924. *Aspects of Stereochemistry. Part VII.* Metal Reduction of Vicinal Epoxy*cyclo*hexanes.*

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Reduction of vicinal epoxy*cyclo*hexanes of the steroid series with lithium–ethylamine is shown to yield axial alcohols. This method can be more powerful and specific than that with lithium aluminium hydride. Thus 7α : 8α- and 9α : 11α-epoxides, which are not reduced by the hydride, are converted into 8α- and 9α-alcohols by metal–amine reduction, and 5β : 6β-epoxycholestane, which yields an exceptionally high proportion (~60%) of the equatorial 5β-alcohol on reduction with hydride, gives a high yield of the axial 6β-alcohol with lithium–ethylamine. The metal–amine reactions are visualized as proceeding by attack of solvated electrons, effectively a nucleophilic reagent of low steric requirements.

Apart from the isolation of propan-2-ol on treatment of propylene oxide with sodium in ammonia,[1] very little appears to be known about directing influences in the metal reduction of unsymmetrical vicinal epoxides. In order to gain some knowledge of the stereochemical course of such reactions, various epoxides of the steroid series have been reduced by the convenient lithioethylamine technique.[2]

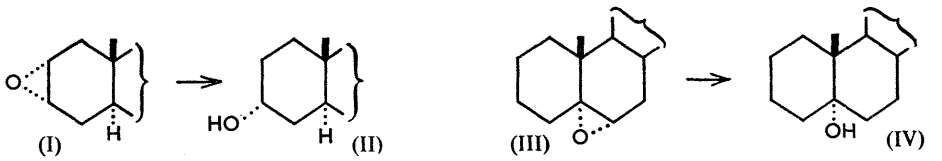
In this way, 2α : 3α- (I) † and 5α : 6α-epoxycholestane (III) gave good yields of the

* Part VI, preceding paper. † Partial steroid formulæ are used in this paper.

[1] Birch, *J. Proc. Roy. Soc. New South Wales*, 1950, **83**, 245.

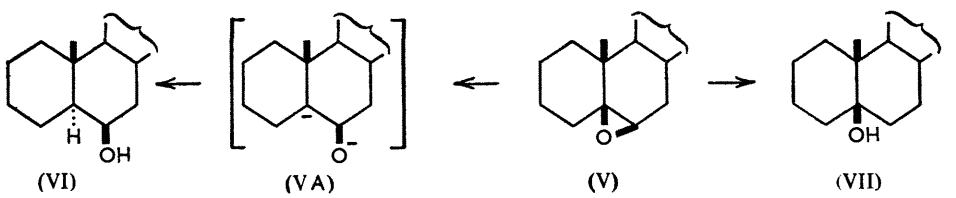
[2] (*a*) Benkeser, Robinson, Sauve, and Thomas, *J. Amer. Chem. Soc.*, 1955, **77**, 3230; (*b*) Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.

axial alcohols (II) and (IV), the reactions proceeding in the same direction as reduction with lithium aluminium hydride,[3] Attack by the nucleophilic aluminium hydride anion is usually considered to be the chief driving force in the opening of epoxide rings by the



latter reagent: in the metal–amine reductions solvated electrons may be regarded as the corresponding nucleophil (cf. below).

Reduction of 5β : 6β-epoxycholestane [4] (V) with lithium–ethylamine gave the axial 6β-alcohol (VI) as the main product (~80%). If this reaction is depicted as proceeding



through an intermediate $C_{(5)}$-carbanion (cf VA), addition of a proton at position 5 takes place from an α-direction to give the more stable *trans*-ring fusion (as do other such reactions [5]). This reduction also afforded a small amount (6%) of the 5β-alcohol (VII), in which the hydroxyl group is equatorial to ring B wherein reaction is taking place. This was the only example where some equatorial-alcohol product was detected, perhaps because the epoxide (V) was the only trisubstituted epoxide investigated where the formation of an axial alcohol requires the nucleophil to attack at the more alkylated position.* Thus it was not surprising to find that reduction of this epoxide with lithium aluminium hydride gave less of the axial alcohol (VI), approach of the bulky aluminium hydride anion to position 5 being inhibited. The large proportion (~60%) of equatorial product (VII) obtained from this reaction with hydride is noteworthy, and appears to be the most extreme example of the violation of the rule of axial opening of epoxide rings flanked by saturated groupings.†

