SECTION C
Organic Chemistry

5α,7α-Cyclosteroids

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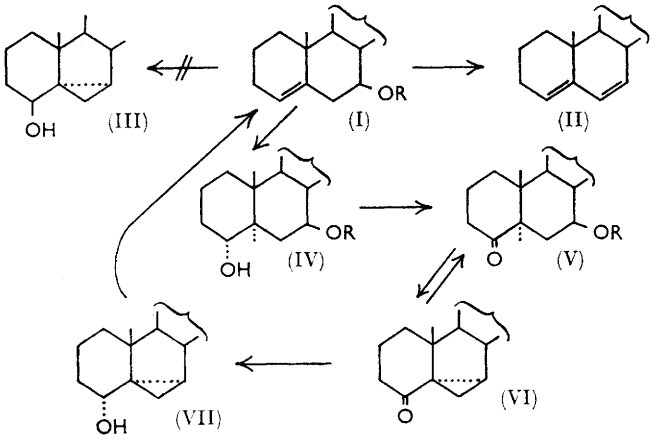
A smooth and conventional route to 5α,7α-cyclosteroids is described.

THE solvolysis of the toluene-*p*-sulphonate of "ψ-cholesterol" (I; R = $CH_3C_6H_4SO_2$) has been shown [1,2] to involve homoallylic interaction between the π-electrons of the 4,5-double bond and a carbonium ion at the 7-position, leading to 7β-substitution with retention of configuration, and cholest-4,6-diene (II) by elimination. Kinetic studies [3] of the acetolysis of cholest-4-en-7β-yl tolune e-p-sulphonate (I; R = $CH_3C_6H_4SO_2$) confirm the conclusion of Shoppee *et al.*[1] Thus, the expectation that 5α,7α-cyclosteroids (III) would be produced was not realised. Two alternative syntheses [4,5] have established the existence of these transannular steroids, but these are relatively inconvenient, because of poor yields. This difficulty is now surmounted by a new synthesis, using essentially the same approach, which provides the 5α,7α-cyclosteroid in high overall yields.



Hydroboration of cholest-4-en-7β-yl benzoate (I; R = C_6H_5CO) gave, after chromatography, 5α-cholestan-4α,7β-diol 7β-benzoate (IV; R = C_6H_5CO) in 95% yield (cf. hydroboration of cholest-4-ene [6]). Oxidation with chromium trioxide in pyridine gave 5α-cholestan-4-one-7β-yl benzoate (V; R = C_6H_5CO) the structure of which was confirmed by optical rotatory dispersion (o.r.d.). This ketone exhibited a negative Cotton effect of amplititude −110 * in agreement with the results of Djerassi *et al.*[8] (10^{-2} a = −94) for 5α-cholestan-4-one. The corresponding 5β-cholestane compounds [9] exhibit a positive Cotton effect of amplitude a = +3. Further confirmation was obtained by reduction of the ketone (V; R = C_6H_5CO) with sodium in propanol to give 5α-cholestan-4α,7β-diol identical with the product of hydrolysis of the hydroxy-benzoate (IV; R = C_6H_5CO).

Basic hydrolysis of the benzoate (V; R = C_6H_5CO) furnished 7β-hydroxy-5α-cholestan-4-one (V; R = H) the structure of which was established by oxidation to the known 5α-cholestan-4,7-dione.[10] The keto-alcohol (V; R = H) was converted to the toluene-*p*-sulphonate ester (V; R = *p*-$CH_3C_6H_4SO_2$) which on treatment with the 5% methanolic potassium hydroxide yielded 5α,7α-cyclocholestan-4-one (VI).

