Steroids and Walden Inversion. Part XVI. The Epimeric Cholestan-7-ols.*

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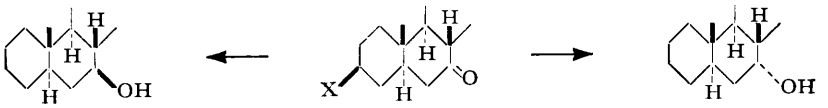
Cholestan-7α-ol has been prepared from cholestan-7-one by reduction with lithium aluminium hydride. The configurations of the epimeric cholestan-7-ols have been determined by conversion with sodium *n*-butoxide of the less thermodynamically stable 7α- into the 7β-epimeride, and by study of the relative rates of alkaline hydrolysis of 7α- and 7β-benzoyloxycholestane, whose elimination reactions have also been studied.

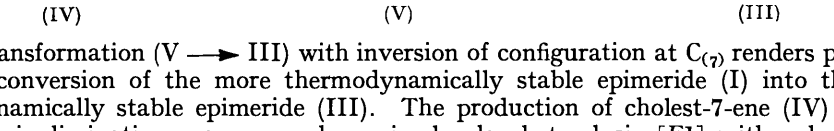
A single cholestan-7-ol, m. p. 119°, $[\alpha]_D$ +51°, has been obtained by reduction with sodium and amyl alcohol of 7-oxocholestan-3β-yl chloride (II; X = Cl) (Marker, Kamm, Fleming, Popkin, and Wittle, *J. Amer. Chem. Soc.*, 1937, **59**, 619) or of cholestan-7-one (II; X = H) (Heilbron, Shaw, and Spring, *Rec. Trav. chim.*, 1938, **57**, 529; Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 2986). Heilbron *et al.* correctly considered their compound to be the 7β-epimeride (I; equatorial) cf. Barton, *Experientia*, 1950, **6**, 316, footnote to Table 1. It has subsequently been prepared, m. p. 112°, $[\alpha]_D$ +38°, by desulphurisation with nickel under pressure of 3ξ-ethylthiocholest-5-en-7-one by Ralls, Dodson, and Riegel (*ibid.*, 1949, **71**, 3320), and we have prepared it, m. p. 113°, $[\alpha]_D$ +52°, by reduction of the ketone (II; X = H) with sodium and butan-1-ol.



(I) (II) (III)

Hydrogenation of the ketone (II; X = H) with platinum black in acetic acid appeared to give cholestane and cholestan-7β-ol (65%)†; a similar result was obtained by use of aluminium *iso*propoxide in *iso*propyl alcohol (yield 73%). Reduction with lithium aluminium hydride gave a small quantity of cholestane, cholestan-7β-ol (~55%), m. p. 113°, $[\alpha]_D$ +52°, and cholestan-7α-ol (~25%) (III), m. p. 98°, $[\alpha]_D$ +11°; the 7α-alcohol was characterised as acetate, benzoate, and 3 : 5-dinitrobenzoate, but the toluene-*p*-sulphonate could not be prepared.

The observation that only cholestan-7β-ol gave a toluene-*p*-sulphonate appeared to afford a method for separation of the epimerides (I, III), which form mixed crystals and require careful and tedious chromatography. It was found, however, that 7β-toluene-*p*-sulphonyloxycholestane (V) is partly decomposed by neutralised aluminium oxide in pentane to give cholest-7-ene (IV), m. p. 82°, $[\alpha]_D$ +12° (cf. Eck and Hollingsworth, *loc. cit.*; Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 248), whilst use of alkaline aluminium oxide in pentane furnished cholest-7-ene (IV) (~30%) accompanied by cholestan-7α-ol (III) (~60%).



(IV) (V) (III)

The transformation (V ⟶ III) with inversion of configuration at $C_{(7)}$ renders practicable the conversion of the more thermodynamically stable epimeride (I) into the less thermodynamically stable epimeride (III). The production of cholest-7-ene (IV) by an apparent *cis*-elimination may occur by unimolecular heterolysis [*E*1] with subsequent

* Part XV, *J.*, 1954, 3418.