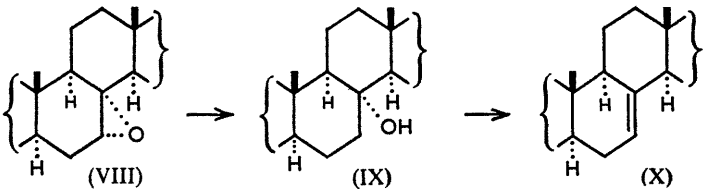
The relative bulkiness of the aluminium hydride anion also appears to be responsible for the fact that 7α : 8α- and 9α : 11α-epoxy-steroids have not been reduced to alcohols by the hydride reagent, top(β)-face approach to the centre of the steroid molecule being prevented by the angular methyl groups. Both epoxides were, however, reduced by the lithium–ethylamine method. The 7α : 8α-epoxide (VIII) gave an alcohol resistant to acetylation under the normal conditions, which is therefore the 8α-alcohol (IX): this again is an axial product, as ring B is in a boat conformation.[8] Dehydration of the 8α-alcohol with

* Attack at position 5 takes place when cholesterol β-epoxide and esters are opened with halogen acids, 5α-halogeno-6β-alcohols being formed.[6] In these reactions protonation of the epoxide-oxygen atom promotes ionization of the bond to the more alkylated 5-position, and attack of an anion at this centre is therefore encouraged. In contrast, in the present reductions, the nucleophilic is likely to be much greater than the electrophilic driving force, and the reactions are therefore more sensitive to steric factors.

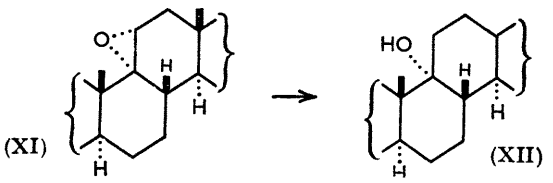
† Reduction of the related cholesterol β-epoxide with lithium aluminium hydride has been reported [7] to give a rather different ratio of products, 3β : 5β-diol (20%) and 3β : 6β-diol (60%).

[3] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.
[4] Preparation as for cholesterol β-epoxide: Davis and Petrow, *J.*, 1949, 2536.
[5] Barton and Robinson, *J.*, 1954, 3045.
[6] Cf. Barton, Miller, and Young, *J.*, 1951, 2598.
[7] Plattner, Heusser, and Feurer, *Helv. Chim. Acta*, 1949, **32**, 587.
[8] Clayton, Henbest, and Jones, *J.*, 1953, 2015.

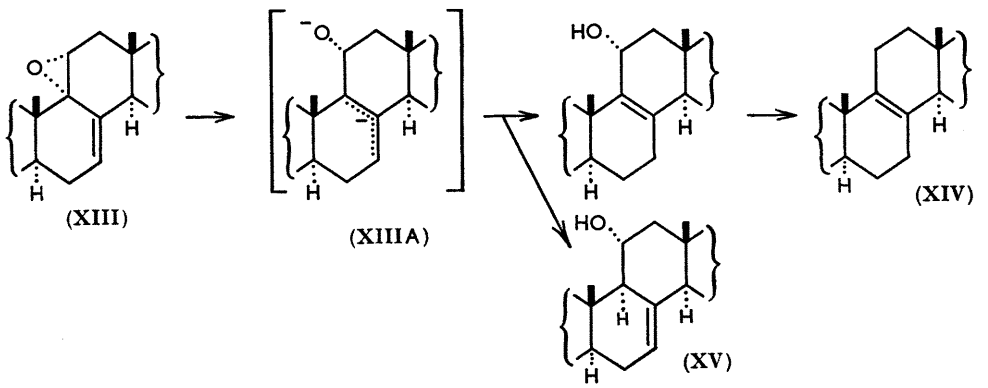
thionyl chloride in pyridine * gave the 7 : 8-unsaturated compound (X), *trans*-elimination towards position 9 or 14 being impossible. It may be noted that an α-configuration was assigned [10] to the starting epoxide (VIII) on the basis of its method of preparation from the reaction of the Δ^7-steroid with peroxyacid. In our opinion this formulation is supported by its resistance to reduction by lithium aluminium hydride, for a 7β : 8β-epoxide should be reduced to an 8β-alcohol with no special difficulty.



The reaction of the 9α : 11α-epoxide (XI) with lithium–ethylamine also generated an axial tertiary hydroxyl group (as in XII); this appears to be the first 9-hydroxy-compound to have been prepared without an adjacent 8- or 11-oxygen substituent.