The structure of this cycloketone is supported by its reactions, which are very similar to those of the analogous 3α,5α-cyclocholestan-6-one.[11]

Catalytic hydrogenation of the ketone (VI) in acetic acid with palladium as catalyst furnished the known 5α-cholestan-4-one. Acid-catalysed hydration of the ketone (VI) gave 7β-hydroxy-5α-cholestan-4-one (V; R = H) whilst reduction with lithium aluminium hydride produced an oil which was chromatographed on aluminium oxide. Elution with benzene followed by crystallisation from methanol–acetone gave an alcohol thought, again by analogy,[11,12] to be 5α,7α-cyclocholestan-4α-ol (VII). It rearranged on treatment with toluene-*p*-sulphonic acid in aqueous dioxan to cholest-4-en-7β-ol (I; R = H) in 85% yield, whereas oxidation with chromium trioxide in pyridine regenerated the ketone (VI).

The ketone (VI) exhibited an absorption peak in the

* For nomenclature see ref. 7.

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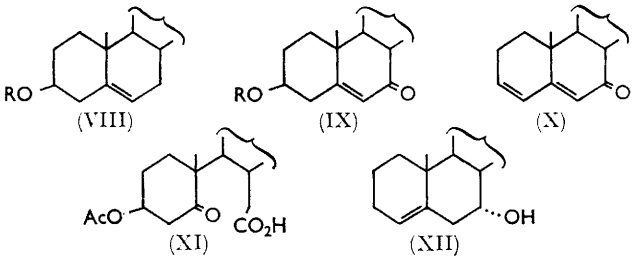
infrared at 1675 cm.$^{-1}$ indicative of a carbonyl group in conjugation with a cyclopropane ring.[13-15] There were also peaks at 1230 and 893 cm.$^{-1}$ which have been attributed to a transannular cyclopropane ring [16] in the steroid molecule. The nuclear magnetic resonance spectrum of the ketone (VI) was characterised by complex absorption between τ 9·6 and 9·9 due to the cyclopropyl protons [13,17,18] and the absence of vinyl proton absorption, thus confirming the presence of the 5α,7α-cyclo-structure.



We now wish to record some observations regarding the well-tried route (VIII) ⟶ (I) [19,20] to the preparation of "ψ-cholesterol" (I; R = H) from cholesteryl acetate (VIII).

The initial allylic oxidation (VIII) ⟶ (IX) although improved by *tert*-butyl chromate [21] is still wasteful of starting material, the principal contaminant being the keto-carboxylic acid (XI) formed by oxidative fission of ring B.[22] The final reduction (X) ⟶ (XII) also furnishes cholest-4-en-7α-ol (XII) in 16% yield, and the required 7β-ol could only be successfully separated from its epimer by long and careful chromatography.

The 7α-alcohol, m. p. 87—90°, $[\alpha]_D$ +43° (*c* 0·9) proved to be identical with that formed by reduction of cholest-4-en-7-one with sodium borohydride.[2]

EXPERIMENTAL

All rotations were determined in chloroform using a Bendix–Ericsson EPL–NPL automatic polarimeter, type 143A. M. p.s were measured on a Kofler hot-stage apparatus. Alumina was activated Spence type H. Thin-layer chromatography was carried out using benzene or cyclohexane–ethyl acetate. Compounds were detected by spraying the plate with a solution of antimony trichloride in ethyl methyl ketone, followed by heating at 120° for 15 min. For the working up procedures see ref. 23.

5α-Cholest-4α,7β-diol 7-Benzoate.—A solution of sodium borohydride (8·6 g.) in diethyleneglycol dimethyl ether (diglyme) (180 ml.) was added dropwise to a solution of boron trifluoride etherate (38 ml.) in diglyme (180 ml.), in a flask previously flushed out with nitrogen. The diborane evolved was passed, in a stream of nitrogen, into a solution of cholest-4-en-7β-yl benzoate (5·7 g.) in tetrahydrofuran (70 ml.) for 2 hr. Methanol (50 ml.) containing potassium hydroxide (2·5 g.) was then added to the tetrahydrofuran solution followed by the addition of hydrogen peroxide (20 ml., 100 vol.), and the mixture was heated at 60° for 5 min., and then poured into water. The product was extracted with ether, and worked up to give an oil (6·2 g.) which was chromatographed on alumina (120 g.). Elution with pentane gave unchanged, cholest-4-en-7β-yl benzoate, (497 mg.), m. p. and mixed m. p. 156—157°.

