## 715. *Aspects of Stereochemistry. Part XVI.* The Effect of a Hydroxyl Group upon the Metal-reduction of Vicinal Epoxides.*

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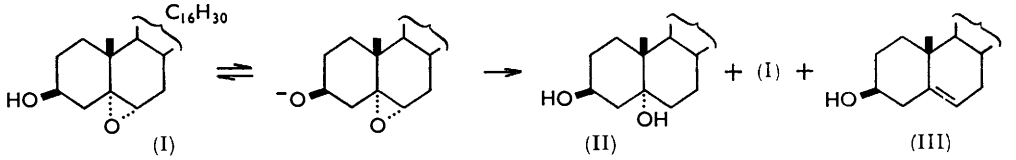
Reduction of a vicinal epoxycyclohexane by lithium–ethylamine normally gives an axial alcohol, but an olefin can be formed in competition if the molecule also contains a hydroxyl group. The cause of this may be that the anion from the hydroxyl group inhibits the formation of the anionic intermediate that leads to the axial alcohol.

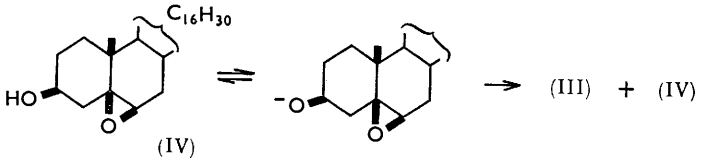
Reduction of the oxetan, 3α,5α-epoxycholestane, gave a mixture of the two axial alcohols, cholestan-3α- and -5α-ols.

High yields of axial alcohols are usually obtained when vicinal epoxides of the steroid series are reduced by the lithium–ethylamine method;[1] the specificity may be due to the small steric requirements of the attacking solvated electrons. The reduction of several epoxy-alcohols related in structure to the simpler epoxides examined before is now reported.

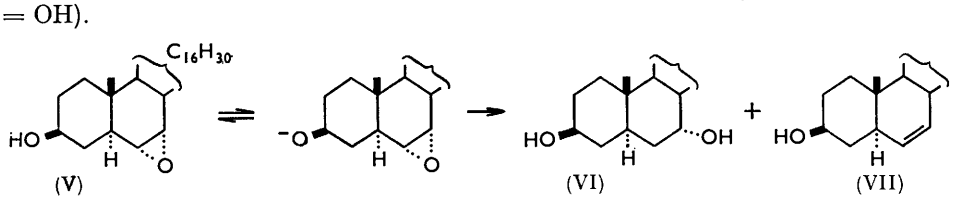
5,6-*Epoxides.*—Cholesterol α- and β-epoxide were each treated with lithium in ethylamine under the same conditions. The α-oxide (I) gave the expected 3β,5α-diol (II) in only moderate yield (40%), the remainder of the product being starting material (17%), and, unexpectedly, cholesterol (III) (40%). Only the 5α-alcohol was obtained on reduction of the related unsubstituted compound, 5α,6α-epoxycholestane.[1]




Reduction of cholesterol β-oxide (IV) gave starting material (80%) and cholesterol (12%). This result is very different from that with 5β,6β-epoxycoprostane where the axial alcohol, cholestan-6β-ol, was obtained as the major product.




6α,7α-*Epoxide.*—Reduction of 6α,7α-epoxycholestan-3β-ol (V) gave the 3β,7α(axial)-diol (VI) as the main product, together with some of the olefinic alcohol (VII). The proportion of olefinic compound formed in this reaction is less than was obtained from the 5α,6α- or 7α,8α-epoxides containing 3β-hydroxyl substituents (*i.e.*, I, or VIII where R = OH).



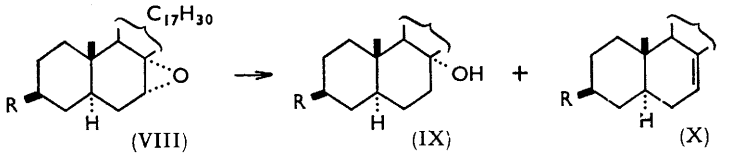

7α,8α-*Epoxides.*—Reductions of the 7α,8α-epoxyergost-22-enes (cf. VIII), containing hydrogen, β-hydroxyl, or β-methoxyl substituents at $C_{(3)}$, were investigated; the compound

* Part XV, preceding paper.