Lithium reduction of the Δ^7-9α : 11α-epoxide (XIII) gave the Δ^8-compound (XIV) and the Δ^7-11α-alcohol (XV) in approximately equal amounts. The epoxide (XIII) contains an allylic ether grouping and, since reduction of allylic ethers by metals is greatly assisted by initial production of a resonance-stabilized carbanion,[2b] the reaction products probably arise from a 7 : 8 : 9-anionic intermediate (cf. XIIIA). A proton can then be provided by the solvent at (i) position 7, to give an 11α-hydroxy-Δ^8-compound which, being an allylic



alcohol, is then reduced further to the Δ^8-steroid (XIV) (the related 11β-hydroxy-Δ^8-compound undergoes this reduction [2b]) or (ii) at position 9 (at the less hindered α-face) to give the other reaction product (XV). The ready acetylation of the hydroxyl group in the

* The greater resistance of this alcohol to dehydration by dilute mineral acid compared with 5α : 8α-diols has already been discussed.[9]

[9] Henbest and Lovell, *J.*, 1957, 1965.
[10] Alt and Barton, *J.*, 1954, 1356.

latter product and its difference from the 9β-compound [11] confirm the structure assigned to it. The alternative possibility that the Δ^8-compound (XIV) is formed by initial attack of solvated electrons on the epoxide at position 11, to give a Δ^7-9α-alcohol which is further reduced, cannot, however, be wholly excluded at present.

These results seem consistent with the idea that reduction of vicinal epoxides by metals takes place by attack of solvated electrons acting as a penetrating nucleophilic reagent. Thus reduction of the hindered 7α : 8α- and 9α : 11α-epoxides shows that the steric requirements of the attacking agent cannot be high, but the isolation of a small amount of equatorial product from the 5β : 6β-epoxide (V) and the formation of propan-2-ol from propylene oxide indicate that the attacking agent has some bulk and this is in agreement with attack by solvated electrons.

Experimental

Cholestan-3α-ol (cf. II).—Reduction of 2α : 3α-epoxycholestane (0·15 g.) with lithium (75 mg.) in ethylamine (10 c.c.) [2b] gave a product which was then chromatographed on deactivated alumina (10 g.). Elution with light petroleum–benzene (1 : 1) gave material (0·105 g.) from which cholestan-3α-ol, m. p. and mixed m. p. 182°, $[\alpha]_D$ +27°, was obtained on one crystallisation from ethanol.

Cholestan-5α-ol (cf. IV).–Reduction of 5α : 6α-epoxycholestane (0·2 g.) with lithium (0·1 g.) in ethylamine (10 c.c.), followed by isolation with ether and one crystallisation from aqueous acetone, gave a high yield of cholestan-5α-ol, m. p. and mixed m. p. 109—110°, $[\alpha]_D$ +22°.

5β : 6β-*Epoxycoprostane* (cf. V).—A mixture of dry chloroform (75 c.c.), pure dimethylaniline (40 c.c.), acetyl chloride (32 c.c.), and cholestane-5α : 6β-diol (4 g.) was heated under reflux for 16 hr. The product was isolated in chloroform and chromatographed on deactivated alumina (300 g.). Elution with light petroleum gave some diene (0·13 g.), m. p. 82—83°, $[\alpha]_D$ −63° (probably therefore a mixture of the 3 : 5- and the 4 : 6-isomer), giving a deep orange colour with tetranitromethane. Elution with light petroleum–benzene (1 : 1) gave the 5α : 6β-diacetate as a gum. This was heated in absolute ethanol (200 c.c.) containing potassium hydroxide (5 g.) for 2·5 hr. Most of the alcohol was distilled off and the steroid isolated with ether. The product in light petroleum was filtered through deactivated alumina, to give the β-epoxide (3 g.), m. p. 80—81°, $[\alpha]_D$ +8°.

Reduction of 5β : 6β-*Epoxycoprostane.*—(a) *With lithium–ethylamine.* The epoxide (0·5 g.) was reduced with lithium (0·25 g.) in ethylamine (25 g.), and the product heated with acetic anhydride and pyridine at 100° for 2 hr. Chromatography on deactivated alumina (50 g.) gave 6β-acetoxycholestane (0·4 g.) (eluted by light petroleum), m. p. 77° (from methanol), $[\alpha]_D$ −7° (lit.,[12] m. p. 75°, $[\alpha]_D$ −7·5°); alkaline hydrolysis gave cholestan-6β-ol, m. p. 80—81°, $[\alpha]_D$ +8°. Further elution with light petroleum–benzene (1 : 1) yielded coprostan-5β-ol (30 mg.), m. p. 81—82° (from methanol), whose infrared spectrum was identical with that prepared by the following method.

