136. *Steroids and the Walden Inversion. Part VI. Reduction of Cholest-5-en-3-one with Lithium Aluminium Hydride.*

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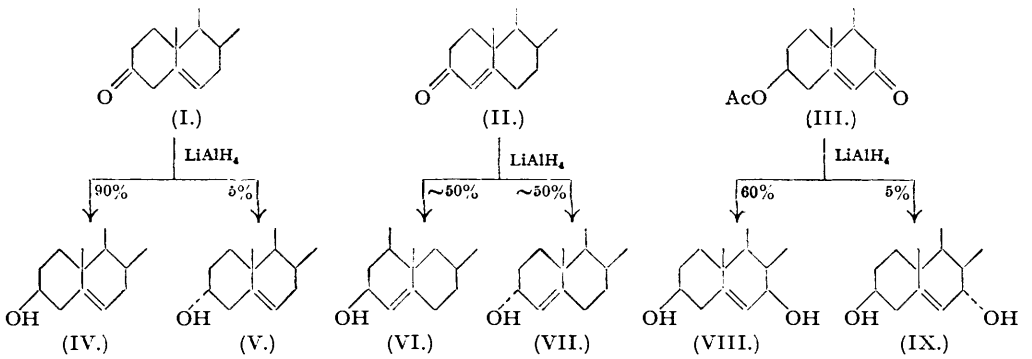
Cholest-5-en-3-one by reduction with lithium aluminium hydride gives unexpectedly much cholesterol and very little *epi*cholesterol; the stereochemical course of the reduction is compared with that of other steroid ketones.

Lithium aluminium hydride (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199) is a valuable reagent for reduction of variants of the carboxyl group: R—CO—X ⟶ R·CH_2·OH (X = H, OH, OR′, Cl) (Nystrom and Brown, *ibid.*, pp. 1197, 1548). Further, ketones give secondary alcohols, whilst amides yield primary amines (Uffer and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397), but simple ethylenic linkages are unaffected.

Reduction of cholest-5-en-3-one (I) without alteration of the position of the double bond can be carried out only in neutral media, since this compound is readily isomerised, *e.g.*, by simple filtration in pentane solution through non-neutralised aluminium oxide, to cholest-4-en-3-one (II). Partial hydrogenation of (I) with Raney nickel in *cyclo*hexane yields considerable but variable quantities of *epi*cholesterol (V) (Ruzicka and Goldberg, *Helv. Chim. Acta*, 1936, **19**, 1407); since reduction with lithium aluminium hydride has been observed sometimes to offer advantages over catalytic hydrogenation (cf. Plattner *et al.*, *ibid.*, 1949, **32**, 265; Salamon, *ibid.*, p. 1306), we have used this reagent to reduce (I). Reduction proceeds smoothly to give cholesterol (IV) and *epi*cholesterol (V) but the yield of the latter is only about 5%.

The one-sided stereochemical course in the reduction of (I) is surprising since similar reduction of cholest-4-en-3-one (II) leads to approximately equal quantities of the epimeric cholest-4-en-3-ols * (McKennis, jun., and Gaffney, *J. Biol. Chem.*, 1948, **175**, 217); this result has been

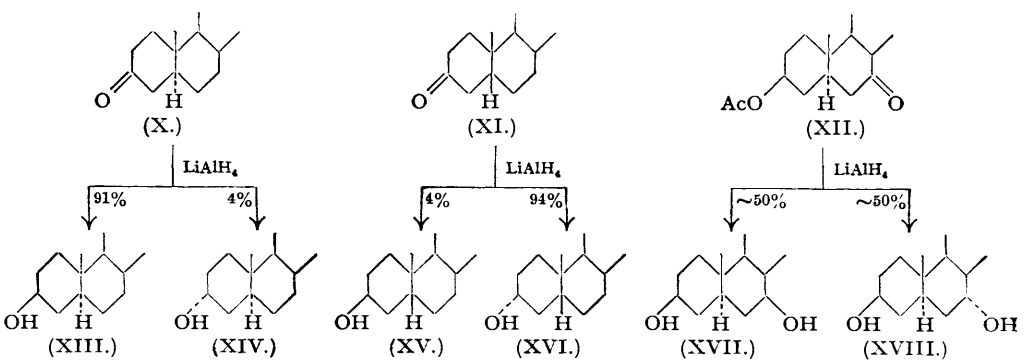
confirmed by Plattner *et al.*, (*loc. cit.*). On the other hand, it has recently been reported that reduction of 7-ketocholesteryl acetate (III) with lithium aluminium hydride proceeds largely in one stereochemical direction to give mainly cholest-5-ene-3β : 7β-diol (VIII) accompanied by 5% of cholest-5-ene-3β : 7α-diol (IX) (Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226).



