# *Steroids and Walden Inversion. Part XVII.* The Configuration of ψ-Cholesterol and the Attempted Preparation of 4β-Methoxy-5 : 7-cyclocholestane.*

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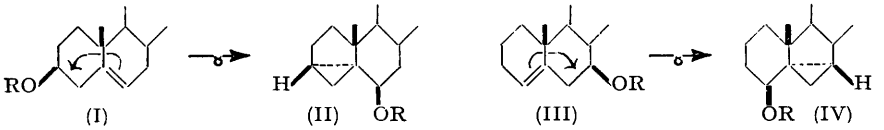
ψ-Cholesterol, by hydrogenation, gives cholestan-7β-ol; ψ-cholesterol is therefore cholest-4-en-7β-ol. It is not epimerised by hot sodium amyloxide or sodium ethoxide.

ψ-Cholesterol with phosphorus pentachloride gives 7β-chlorocholest-4-ene with retention of configuration at $C_{(7)}$; although the chloride could not be obtained crystalline, the configuration of the 7-chlorine atom is established by hydrogenation to 7β-chlorocholestane, followed by acetolysis, and alkaline hydrolysis, to afford cholestan-7α-ol.

Attempts to convert ψ-cholesteryl toluene-*p*-sulphonate into 4β-methoxy-5 : 7-*cyclo*cholestane were unsuccessful; methanolysis in the presence or absence of potassium acetate gave a non-crystalline methyl ether, which appeared to be identical with ψ-cholesteryl methyl ether, prepared from ψ-cholesterol by methylation with potassium and methyl iodide. Hydrolysis of ψ-cholesteryl toluene-*p*-sulphonate occurs on alkaline aluminium oxide with retention of configuration at $C_{(7)}$ to regenerate ψ-cholesterol; a small proportion of cholesta-4 : 6-diene is also produced.

The general symmetry of the 3- and the 7-position in the steroid nucleus suggests that the conversion of 3β-substituted $\Delta^5$-steroids (I) into 6β-substituted 3 : 5-*cyclo*steroids (II) (cf. Shoppee and Summers, *J.*, 1952, 3361, for a summary of earlier work) might be paralleled by transformation of 7β-substituted $\Delta^4$-steroids (III) into 4β-substituted 5 : 7-*cyclo*steroids (IV). We therefore commenced a study of the reactions of ψ-cholesterol.




(I) (II) (III) (IV)

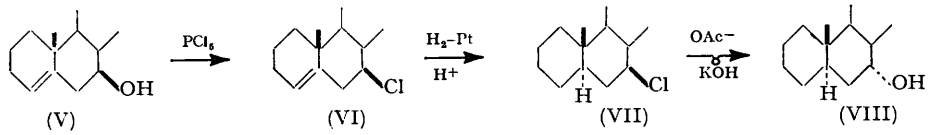
ψ-Cholesterol, m. p. 116°, $[\alpha]_D$ + 58°, $\lambda_{max.}$ 211 mμ, log ε 3·51, was obtained 40 years ago by reduction of cholesta-3 : 5-dien-7-one with sodium and ethanol by Windaus and Resau (*Ber.*, 1915, **48**, 851), who characterised it by preparation of the benzoate. Since the 3 : 5-*cyclo*steroid rearrangement fails with 3α-substituted $\Delta^5$-steroids (Evans and Shoppee, *J.*, 1953, 540), an essential preliminary was to show that the hydroxyl group in ψ-cholesterol is β-orientated. ψ-Cholesterol, characterised as the acetate and 3 : 5-dinitrobenzoate, was hydrogenated with platinum in ethyl acetate in the presence of a trace of perchloric acid (cf. Hershberg *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1144) to give cholestan-7β-ol (Cremlyn and Shoppee, *J.*, 1954, 3515); this establishes the β-configuration of the hydroxyl group in ψ-cholesterol (V).