Elution with ether–methanol (19 : 1) (10 × 25 ml.) yielded *5α-cholestan-4α,7β-diol 7-benzoate* (5·4 g.) as long needles after crystallisation from acetone, m. p. 161·5—162°, $[\alpha]_D$ +77° (*c* 1·04) (Found: C, 80·1; H, 10·7. $C_{34}H_{52}O_3$ requires C, 80·25; H, 10·3%).

4-Oxo-5α-Cholestan-7β-yl Benzoate.—A solution of 5α-cholestan-4α,7β-diol 7-benzoate (3·05 g.) in pyridine (30 ml.) was added to a mixture of chromium trioxide (3·61 g.) and pyridine (35 ml.) at 0° and the reaction mixture left at 25° for 12 hr. Pentane was then added and the precipitate removed by filtration through a pad of "Super-Cel". The filtrate was worked up to give *4-oxo-5α-cholestan 7β-yl benzoate* (2·9 g.) as needles after crystallisation from methanol–acetone, m. p. 190—192°, $[\alpha]_D$ 108·5° (*c* 0·93); $\nu_{max.}$ 1710 cm.$^{-1}$ (4-ketone, 7-benzoate). O.r.d. optical trough, −2700° (308 mμ); peak, +8300° (263 mμ); amplitudes −110 (Found: C, 81·0; H, 9·8. $C_{34}H_{50}O_3$ requires C, 80·6; H, 9·95%).

Reduction of 4-Oxo-5α-cholestan-7β-yl Benzoate by Sodium in Propanol.—Sodium metal (0·69 g.) was added over a period of 15 min., to a solution of 4-oxo-5α-cholestan-7β-yl benzoate (79 mg.) in n-propanol (7·5 ml.) and the mixture was heated under reflux for 2·5 hr. Dilution with water and work up gave *4α,7β-dihydroxy-5α-cholestane* (65 mg.) as needles after crystallisation from acetone, m. p. 132—134°, $[\alpha]_D$ +37·5° (*c* 1·06) (Found: C, 80·1; H, 12·2. $C_{27}H_{48}O_2$ requires C, 80·15; H, 11·95%).

Hydrolysis of 5α-Cholestan-4α,7β-diol 7-Benzoate by Lithium Aluminium Hydride.—A suspension of lithium aluminium hydride (66·4 mg.) in anhydrous ether (10 ml.) was added to a solution of 5α-cholestan-4α,7β-diol 7-benzoate (61·5 mg.) in anhydrous ether (15 ml.) and the mixture heated under reflux for 30 min. Work up gave 4α,7β-dihydroxy-5α-cholestane (50 mg.) as needles, m. p. and mixed m. p. 132—134°, $[\alpha]_D$ +40° (*c* 0·97).

7β-Hydroxy-5α-cholestan-4-one.—A mixture of 4-oxo-5α-cholestan-7β-yl benzoate (2·5 g.) and potassium hydroxide (1·75 g.) in methanol (70 ml.) was heated under reflux for 1·5 hr. Carbon dioxide was then passed into the solution until precipitation of potassium carbonate was complete, after which the solvent was removed under reduced pressure. Water and ether was added to the residue and the ethereal solution was worked up to give 7β-hydroxy-5α-cholestan-4-one (1·75 g.) as platelets on crystallisation from pentane, m. p. 153—153·5°, $[\alpha]_D$ +66° (*c* 0·6); $\nu_{max.}$ 1715 cm.$^{-1}$ (C=O).