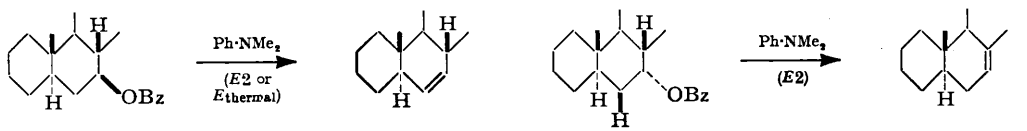
† After this work was completed, Dauben, Dickel, Jeger, and Prelog (*Helv. Chim. Acta*, 1953, **36**, 325) by hydrogenation of (II) with platinum oxide in acetic acid obtained cholestane, cholestan-7β-ol (I), m. p. 114—115°, $[\alpha]_D$ +55°, and cholestan-7α-ol (III), m. p. 98°, $[\alpha]_D$ +10°.

internal depolarisation of the resulting carbonium ion; similar observations of apparent *cis*-elimination have recently been made concerning the conversion of 11-hydroxy-steroids into 9(11)-unsaturated steroids (Fried and Sabo, *J. Amer. Chem. Soc.*, 1953, **75**, 2273; Casanova, Shoppee, and Summers, *J.*, 1953, 2983; Bernstein, Littel, and Williams, *J. Amer. Chem. Soc.*, 1953, **75**, 4830; Bernstein, Lenhard, and Williams, *J. Org. Chem.*, 1954, **19**, 41; Herzog, Payne, and Hershberg, *J. Amer. Chem. Soc.*, 1954, **76**, 930).

The conversion of cholestan-7α-ol (III; OH, axial) into the more thermodynamically stable cholestan-7β-ol (I; OH, equatorial) occurs by treatment with sodium in boiling butan-1-ol, and is consistent with the configurations assigned. Confirmation of these assignments has been obtained by study of the relative rates of alkaline hydrolysis [S_N2] (cf. Barton, *Experientia*, 1950, **6**, 312) of the epimeric 7-benzoyloxy-cholestanes; the 7β-benzoate (VI; OBz, equatorial) was found to be hydrolysed roughly thrice as fast as the 7α-benzoate (VIII; OBz, axial). It is interesting to observe that the 1 : 3-compressions of the 7α-benzoyloxy-group by the axial hydrogen atoms attached to $C_{(5)}$, $C_{(9)}$, and $C_{(14)}$ are more effective than the 1 : 4-compressions of the 7β-benzoyloxy-group by the angular methyl groups attached to $C_{(10)}$ and $C_{(13)}$; this may be compared with the corresponding deduction (Shoppee, *Hormones and Vitamins*, 1951, **8**, 288) from the relative rates of alkaline hydrolysis of the epimeric cholestan-3-yl acetates and benzoates which are 3β>3α [acetates, 3·1 : 1; benzoates, 3·4 : 1] (Ruzicka, Furter, and Goldberg, *Helv. Chim. Acta*, 1938, **21**, 498).

Further support for our assignment of configuration is provided by molecular-rotation differences. For 7β-acetoxycholestane ΔA is found to be +172°, whilst the standard value for ΔA[5α] : 7β is +208° (Barton and Klyne, *Chem. and Ind.*, 1948, 755); for 7α-acetoxy-cholestane ΔA is −144° in excellent agreement with the standard value for ΔA[5α] : 7α of −143° (Barton and Klyne, *loc. cit.*).

The pyrolysis of the epimeric 7-benzoyloxycholestanes at 320°/17 mm. has been examined. It has been shown that mechanistically unimolecular pyrolytic elimination reactions require *cis*-geometry and, if possible, coplanarity of the four centres involved (Barton, *J.*, 1949, 2714). 7β-Benzoyloxycholestane (VI), in which the 6β- or 8β-hydrogen atom (axial) and the 7β-benzoyloxy-group (equatorial) are *cis* but cannot be coplanar, was completely resistant to pyrolysis and was recovered unchanged. 7α-Benzoyloxycholestane (VIII), in which only the 6α-hydrogen atom (equatorial) is *cis* to the 7α-benzoyloxy-group



(VI) (VII) (VIII) (IV)

(axial) but not coplanar, was also partly unchanged by pyrolysis at 320°/17 mm., but gave pure cholest-6-ene (VII), m. p. 85°, $[\alpha]_D$ −88°, in good agreement with the constants, m. p. 86—87°, $[\alpha]_D$ −88°, previously reported (Fischer, Lardelli, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 1577).