[1] Hallsworth and Henbest, *J.*, 1957, 4604.

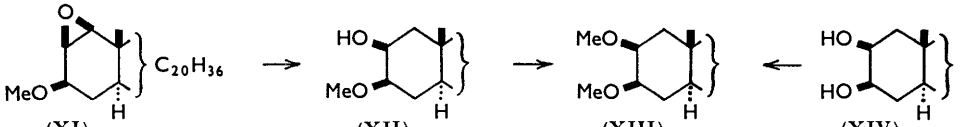
with a 3β-acetoxyl group had been previously [1] found to give a mixture of the 3β,8α(axial)-diol (IX; R = OH) and the olefinic alcohol (X; R = OH). The following table shows that the alcohol : olefin ratio is highest when there is no 3-oxygen substituent and lowest when the 3-substituent is hydroxyl (cf. discussion below).

| 3β-Substituent | H | OMe | OAc | OH |
|---|---|---|---|---|
| Alcohol : olefin ratio | 7·7 | 5·2 | 1·5 | 0·67 |



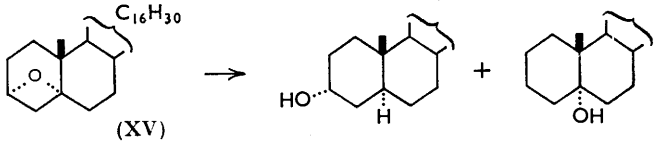

(VIII) (IX) (X)

3β-*Methoxy*-1β,2β-*epoxide*.—The experiments with 7α,8α-epoxides indicate that the alcohol : olefin ratio is not greatly affected when a 3β-hydrogen is replaced by a 3β-methoxyl substituent. A methoxyl group placed more closely to an epoxide group might have more effect on the reaction course, and 1β,2β-epoxy-3β-methoxycholestane (XI) was therefore prepared and reduced. The normal reaction occurred to give an axial alcohol (XII). This compound was not isolated but was converted by methylation into β,3β-dimethoxycholestane (XIII), synthesised from the known 2β,3β-diol (XIV).




(XI) (XII) (XIII) (XIV)

3α,5α-*Epoxide*.—Oxetans have not apparently been reduced by metals in ammonia or amines. Treatment of the endo-epoxide, 3α,5α-epoxycholestane [2] (XV) with lithium–ethylamine yielded the axial alcohols, cholestan-3α- and -5α-ol, in a 3 : 7 ratio.




(XV)

*Discussion*.—Two competing reactions evidently occur when vicinal epoxycyclohexanes are reduced with lithium in ethylamine: (*a*) an axial alcohol is formed and (*b*) the epoxide is reduced to the corresponding olefin. Reaction (*a*) is dominant for epoxides not containing nearby hydroxyl groups; however, the formation of a small amount of the olefin (X; R = H) from the epoxide (VIII; R = H) shows that reaction can occur in an epoxide not containing a hydroxyl group.

The experiments with the cholesterol α- and β-oxide in which cholesterol was formed and starting materials were partially recovered indicate that reaction (*b*) occurs (to give cholesterol) because reaction (*a*) is inhibited. Inhibition of reaction (*a*) may be caused by rapid conversion of the hydroxyl group (by lithium or lithium ethylamide) into its conjugate anion, which then inhibits the formation of an anionic species that is an intermediate for the formation of an axial alcohol. Thus the greatest recovery of starting material, corresponding to the greatest inhibition of reaction (*a*), was observed with cholesterol β-oxide (IV) where reaction (*a*) could give a 5-carbanionic intermediate. With cholesterol α-oxide the corresponding intermediate is placed one carbon farther away, at $C_{(6)}$; reaction (*a*) is, therefore, less inhibited than in the β-oxide and takes place at a

[2] Clayton, Henbest, and Smith, *J.*, 1957, 1982.

similar rate to reaction (*b*), about equal amounts of the axial alcohol and the olefin being formed. The anion of the 3β-hydroxy-group still maintains an effect across two rings to $C_{(7)}$, comparable amounts of 8α-alcohol and olefin being obtained from the 7α,8α-epoxide (VIII; R = OH). Further studies of these effects are being made.