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O.r.d. trough, −2200° (308 mμ) [lit.,[4,5] m. p. 151—153°, $[\alpha]_D$ +62°; m. p. 152—153°, $[\alpha]_D$ +50°)].

5α-Cholestan-4,7-dione.—Chromium trioxide (250 mg.) in a mixture of water (2 ml.) and glacial acetic acid (2 ml.) was added to a solution of 7β-hydroxy-5α-cholestan-4-one (350 mg.) in glacial acetic acid (10 ml.) and the mixture left at room temperature for 10 hr. Ethanol was added, followed by water and the solid precipitate was filtered off and dissolved in ether. The ethereal solution was worked up to give an oil which crystallised from ethanol to yield 5α-cholestan-4,7-dione as plates, m. p. 145—146°, $[\alpha]_D$ −21° (*c* 1·34) (lit.,[4,10] m. p. 146—147°, 144—146°).

*4-Oxo-5α-cholestan-7β-yl Toluene-*p*-sulphonate.*—Toluene-*p*-sulphonyl chloride (1·5 g.) was added to a solution of 7β-hydroxy-5α-cholestan-4-one (1·16 g.) in pyridine (20 ml.) and the solution left at room temperature for 1 week. Addition of water precipitated an oil which crystallised on standing for 1 week; the solid was filtered off, dissolved in ether and the ethereal solution worked up to give an oil which crystallised on trituration with a seed and acetone, m. p. 125—137°, $[\alpha]_D$ +50° (*c* 1·07) (Found: C, 73·6; H, 9·3. $C_{34}H_{52}O_4S$ requires C, 73·35; H, 9·4%).

*Solvolysis of 4-Oxo-5α-cholestan-7β-yl Toluene-*p*-sulphonate.*—The toluene-*p*-sulphonate ester (1 g.) was dissolved in ethanol (30 ml.) and potassium hydroxide (1·5 g.) was added. The solution was heated under reflux for 1 hr. and then worked up to give an oil which was chromatographed on alumina (30 g.) (Woelm basic Activity 1). Pentane–benzene (4 : 1) eluted 5α,7α-cyclocholestan-4-one (0·9 g.) as plates after crystallisation from acetone, m. p. 85—86°, $[\alpha]_D$ +121° (*c* 1·38), $\nu_{max.}$ 1675 cm.$^{-1}$ (C=O) (Found: C, 84·1; H, 11·5. $C_{27}H_{44}O$ requires C, 84·3, 11·55%).

Hydrogenation of 5α,7α-Cyclocholestan-4-one.—5α,7α-Cyclocholestan-4-one (160 mg.) was hydrogenated in the presence of palladium oxide (94 mg.) in acetic acid (10 ml.). After absorption of 1 mol. of hydrogen, the reduction was stopped, the catalyst removed, and the filtrate evaporated under reduced pressure. The product was chromatographed on alumina (5 g.) and elution with pentane gave 5α-cholestan-4-one, m. p. 95—96°, $[\alpha]_D$ +25° (*c* 0·9), after crystallisation from methanol (lit.,[21,24,25] m. p. 96°, $[\alpha]_D$ +27°; m. p. 96—98°, $[\alpha]_D$ +28°; m. p. 96—98°)

Acid Catalysed Hydration of 5α,7α-Cyclocholestan-4-one—The 5α,7-cycloketone (65 mg.) was warmed for 4 hr. in acetic acid (20 ml.) containing concentrated sulphuric acid (0·1 ml.) after which the reaction mixture was diluted with water and the product extracted with ether. Work up gave a brown oil (70 mg.) which was crystallised from pentane to yield 7β-hydroxy-5α-cholestan-4-one, m. p. and mixed m. p. 152—153°, $[\alpha]_D$ +64° (*c* 0·9).