A study was also made of the action of dimethylaniline at 194° on the epimeric 7-benzoyloxycholestanes; this method for 1 : 2-elimination of benzoic acid has been used in connection with the preparation of 7-dehydrocholesterol by Haslewood (*J.*, 1938, 224) and by Buser (*Helv. Chim. Acta*, 1947, **30**, 1384). Both epimerides were largely unchanged, but whereas 7β-benzoyloxycholestane (VI) gave cholest-6-ene (VII), m. p. 79—82°, $[\alpha]_D$ −70° [probably contaminated with ~10% of cholest-7-ene (IV)], 7α-benzoyloxycholestane (VIII) gave cholest-7-ene (IV), m. p. 82°, $[\alpha]_D$ +12°. The elimination (VI ⟶ VII) could involve either the equatorial 6α-hydrogen atom *trans* to the equatorial 7β-benzoyloxy-group (*E*2) or the axial 6β-hydrogen atom *cis* to the equatorial 7β-benzoyloxy-group ($E_{thermal}$); the elimination (VIII ⟶ IV), involving the tertiary axial 8β-hydrogen atom, however, suggests that the dimethylaniline functions as a base and not as a thermal medium, and that the reaction is an ionic elimination (*E*2) of super-Saytzeff type (cf. Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093) requiring *trans*-geometry and coplanarity of the four participating centres (cf. Curtin, *J. Amer. Chem. Soc.*, 1953, **75**, 6011).

Experimental

For general directions see *J.*, 1954, 3418. $[\alpha]_D$ were measured in $CHCl_3$, and ultra-violet absorption spectra were determined in ethanol on a Unicam SP.500 spectrophotometer with corrected scale.

Cholestan-7-one.—Cholesteryl acetate was oxidised with chromium trioxide–acetic acid (Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226) to 7-oxocholesteryl acetate, which was converted in 70% yield into cholesta-3 : 5-dien-7-one, m. p. 112—114°, by alkaline hydrolysis, dehydration with anhydrous copper sulphate in benzene at 80°, and chromatography on aluminium oxide [eluant : benzene–pentane (1 : 2)] (cf. Mauthner and Suida, *Monatsh.*, 1896, **17**, 579; Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567). Hydrogenation of cholesta-3 : 5-dien-7-one as described by Heilbron, Shaw, and Spring (*Rec. Trav. chim.*, 1938, **57**, 529) gave cholestan-7-one, plates (from acetone), m. p. 116—118°, characterised as the 2 : 4-*dinitrophenylhydrazone*, yellow plates (from benzene–ethanol), m. p. 205—207° [Found (after drying at 100°/0·01 mm. for 2 hr.) : C, 69·6; H, 8·7. $C_{33}H_{50}O_4N_4$ requires C, 69·9; H, 8·9%].

Cholestan-7β-ol.—This alcohol, m. p. 112—113°, $[\alpha]_D$ +52° (*c*, 1·1), prepared by reduction of cholestan-7-one with sodium in boiling butan-1-ol, gave no precipitate with a 0·5% solution of digitonin in ethanol, and was characterised by the *acetate* (acetic anhydride–pyridine at 20°), m. p. 66°, $[\alpha]_D$ −61° (*c*, 0·69), after chromatography and recrystallisation from ether–methanol [Found (after drying at 50°/0·02 mm. for 9 hr.) : C, 80·9; H, 11·4. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%], the *benzoate* (benzoyl chloride–pyridine at 20°), m. p. 106—108°, $[\alpha]_D$ +87° (*c*, 1·4), after recrystallisation from acetone [Found (after drying at 50°/0·02 mm. for 9 hr.) : C, 83·2; H, 10·7. $C_{34}H_{52}O_2$ requires C, 82·9; H, 10·6%], the 3 : 5-*dinitrobenzoate*, m. p. 151—152°, $[\alpha]_D$ +105° (*c*, 2·65), after two recrystallisations from acetone [Found (after drying at 20°/0·01 mm. for 12 hr.) : C, 70·0; H, 8·8. $C_{34}H_{50}O_6N_2$ requires C, 70·0; H, 8·7%], and the *toluene*-p-*sulphonate* (toluene-*p*-sulphonyl chloride–pyridine at 20° for 60 hr.), m. p. 158—159°, $[\alpha]_D$ +38° (*c*, 1·14), after recrystallisation from acetone [Found (after drying at 60°/0·01 mm. for 10 hr.) : C, 75·3; H, 10·2. $C_{34}H_{54}O_3S$ requires C, 75·2; H, 10·0%].