The alcohol : olefin product ratio is higher on reduction of the 3-hydroxy-6α,7α-epoxide (V) than of the 3-hydroxy-7α,8α-epoxide (VIII; R = OH), although the 3-hydroxyl group is closer to the group to be reduced in the former compound. Thus the product containing a trisubstituted $\Delta^7$-bond is apparently more easily formed than that containing a disubstituted $\Delta^6$-bond, indicating that the extent of reaction (*b*) for a particular compound can depend on the environment (especially the degree of substitution) of the epoxide as well as on the presence of a hydroxyl group and the distance of this group from the site of reaction.

Evidence accrues that the metal-reduction of aromatic compounds can involve two single-electron addition stages.[3,4] The possibility that additions of single electrons occur as intervening steps in the overall reaction paths (*a*) or (*b*) for the reduction of epoxides needs therefore to be examined.

The formation of both axial alcohols from the reduction of the 3α,5α-epoxide (XV) shows that, in this compound, the direction of ring opening is not strongly influenced by the secondary *versus* tertiary character of the 3- and 5-atoms at which reduction occurs.

## Experimental

M. p.s were determined on a Kofler block. Rotations were determined for $CHCl_3$ solutions. The infrared absorptions of products were in each case consistent with the structures assigned. Light petroleum refers to the fraction of b. p. 40—60°. P. Spence alumina (grade H) was used for chromatography; when necessary it was deactivated with dilute acetic acid.

*Reduction of* 5α,6α-*Epoxycholestan*-3β-*ol* (I).—The epoxy-alcohol (0·5 g.) was reduced with lithium (0·25 g.) in ethylamine (25 g.) for 1 hr. and the product chromatographed on deactivated alumina (50 g.). Elution with benzene gave cholesterol (0·206 g.), m. p. and mixed m. p. 147—148°, $[\alpha]_D$ −40°. Benzene–ether (9 : 1) eluted starting material (83 mg.), m. p. and mixed m. p. 141°, $[\alpha]_D$ −46°, whilst elution with ether gave cholestane-3β,5α-diol (0·2 g.), m. p. and mixed m. p. 223—225°, $[\alpha]_D$ +20°, after one crystallisation from ethyl acetate–methanol.

*Reduction of* 5β,6β-*Epoxycholestan*-3β-*ol* (IV).—The epoxy-alcohol (0·5 g.) was treated with lithium (0·25 g.) in ethylamine (15 g.) for 1 hr. Isolation *via* ether gave a product (0·495 g.), which was chromatographed on deactivated alumina (50 g.). Benzene eluted cholesterol (60 mg.), m. p. and mixed m. p. 148° (from ethanol), $[\alpha]_D$ −39°. Further elution with benzene–ether (9 : 1) afforded starting material (0·4 g.), m. p. and mixed m. p. 132°, $[\alpha]_D$ +11°.

*Preparation and Reduction of* 6α,7α-*Epoxycholestan*-3β-*ol* (V).—3β-Acetoxycholest-6-ene (0·5 g.) in dry benzene (10 ml.) was treated with a 0·508M-solution (2·5 ml., 1·1 mol.) of perbenzoic acid in benzene for 10 hr. at 20°. Potassium hydroxide (0·5 g.) in methanol (50 ml.) was added and the mixture was kept at 20° for 18 hr. The product (0·47 g.) was isolated with ether and chromatographed on deactivated alumina (50 g.). Elution with benzene–ether (9 : 1) yielded 6α,7α-*epoxycholestan*-3β-*ol* (0·465 g.), m. p. 142—143° (from methanol), $[\alpha]_D$ −40° (Found: C, 80·5; H, 11·5. $C_{27}H_{46}O_2$ requires C, 80·55; H, 11·5%).

The epoxy-alcohol (0·2 g.) was reduced with lithium (0·1 g.) in ethylamine (10 g.) (solution blue for 1 hr.). Isolation *via* ether afforded a product (0·2 g.) that was chromatographed on deactivated alumina (20 g.). Elution with benzene gave cholest-6-en-3β-ol (40 mg.), m. p. and mixed m. p. 122—124° (from methanol), $[\alpha]_D$ −90°. Elution with ether yielded cholestane-3β,7α-diol (0·16 g.), m. p. 152—153°, $[\alpha]_D$ +10°, after crystallisation from methanol. Acetylation of the diol with acetic anhydride–pyridine at 20° gave the diacetate, m. p. 137—138°, $[\alpha]_D$ −16° (recorded data for 3β,7α-diol are m. p. 152—153°, $[\alpha]_D$ +8°, and for its diacetate, m. p. 138—139°, $[\alpha]_D$ −17°).