Reduction of 5α,7α-Cyclocholestan-4-one by Lithium Aluminium Hydride.—A suspension of lithium aluminium hydride (475 mg.) in anhydrous ether (60 ml.) was added to a solution of the 5α,7α-cycloketone (250 mg.) in anhydrous ether (30 ml.) and the reaction mixture heated under reflux for 0·5 hr. Ethyl acetate was added to destroy the excess of reagent and the reaction mixture was worked up to give an oil. Crystallisation of the oil from acetone at −10° yielded 5α,7α-cyclocholestan-4α-ol (100 mg.) as prisms, m. p. 90—91°, $[\alpha]_D$ +6° (*c* 0·87) (Found: C, 84·05; H, 12·3. $C_{27}H_{46}O$ requires C, 83·85; H, 11·9%).

Rearrangement of 5α,7α-Cyclocholestan-4α-ol.—Water (2 ml.) and toluene-*p*-sulphonic acid (2 g.) was added to a solution of 5α,7α-cyclocholestan-4α-ol (330 mg.) in dioxan (10 ml.) and the reaction mixture was heated on a water bath for 3 hr. The reaction mixture was then diluted with water and worked up to give an oil (340 mg.) which was chromatographed in alumina (12 g.) (Woelm basic, Activity 1). Benzene eluted 7β-hydroxy-cholest-4-ene which crystallised from acetone–methanol as needles, m. p. and mixed m. p. 120—121°, $[\alpha]_D$ +60° (*c* 1·12).

Oxidation of 5α,7α-Cyclocholestan-4α-ol by Chromium Trioxide in Pyridine.—A solution of 5α,7α-cyclocholestan-4α-ol (275 mg.) in pyridine (2·75 ml.) was added to a mixture of chromium trioxide (320 mg.) and pyridine (3 ml.) and the reaction mixture left at room temperature for 15 hr. Benzene was then added and the precipitate filtered off and washed thoroughly with ether. The filtrate and washings were combined and worked up to give an oil which crystallised from acetone to yield 5α,7α-cyclocholestan-4-one (130 mg.) as plates, m. p. and mixed m. p. 85—86°, $[\alpha]_D$ +123° (*c* 1·21).

Reduction of Cholest-3,5-diene-7-one by Sodium in n-Propanol.—Sodium metal (120 g.) was added over 4 hr. to a boiling solution of cholest-3,5-dien-7-one (m. p. 113—114°, $[\alpha]_D$ −310°) (73 g.) in n-propanol (1700 ml.). The mixture was heated under reflux for a further hour, cooled to room temperature and the excess of sodium destroyed by the addition of methanol (50 ml.). Solid carbon dioxide was then added until precipitation of sodium carbonate was complete, after which the n-propanol was evaporated under reduced pressure. The residue was dissolved in ether and water and the ethereal solution worked up to give an oil (70 g.), which was chromatographed on alumina (900 g.) in two batches of 35 g. Pentane–benzene (9 : 1) (4 × 1500 ml.) eluted an oil (4·8 g.) which crystallised from acetone to give 7α-hydroxycholest-4-ene as small needles, m. p. 87—90° $[\alpha]_D$ +43° (*c* 0·9) (lit.,[2] m. p. 85—86·4°, $[\alpha]_D$ +44·5°). Further elution with pentane–benzene (9 : 1) (2 × 1500 ml.) gave an oil (13·1 g.), which was shown by thin-layer chromatography to be a mixture of 7α-hydroxy-cholest-4-ene and 7β-hydroxycholest-4-ene. Continued elution with pentane–benzene (9 : 1) (3 × 1500 ml.) and then benzene gave a white solid (16·2 g.) which yielded 7β-hydroxycholest-4-ene on crystallisation from acetone–methanol, m. p. 120·5—121·5°, $[\alpha]_D$ +57° (*c* 0·85) (lit.,[2] m. p. 116°, $[\alpha]_D$ 57·6°; lit.,[4] m. p. 122·5—124°, $[\alpha]_D$ +90°; lit.,[26] m. p. 116—117°, $[\alpha]_D$ +67°).

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