Cholestan-7α-ol.—Cholestan-7-one (5·6 g.) was reduced with lithium aluminium hydride (4·8 g.) in ether according to the directions of Shoppee and Summers (*J.*, 1950, 687). The resultant colourless oil was chromatographed on aluminium oxide (450 g.) in pentane (58 fractions); elution with pentane gave cholestane (108 mg.), m. p. 78—80° after recrystallisation from acetone. Elution with benzene–pentane (1 : 6) gave *cholestan-7α-ol* (1·27 g.), m. p. 94—97°, raised by recrystallisation from methanol to 98°, $[\alpha]_D$ +11° (*c*, 1·04) [Found (after drying at 60°/0·01 mm. for 10 hr.) : C, 83·5; H, 12·4. $C_{27}H_{48}O$ requires C, 83·4; H, 12·4%]. Further elution with benzene–pentane (1 : 6) gave mixtures of the epimerides, m. p. 90—106°, whilst use of benzene–pentane (1 : 3) gave cholestan-7β-ol (2·4 g.), m. p. 108—112°, raised by recrystallisation from ether–methanol to 112—113°.

Cholestan-7α-ol was characterised by preparation of the *acetate*, m. p. 117°, $[\alpha]_D$ −12° (*c*, 1·2), after two recrystallisations from acetone–methanol (1 : 1) [Found (after drying at 60°/0·01 mm. for 6 hr.) : C, 81·0; H, 11·6%], the *benzoate*, m. p. 163—165°, $[\alpha]_D$ −22° (*c*, 0·56), after two recrystallisations from acetone [Found (after drying at 65°/0·01 mm. for 6 hr.) : C, 82·9; H, 10·4%], and the 3 : 5-*dinitrobenzoate*, m. p. 176—177°, $[\alpha]_D$ −24° (*c*, 2·1), after two recrystallisations from acetone [Found (after drying at 20°/0·01 mm. for 12 hr.) : C, 70·0; H, 8·7%].

Conversion of Cholestan-7α- into Cholestan-7β-ol.—Cholestan-7α-ol (m. p. 98°; 100 mg.) was dissolved in butan-1-ol (purified according to the instructions of Clarke, Robinson, and Smith *J.*, 1927, 2647), and sodium was gradually added to the refluxing solution until no more would dissolve. After 6 hr., butanol was largely removed under reduced pressure, and the mixture worked up in the usual way to yield an oil (80 mg.). This crystallised and by recrystallisation from ether–methanol gave cholestan-7β-ol, m. p. and mixed m. p. 110—112°.

Conversion of Cholestan-7β- into Cholestan-7α-ol.—When 7β-toluene-*p*-sulphonyloxycholestane (75 mg.), dissolved in pentane, was introduced on to a column of neutralised aluminium oxide (4 g.; Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 305), prepared in pentane; elution with pentane (100 c.c.) gave after evaporation a colourless oil, which crystallised when rubbed with acetone–methanol; recrystallisation from acetone afforded cholest-7-ene, m. p. and mixed m. p. 78°, $[\alpha]_D$ +12° (*c*, 1·07), giving a yellow colour with tetranitromethane–chloroform. Similar treatment of the ester (100 mg.) in pentane with alkaline aluminium oxide (6 g.; Spence type H, 200 mesh, activity ~11, scale of Brockmann and Schodder, *Ber.*, 1941, **74**, 73), and

elution with pentane (100 c.c.), gave a solid (28 mg.), which by recrystallisation from methanol furnished cholest-7-ene, m. p. and mixed m. p. 80—82°. Further elution with benzene–pentane (1 : 1) yielded a solid (65 mg.), which by recrystallisation from acetone gave cholestan-7α-ol, m. p. and mixed m. p. 97—99°.

In an attempt to utilise the non-formation of a toluene-*p*-sulphonate by cholestan-7α-ol to separate the epimeric cholestan-7-ols, the isomorphous mixture of cholestan-7-ols (m. p. 86—92°; 1 g.) was treated with toluene-*p*-sulphonyl chloride (800 mg.) in pyridine (10 c.c.), and the oily product (1·1 g.) was dissolved in pentane and chromatographed on neutralised aluminium oxide (38 g.). Elution with pentane gave cholest-7-ene (393 mg.), m. p. 74—80° after crystallisation from acetone, giving a yellow colour with tetranitromethane–chloroform. Elution with benzene–pentane (1 : 1) gave crystals (130 mg.), which on recrystallisation from acetone gave cholestan-7α-ol, m. p. and mixed m. p. 95—98°; further elution with benzene–pentane (1 : 1) gave a colourless oil (84 mg.), which solidified and by recrystallisation from ether–methanol gave cholestan-7β-ol, m. p. and mixed m. p. 110—112°.

