are regarded[10] as olefin equilibrations, in which the double bond ultimately arrives at its most stable location in the steroid nucleus. The $\Delta^{13(17)}$-position is apparently favoured because it leaves the perhydrophenanthrene part of the molecule in the "all-chair" *trans-anti-trans* form, with ring D almost planar. The conformational change in ring D relieves the quite considerable strain (4–6 kcal/mole)[11] inherent in the original 13β,14α-*trans*-fusion to ring C. Similar strain relief in ring D explains the well-known isomerization of cholest-7-ene, *via* the -8(14)-ene, to give cholest-14-ene.[13]

EXPERIMENTAL

Rotations were measured for ca. 1% solns in $CHCl_3$ at room temp. ORD curves were kindly determined by Professor W. Klyne. NMR spectra were determined at 60 mc in CCl_4, with Me_4Si as internal standard. UV spectra were recorded for EtOH solns. Alumina was P. Spence, Grade H. "Deactivated alumina" refers to Grade H to which 5% of 10% AcOH has been added. BF_3-etherate was B.D.H., freshly redistilled before use. Gas chromatography was kindly carried out by Mr. M. A. Wilson, using a column of 3% SE30 on "Anakrom-ABS" at 200°. Products (VIb) and (VIc) were gums, which rapidly auto-oxidized in air to a mixture of polar products. This is a common feature of $\Delta^{13(17)}$-olefins, which made it impossible to obtain reliable microanalyses.

Isomerization of cholest-5-ene (II). A soln of cholest-5-ene (2 g) and toluene-*p*-sulphonic acid (2 g) in AcOH (60 ml) and cyclohexane (20 ml) was distilled slowly until the b.p. reached 117° (15 min), then heated under reflux for a further 15 min. The product, isolated by means of ether, was decolorized by passage through alumina (20 g, Grade H) in light petroleum. The resulting mixture of olefins was an oil, $[\alpha]_D$ +21°, containing ca. 70% of the rearranged 13(17)-*ene* (III) and at least three minor components (GLC); ν_{max} 1207, 1175, 1151, 1130, 958, 937, and 840 cm^{-1}; NMR: δ = 0·83 ppm (5β-Me), 0·88 (14β-Me), 0·95 (21-Me; doublet, J = 6 c/s, decoupled by a signal 88 c/s down-field), 0·79, 0·88 (26, 27-Me_2).

Allylic oxidation of the 13(17)-*olefin* (III). The crude olefin (1·5 g) in AcOH (100 ml) and benzene (40 ml) was stirred with powdered $Na_2Cr_2O_7$ (4·5 g) at 80–85° for 45 min. Chromatography of the product on deactivated alumina (100 g) gave gummy fractions (eluted by light petroleum containing up to 2% benzene) which contained at least two compounds (TLC). One of these appeared to be a saturated ketone, ν_{max} 1725 cm^{-1}, but was not obtained in pure form. Elution with light petroleum–benzene (100:3 and 100:5) gave the 13(17)-*en*-16-*one* (IV) as a gum, $[\alpha]_D$ −5°, ν_{max} 1713, 1660 cm^{-1}; λ_{max} 245 nm (ε 12,000); ORD (dioxan): $[\phi]_{348}$ −2500°, $[\phi]_{297}$ +3270°; (MeOH): $[\phi]_{333}$ −2250°, $[\phi]_{288}$ +4750°, $[\phi]_{251}$ +2220°, $[\phi]_{222}$ +22,200°! Mass spectrum: M^+, 384 ($C_{27}H_{44}O$ requires 384), principle fragment ions at m/e 299 (M—C_6H_{13}) and m/e 271 (M—C_8H_{17}). NMR: δ = 0·78, 0·875 ppm (26, 27-Me_2), 0·85 (5β-Me), 1·08 (14β-Me), 1·08 (21-Me, doublet, J = 7 c/s, decoupled by a signal 90 c/s down-field), 2·02 (15 $>CH_2$), 2·58 (20-H, broad multiplet).

The 2,4-*dinitrophenylhydrazone* crystallized from EtOH, m.p. 111–113°, λ_{max} 394 nm (ε = 20,500), (Found: C, 69·8; H, 8·4; N, 10·5. $C_{33}H_{48}N_4O_4$ requires: C, 70·2; H, 8·6; N, 9·9%).

Rearrangement of 5,6α-*epoxy*-5α-*cholestane* (VII). The epoxide (1 g) in benzene (1·5 ml) was treated with BF_3-etherate (1 ml) for 45 sec. After pouring the mixture into ether and washing with $NaHCO_3$aq, the isolated product was adsorbed on to alumina (50 g) in light petroleum. This solvent eluted VIII (56%), m.p. 130–131° from acetone, $[\alpha]_D$ −42°, ORD: $[\phi]_{307}$ −7090°, $[\phi]_{269}$ +9000°. [Lit.[7] m.p. 133°, $[\alpha]_D$ −44°].