(b) *With lithium aluminium hydride.* A mixture of the epoxide (0·5 g.) and hydride (0·5 g.) and dry ether (20 c.c.) was heated under reflux for 18 hr. The product was isolated with ether, acetylated as before, and then chromatographed on deactivated alumina (50 g.). Elution as described above gave 6β-acetoxycholestane (0·155 g.), m. p. 77°, $[\alpha]_D$ −6·5°, and *coprostan-5β-ol* (0·305 g.), m. p. 81—82°, $[\alpha]_D$ +37° (Found: C, 83·9; H, 12·5. $C_{27}H_{48}O$ requires C, 83·45; H, 12·45%). Infrared spectrum (in CS_2): OH peak at 3615 $cm.^{-1}$. This alcohol apparently separates as a solvate from methanol, the crystalline material changing to a powder on warming and/or drying.

3β-*Acetoxyergost-22-en-8α-ol* (cf. IX).—3β-Acetoxy-7α : 8α-epoxyergost-22-ene (0·5 g.) was reduced with lithium (0·2 g.) in ethylamine (25 g.). The product was isolated with ether, acetylated, and chromatographed on deactivated alumina (25 g.). Elution with benzene–light petroleum (1 : 4) afforded 3β-acetoxyergosta-7 : 22-diene (0·24 g.), m. p. and mixed m. p. 179—181°. Elution with benzene–ether (19 : 1) gave the 8α-*alcohol* (0·18 g.), m. p. 127—129° (from methanol), $[\alpha]_D$ −25° (Found: C, 78·4; H, 10·85. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Infrared spectrum (in CS_2): peaks at 3685 (OH), 1735, 1245 (OAc) and 975 $cm.^{-1}$ (Δ^{22}).

This compound (50 mg.) in pyridine (2 c.c.) was treated with thionyl chloride (0·1 c.c.) at 20°.

[11] Crawshaw, Henbest, Jones, and Wagland, *J.*, 1955, 3420.
[12] Shoppee and Summers, *J.*, 1952, 3361.

After 30 min. the product was isolated with ether, then dissolved in light petroleum and filtered through deactivated alumina. Crystallisation of this material (40 mg.) from methanol gave 3β-acetoxyergosta-7 : 22-diene, m. p. and mixed m. p. 178—181°, $[\alpha]_D$ −20°.

3β-*Acetoxyergostan*-9α-*ol* (cf. XII).—3β-Acetoxy-9α : 11α-epoxyergostane (50 mg.) was reduced with lithium (50 mg.) in ethylamine (10 c.c.), the mixture being shaken until the blue colour disappeared. The product was isolated with ether, acetylated, and chromatographed on deactivated alumina (5 g.). Elution with benzene–light petroleum (1 : 1) gave material (47 mg.) which, after one crystallisation from methanol, yielded the 9α-*alcohol*, m. p. 168—169°, $[\alpha]_D$ −1° (Found: C, 78·15; H, 11·6. $C_{30}H_{52}O_3$ requires C, 78·15; H, 11·4%). Infrared spectrum (in CS_2): peaks at 3685 (OH), 1730 and 1245 cm.$^{-1}$ (OAc).

Reduction of 3β-*Acetoxy*-9α : 11α-*Epoxyergosta*-7 : 22-*diene* (cf. XIII).—The epoxide (1 g.) was reduced with lithium (1 g.) in ethylamine (100 g.) for 2 hr. Isolation with ether and acetylation gave material (0·983 g.) which in light petroleum was adsorbed on to deactivated alumina (50 g.). Elution with light petroleum gave 3β-acetoxyergosta-8 : 22-diene (0·35 g.), m. p. and mixed m. p. 162—164°, $[\alpha]_D$ +14°. Elution with light petroleum–benzene (1 : 1) gave 3β : 11α-*diacetoxyergosta*-7 : 22-*diene* (0·31 g.), m. p. 123° (from methanol), $[\alpha]_D$ −21° (Found: C, 77·1; H, 10·1. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%).

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