In reduction by lithium aluminium hydride the active entity appears to be the anion $AlH_4^{\ominus}$ and, since in the reductive fission of epoxides attack at carbon is accompanied by inversion of configuration, it has been suggested that the reaction is a bimolecular nucleophilic replacement, S_N2 (Trevor and Brown, *ibid.*, p. 1675). Reduction of a carbonyl group is a bimolecular addition reaction, so that steric factors should operate (cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173).

Although the presence in (I), (II), and (III) of a double bond at the bridgehead ensures that the lower portions of rings A and B are essentially flat, steric hindrance by the angular methyl group at $C_{(10)}$, arising from repulsion by the electrons of the three C–H bonds, might impede frontal as compared with rearward attack at $C_{(3)}$ by the anion $AlH_4^{\ominus}$. Such hindrance would be consistent with the predominance of the 3β-hydroxy-epimeride (IV) and the 7β-hydroxy-epimeride (VIII), but would be expected also to lead to production of (VI) as the major epimeride.

We have also examined the reduction by lithium aluminium hydride of cholestan-3-one (X) and coprostan-3-one (XI); the former gives cholestanol (XIII) with ~4% of *epi*cholestanol (XIV), whilst the latter yields *epi*coprostanol (XVI) accompanied by ~4% of coprostanol (XV). These results closely resemble those obtained by catalytic hydrogenation in neutral media (Diels and Abderhalden, *Ber.*, 1906, **39**, 884; Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407). The production of (XIII) as principal product is consistent with lesser hindrance at $C_{(3)}$ by the angular methyl group at $C_{(10)}$; in the favoured formation of (XVI) this is not the case, unless the numerous constellations accessible to rings A and B in derivatives of coprostane (Shoppee, *Ann. Reports*, 1946, **43**, 200) combine effectively to eliminate steric hindrance by the angular methyl group at $C_{(3)}$. If hindrance by the hydrogen atom at $C_{(5)}$ is envisaged, as in discussion of the differential rates of alkaline hydrolysis [S_N2] of the 3-acyl derivatives of the alcohols (XIII—XVI) (Ruzicka,



Furter, and Goldberg, *Helv. Chim. Acta*, 1938, **21**, 498), then frontal attack by the anion $AlH_4^{\ominus}$ at $C_{(3)}$ in (X), and similar but rearward attack in (XI), should be the less hindered, leading

* Formerly called "allocholesterol" and "*epi*allocholesterol."

respectively to predominant production of (XIV) not (XIII), and (XV) not (XVI). From both points of view it is curious that in the cholestane series, where ring B is certainly a rigid chair-form, it has been found that reduction of 7-ketocholestanyl acetate (XII) with lithium aluminium hydride gives approximately equal quantities of cholestane-3β : 7β-diol (XVII) and of the 3β : 7α-diol (XVIII) (Fieser, Fieser, and Chakravarti, *loc. cit.*; cf. Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503).

Finally, it may be remarked that asymmetric induction at $C_{(3)}$ by the other six nuclear asymmetric centres might be expected to produce a considerable effect because they occupy fixed positions, relative to $C_{(3)}$, in a polycyclic system; for the same reason variation of such an effect in opposite senses would not be expected.

Experimental.

(M. p.s were determined thermo-electrically on a Kofler block, and are therefore corrected; limit of error ±2°. All solvents were rigorously purified and dried.)

Cholest-5-en-3-one (I).—This was prepared by the method of Butenandt and Schmidt-Thomé (*Ber.*, 1936, **69**, 882; cf. Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244); the crude product, m. p. 120—124°, is readily purified by dissolution in pentane, filtration of the solution through a column of neutralised aluminium oxide * (activity II—III, 30 × wt. of the crude product) prepared in pentane, and subsequent washing with pentane. The material so eluted, by a single recrystallisation from acetone or ethanol, gave the ketone as needles, m. p. 127°.