*Preparation and Reduction of* 7α,8α-*Epoxyergost*-22-*ene* (VIII; R = H).—Ergosta-7,22-diene (1 g.), in dry benzene (20 ml.), was treated with a 0·473M-solution (6 ml., 1·1 mol.) of perbenzoic

[3] Birch and Nasipuri, *Tetrahedron*, 1959, **6**, 148.
[4] Wawzonek and Wearring, *J. Amer. Chem. Soc.*, 1959, **81**, 2067, where earlier references are given.

acid in benzene for 8 hr. at 20° (no peracid remained). After being shaken with 10% aqueous potassium hydroxide and water, the solution was dried by azeotropic distillation and evaporated to give a product (1·03 g.) which, on recrystallisation from acetone, gave 7α,8α-*epoxyergost*-22-*ene* (0·75 g.), m. p. 141·5—143°, $[\alpha]_D$ −10° (Found: C, 84·3; H, 11·55. $C_{28}H_{46}O$ requires C, 84·35; H, 11·65%), $\nu_{max.}$ (in $CS_2$) 975 cm.$^{-1}$ ($\Delta^{22}$).

The epoxide (0·5 g.) was reduced with lithium (0·25 g.) in ethylamine (40 g.) (solution blue for 1 hr.). The product (0·5 g.) was isolated with ether and chromatographed on alumina (50 g.). Light petroleum eluted ergosta-7 : 22-diene (60 mg.), m. p. and mixed m. p. 125—126°, $[\alpha]_D$ −16°. Elution with benzene–ether (19 : 1) afforded *ergost*-22-*en*-8α-*ol* (0·44 g.), m. p. 117—118° (from methanol), $[\alpha]_D$ −26° (Found: C, 83·9; H, 12·0. $C_{28}H_{48}O$ requires C, 83·95; H, 12·1%), $\nu_{max.}$ (in $CS_2$) 3620 (OH) and 975 cm.$^{-1}$ ($\Delta^{22}$).

*Preparation and Reduction of* 3β-*Methoxy*-7α,8α-*epoxyergost*-22-*ene* (VIII; R = OMe).—3β-Methoxyergosta-7,22-diene (4·12 g.; m. p. 150—151°) in dry benzene (75 ml.) was treated with a 0·493M-solution (23 ml., 1·1 mol.) of perbenzoic acid in benzene for 7 hr. at 20° (no peracid remained). The solution was then filtered through deactivated alumina (15 g.) and evaporated under reduced pressure to give 3β-*methoxy*-7α,8α-*epoxyergost*-22-*ene* (4·1 g.), m. p. 143·5—144° (from acetone), $[\alpha]_D$ −18° (Found: C, 81·5; H, 11·45. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%).

The epoxide (0·5 g.) was reduced with lithium (0·25 g.) in ethylamine (25 g.) for 1 hr. Isolation with ether afforded a product (0·5 g.) that was chromatographed on deactivated alumina (50 g.). Elution with light petroleum gave 3β-methoxyergosta-7,22-diene (80 mg.), m. p. and mixed m. p. 150—151°, $[\alpha]_D$ −22°. Light petroleum–benzene (1 : 1) eluted 3β-*methoxyergost*-22-*en*-8α-*ol* (0·42 g.), m. p. 152—153° (from methanol), $[\alpha]_D$ −30° (Found: C, 81·1; H, 11·65. $C_{29}H_{50}O_2$ requires C, 80·85; H, 11·7%), $\nu_{max.}$ (in $CS_2$) 3620 (OH), 1108 (OMe), and 975 cm.$^{-1}$ ($\Delta^{22}$).

The methoxy-8α-alcohol (50 mg.) in pyridine (2 ml.) was treated with thionyl chloride (0·1 ml.) at 20°. After 30 min. the product was isolated with ether, then dissolved in light petroleum and filtered through deactivated alumina. Crystallisation of this material (45 mg.) from acetone gave 3β-methoxyergosta-7,22-diene, m. p. and mixed m. p. 149—150°, $[\alpha]_D$ −22°.