Benzene–light petroleum (1:19) eluted the 6α-*hydroxy*-13(17)-*ene* (VIc; 18%) as a gum, homogeneous by TLC, $[\alpha]_D$ +43°, ν_{max} 3600 cm^{-1}; UV spectrum: $\varepsilon_{200\,nm}$ 11,000, ε_{205} 9400, ε_{210} 7200; NMR: δ = 0·825 ppm (5β-Me), 0·88 (14β-Me), 0·95 (21-Me, doublet, J = 6 c/s), 3·30 (6β-H, doublet, $W_{\frac{1}{2}}$ = 5·5 c/s).

In another experiment (by Dr. J. M. Coxon and Mr. W. J. Rae) the 5α,6α-epoxide (2·009 g) in benzene (100 ml) reacted with BF_3-etherate (0·75 ml) for 1·5 min. Chromatography of the product on silica gel gave the following fractions:

(i) Cholesta-3,5-diene (103 mg), eluted by light petroleum, m.p. 77–78°, $[\alpha]_D$ −118°, λ_{max} 230 nm (ε 17,200), 237 nm (ε 18,800), and 245 nm (ε 12,100). [Lit.[13] m.p. 80°, $[\alpha]_D$ −123°, λ_{max} 235 nm].

(ii) *An aldehyde* (116 mg) probably IX, eluted by light petroleum as a gum, ν_{max} 2605, 1709 cm^{-1}; NMR: δ = 9·78 ppm (—CHO), 0·92, 0·82, (side-chain methyl groups), 0·875 (19-Me), 0·65 (18-Me).

(iii) 5β-Cholestan-6-one (1·028 g), m.p. 130–131°, $[\alpha]_D$ −42°, eluted by light petroleum with 1–4% benzene.

(iv) The rearranged VIc (328 mg), eluted by light petroleum–benzene (10:1) as a gum, $[\alpha]_D$ +43°, ν_{max} 3600 cm^{-1}, UV: $\varepsilon_{204\,nm}$ 7300, ε_{210} 6100, ε_{215} 4200.

(v) A *hydroxy-olefin*, probably X (99 mg), eluted by light petroleum–benzene (2:1) as a gum, $[\alpha]_D$ +13°, ν_{max} 3605 cm^{-1}; UV: $\varepsilon_{215\,nm}$ 4700, ε_{210} 6050, ε_{208} 6200; NMR: δ = 3·50 ppm (6β-H; quartet, apparent $J_{6\beta,7\alpha}$ 11 c/s, $J_{6\beta,7\beta}$ 3 c/s), 1·18 (5β-Me), 0·92, 0·82 (side-chain Me groups) 0·75 (18-Me). (Found: C, 83·75; H, 12·0. $C_{27}H_{46}O$ requires: C, 83·9; H, 12·0%).

The 13(17)-*unsaturated* 6-*ketone* (VIb).

(a) Oxidation of VIc in acetone with 8N chromic acid gave crude VIb as a gum, homogeneous by TLC, $[\alpha]_D$ +54°; ORD (MeOH): $[\phi]_{310}$ +5880°, $[\phi]_{268}$ −7600°; ν_{max} 1707 cm^{-1}, NMR: δ = 1·09 ppm (5β-Me), 0·975 ppm (14β-Me).

(b) Compound V[6] (60 mg) in diethylene glycol (2 ml) and hydrazine hydrate (0·06 ml) was heated for 30 min, then a soln of Na (60 mg) in diethylene glycol (0·6 ml) was added, and the mixture was heated at 200° for 5·5 hr. The product, isolated with ether, was VIa, needles, m.p. 97–99° from acetone, ν_{max} 3615 cm^{-1}; NMR: δ = 0·79 ppm (5β-Me), 0·90 (14β-Me), 0·95 (21-Me, doublet, J = 6 c/s), 0·88, 0·79 (26, 27-Me_2), 3·20 (6αH, $W_{\frac{1}{2}}$ = 11 c/s). Oxidation of this alcohol with 8N chromic acid in acetone gave gummy VIb, identical in all respects ($[\alpha]_D$, IR, NMR, TLC) with the sample prepared under (a).

Huang–Minlon reduction of VIb with hydrazine as described above gave III in purer condition than the product obtained by isomerization of cholest-5-ene, though still as an oil. The essential identity of these olefinic materials was confirmed from their IR and NMR spectra.

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