Reduction with lithium aluminium hydride. To a vigorously stirred solution of lithium aluminium hydride (2·17 g.) in ether (150 c.c.) cholest-5-en-3-one (I) (m. p. 127°; 2·56 g.), dissolved in ether (100 c.c.), was added during 25 minutes. The mixture was stirred for 2 hours with addition of ether from time to time, the solution becoming opaque; thereafter the reaction-flask was cooled in ice, and excess of lithium aluminium hydride destroyed with ice-cold 0·1N-sulphuric acid. The ethereal layer was separated, the acidic solution extracted twice with ether, and the combined ethereal solutions washed with water, sodium hydrogen carbonate solution, and again with water, dried (Na_2SO_4), and evaporated to give a white solid (2·56 g.; m. p. 133—138°). A portion (326 mg.) of the reduction product, dissolved in ethanol (50 c.c.), was treated with a warm 1% solution of digitonin in 95% ethanol (200 c.c.). After being kept overnight, the precipitate of cholesterol digitonide was filtered off and dried (1·2363 g., ≡ 295 mg. of cholesterol); decomposition of the digitonide by dissolution in pyridine (15 c.c.) and precipitation of digitonin with ether (200 c.c.), followed by working up of the resulting filtrate, gave cholesterol (290 mg.), m. p. 148° after crystallisation from ethanol. The original alcoholic filtrate was evaporated completely in a vacuum, and the residue repeatedly extracted with ether; the combined ethereal extracts, after being washed with 2N-hydrochloric acid, water, sodium hydrogen carbonate solution, and water, were dried (Na_2SO_4) and evaporated to yield an oil which solidified on cooling. Crystallisation from aqueous ethanol gave *epi*cholesterol (12 mg.) as plates, m. p. 140°, mixed m. p. 140—141°. The proportion of cholesterol in the reduction product was thus 90·5%.

Conversion into Cholest-4-en-3-one (II). Cholest-5-en-3-one (m. p. 127°; 320 mg.), dissolved in pentane (30 c.c.), was filtered through a column of aluminium oxide (Spence type H, activity II, 10 g.) prepared in pentane. Evaporation of the filtrate gave crystalline material (m. p. 80—81° after slight softening; 102 mg.); elution with pentane, with benzene–pentane mixtures, and with benzene gave various fractions (m. p. 73° to 80°; 215 mg.). All fractions were united and recrystallised from ether–methanol to give cholest-4-en-3-one (III), m. p. 80—81°, undepressed by admixture with an authentic specimen.

Reduction of Cholestan-3-one (X) *with Lithium Aluminium Hydride.*—The procedure was that described for cholest-5-en-3-one (I). Cholestan-3-one (m. p. 129—130°; 884 mg.) gave a reduction product (890 mg.); a portion (350 mg.), dissolved in ethanol (100 c.c.), was treated with a warm 1·33% solution of digitonin in 95% ethanol (150 c.c.). The insoluble digitonide was filtered off and gave by appropriate treatment cholestan-3β-ol (319 mg.), double m. p. 125° and 140—141° after crystallisation from methanol. The alcoholic filtrate by evaporation and ether-extraction of the residue yielded cholestan-3α-ol (12 mg.), m. p. 180—181° after crystallisation from aqueous methanol. The proportion of cholestan-3β-ol in the reduction product was thus 91%.

Reduction of Coprostan-3-one (XI) *with Lithium Aluminium Hydride.*—The procedure was that described above; coprostan-3-one (m. p. 59—61°; 950 mg.) gave a reduction product (948 mg.), a portion of which (318 mg.) was separated by treatment with digitonin as above. Only a small precipitate was obtained after storage overnight; this by appropriate treatment gave material (18 mg.) which after crystallisation from methanol yielded coprostan-3β-ol as needles, m. p. 100°, undepressed by admixture with a genuine specimen. Evaporation of the alcoholic filtrate and ether-extraction of the residue furnished crystals (m. p. 102—106° crude); recrystallisation from acetone gave coprostan-3α-ol (300 mg.), m. p. 115—116°, alone or mixed with an authentic specimen. The proportion of coprostan-3-α-ol in the reduction product was thus 94%.

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* Prepared by washing with warm aqueous sodium hydroxide and then warm acetic acid and then washed to neutrality with water; reactivated at 200° for 30 hours.