*Preparation and Reduction of* 7α,8α-*Epoxyergost*-22-*en*-3β-*ol* (VIII; R = OH).—A solution of 3β-acetoxy-7α,8α-epoxyergost-22-ene (0·9 g.) in 1% ethanolic potassium hydroxide (200 ml.) was left for 18 hr. at 20°. Isolation with ether gave the *epoxy-alcohol* (0·815 g.), m. p. 153—154° (from methanol), $[\alpha]_D$ −10·5° (Found: C, 81·1; H, 11·1. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

The epoxy-alcohol (0·5 g.) was reduced with lithium (0·25 g.) in ethylamine (25 g.) for 1 hr. Isolation with ether gave material (0·485 g.) which was adsorbed on deactivated alumina (50 g.). Elution with benzene yielded ergosta-7,22-dien-3α-ol (0·29 g.), m. p. and mixed m. p. 173—174° (from ethanol). Ether eluted *ergost*-22-*ene*-3β,8α-*diol* (0·195 g.), m. p. 190—191° (from methanol), $[\alpha]_D$ −23·5° (Found: C, 80·7; H, 11·6. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

Similar reduction of 3β-acetoxy-7α,8α-epoxyergost-22-ene (0·5 g.) gave ergosta-7,22-dien-3β-ol (0·18 g.) and the 3β,8α-diol (0·27 g.).

*Preparation and Reduction of* 1β,2β-*Epoxy*-3β-*methoxycholestane* (XI).—1β,2β-Epoxycholestan-3β-ol (0·3 g.) was dissolved in a M-solution (20 ml.) of potassium t-butoxide in t-butyl alcohol; methyl iodide (1·5 ml.) was added, and the mixture was kept at 20° for 1 hr. The product (0·305 g.) was isolated with ether and chromatographed on deactivated alumina (20 g.). Elution with light petroleum–benzene (9 : 1) afforded 1β,2β-*epoxy*-3β-*methoxycholestane* (0·245 g.), m. p. 102—103° (from methanol), $[\alpha]_D$ +63° (Found: C, 80·7; H, 10·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

The epoxide (0·25 g.) was reduced with lithium (0·125 g.) in ethylamine (15 g.). Isolation with ether gave a product (0·25 g.) which was dissolved in a M-solution (30 ml.) of potassium t-butoxide in t-butyl alcohol, and methyl iodide (2 ml.) was then added. The whole was kept at 20° for 1 hr., and the steroid was isolated with ether. This material was remethylated by the same procedure, to yield a final product (0·245 g.) from which 2β,3β-dimethoxycholestane (0·195 g.) (XIII), m. p. and mixed m. p. 88—90° (from methanol), $[\alpha]_D$ +36°, was obtained.

2β,3β-*Dimethoxycholestane* (XIII).—Cholestane-2β,3β-diol (XIV) (0·1 g.) was dissolved in a M-solution (10 ml.) of potassium t-butoxide in t-butyl alcohol, and methyl iodide (0·7 ml.) added. After the mixture had been kept at 20° for 1 hr., the product was isolated with ether. This material was remethylated by the same procedure, to give a final product (95 mg.) that was adsorbed on to deactivated alumina (5 g.) from light petroleum. Elution with light

petroleum gave the *dimethyl ether* (65 mg.), m. p. 91—92° (from methanol), $[\alpha]_D$ +36° (Found: C, 80·3; H, 12·1. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%), $\nu_{max.}$ (in $CS_2$) 1105 cm.$^{-1}$ (OMe) (no hydroxyl band).

*Reduction of* 3α,5α-*Epoxycholestane* (XV).—The epoxide (50 mg.) was reduced with lithium (50 mg.) in ethylamine (10 g.). Isolation with ether gave material (50 mg.) that was chromatographed on deactivated alumina (5 g.). Light petroleum eluted cholestan-5α-ol (35 mg.), m. p. and mixed m. p. 108—109° (from acetone), $[\alpha]_D$ +22°. Elution with light petroleum–benzene (1 : 1) gave cholestan-3α-ol (15 mg.), m. p. and mixed m. p. 181—182°, having an infrared spectrum identical with that of an authentic sample.

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