Alkaline Hydrolysis of the 7-Benzoyloxycholestanes.—Samples of the epimeric benzoates (40 mg.) were dissolved in methanol (5 c.c.), mixed each with 2·00 c.c. of methanolic 0·243N-sodium hydroxide, and heated under reflux with exclusion of moisture and carbon dioxide; corresponding blank experiments were run, and after various periods the amount of alkali used was estimated by titration with 0·048N-hydrochloric acid (cf. Reichstein and Shoppee, *Helv. Chim. Acta*, 1940, **23**, 979). The following results were obtained:

	7β-Benzoyloxycholestane (VI)								7α-Benzoyloxycholestane (VIII)					
Time of reflux (hr.)	3	8	12	25	46	72	168	260	30	47	72	150	288	430
0·233N-NaOH used (c.c.)	0·14	0·16	0·18	0·42	0·52	0·70	1·24	1·45	0·15	0·20	0·38	0·50	0·84	1·20
Hydrolysis (%)	9·2	10·5	11·8	27·6	34·2	46	82·7	95·4	9·8	13·2	25	33	55·3	80

Pyrolysis of the 7-Benzoyloxycholestanes.—(*a*) 7β-Benzoyloxycholestane (m. p. 106—108°; 1·4 g.) was heated in a stream of dry oxygen-free nitrogen at 320°/17 mm. for 3 hr.; the material was then distilled rapidly at 0·02 mm. The usual working up yielded no benzoic acid; the neutral product was chromatographed on neutralised aluminium oxide in pentane. Elution with pentane (2 × 150 c.c.) furnished crystals (1·2 g.), which by recrystallisation from acetone gave 7β-benzoyloxycholestane, m. p. and mixed m. p. 106—108°. The material (189 mg.) from the acetone mother-liquor was pyrolysed again, at 290—350°/17 mm. for 3 hr., but after similar treatment yielded only unchanged 7β-benzoyloxycholestane (170 mg.), m. p. 105—108°.

(*b*) 7α-Benzoyloxycholestane (m. p. 164—165°; 836 mg.) was pyrolysed similarly, and gave some benzoic acid. The neutral product crystallised spontaneously and was chromatographed on neutralised aluminium oxide (25 g.); elution with pentane (3 × 100 c.c.) gave a solid (560 mg.), which by recrystallisation from acetone furnished 7α-benzoyloxycholestane, m. p. and mixed m. p. 165—166°. The material (140 mg.) from the acetone mother-liquor by repeated recrystallisation from acetone gave more unchanged starting material, and finally a fraction, m. p. 82—86°, giving a yellow colour with tetranitromethane. Recrystallisation from acetone gave cholest-6-ene (20 mg.), m. p. 83—85°, $[\alpha]_D$ −88° (*c*, 0·70), $\lambda_{max.}$ 207 mμ, log ε 3·28.

Treatment of the 7-Benzoyloxycholestanes with Dimethylaniline.—(*a*) 7β-Benzoyloxycholestane (200 mg.) was refluxed with dimethylaniline for 20 hr. After removal under reduced pressure of most of the dimethylaniline, the residual oil was worked up in the usual way to give a colourless oil (180 mg.), which crystallised spontaneously and by recrystallisation from acetone gave 7β-benzoyloxycholestane, m. p. and mixed m. p. 106—108°. Repeated recrystallisation of material from the mother-liquor gave further small amounts of the 7β-benzoate, and finally a product, m. p. 76°, giving a yellow colour with tetranitromethane–chloroform. Recrystallisation of this from acetone gave nearly pure cholest-6-ene (10 mg.), m. p. 79—82°, $[\alpha]_D$ −70° (*c*, 0·47).

(*b*) 7α-Benzoyloxycholestane (200 mg.) was refluxed with dimethylaniline for 12 hr. The product (175 mg.) crystallised, and by recrystallisation from acetone gave 7α-benzoyloxycholestane, m. p. and mixed m. p. 165—167°. The mother-liquor gave a second crop, m. p. 164—166°, and, after removal of further small amounts of the 7α-benzoate, afforded by crystallisation from acetone cholest-7-ene (9 mg.), m. p. and mixed m. p. 81—83°, $[\alpha]_D$ +12° (*c*, 0·88), $\lambda_{max.}$ 212 mμ, log ε 3·45, giving a yellow colour with tetranitromethane–chloroform.

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