This assignment (7β-OH; equatorial †) is consistent with the fact that ψ-cholesterol is unchanged by treatment with hot sodium–amyl alcohol or with sodium ethoxide at 180°. Attempted confirmation by the method of molecular-rotation differences fails, probably owing to vicinal action. Calculated values of $[M]_D$ for ψ-cholesterol and *epi*-

* Part XVI, *J.*, 1954, 3515.

† Ring B in cholest-4-ene is a strained chair-form; carbon atoms $C_{(10)}$, $C_{(5)}$, and $C_{(6)}$ are coplanar, lying in the general plane of the tetracyclic system, and the bond axis $C_{(7)}$–$C_{(8)}$ is no longer parallel to the bond axis $C_{(10)}$–$C_{(5)}$, but inclined thereto with $C_{(7)}$ lying a little behind the plane containing $C_{(10)}$, $C_{(5)}$, $C_{(6)}$, and $C_{(8)}$, so that substituents at $C_{(7)}$ deviate only slightly from normal equatorial and axial conformations as in *cyclo*hexane. Ring A has the " half-chair " conformation as in *cyclo*hexene with four contiguous coplanar carbon atoms [$C_{(3)}$, $C_{(4)}$, $C_{(5)}$, and $C_{(10)}$] (cf. Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21).

ψ-cholesterol are +371° * and +190°,* or +351° † and +179°,† whereas the observed value for ψ-cholesterol is +233°, which suggests that the 7-hydroxyl group is α-orientated; the calculated values for the epimeric acetates are +456° † and +104°,† whereas the observed value for ψ-cholesteryl acetate is +281°.

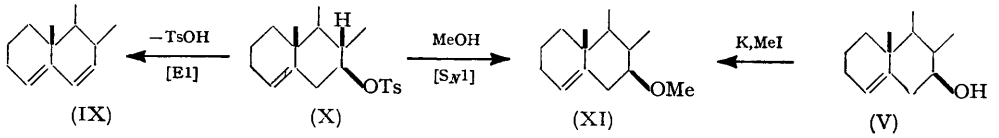



(V) (VI) (VII) (VIII)

It is now generally agreed that intervention of the π-electrons of the 5 : 6-double bond at $C_{(3)}$ (as I) leads, according to the experimental conditions, (*a*) to replacement with retention of configuration at $C_{(3)}$, or (*b*) to rearrangement with inversion at $C_{(3)}$ and production of a 3 : 5-*cyclo*steroid as (II). It seemed accordingly desirable next to examine the stereochemical course of replacement of hydroxyl by chlorine in ψ-cholesterol.

Windaus and Resau (*loc. cit.*) by treatment of ψ-cholesterol with phosphorus pentachloride obtained a non-crystalline chloride, which they reduced with sodium–ethanol to cholest-4-ene. Similarly, we obtained ψ-cholesteryl chloride (VI) as an oil, $[\alpha]_D$ +71°, $\lambda_{max.}$ 212, log ε 3·44 (in $Et_2O$), which by hydrogenation with platinum–ethyl acetate–perchloric acid (trace) gave 7β-chlorocholestane (VII), m. p. 65—68°, $[\alpha]_D$ +77° (Cremlyn and Shoppee, following paper); this by acetolysis and subsequent alkaline hydrolysis gave cholestan-7α-ol (VIII) (Cremlyn and Shoppee, *loc. cit.*) accompanied by cholest-7-ene. These results show that the replacement (V ⟶ VI) occurs with retention of configuration. By use of thionyl chloride ψ-cholesterol gave a non-crystalline and somewhat less pure preparation of ψ-cholesteryl chloride, $[\alpha]_D$ +54°, $\lambda_{max.}$ 211 mμ, log ε 3·27 (in $Et_2O$).

ψ-Cholesteryl toluene-*p*-sulphonate (X), when refluxed with methanol in the presence of potassium acetate, gave (*a*) cholesta-4 : 6-diene (IX), m. p. 88°, $[\alpha]_D$ +4°, $\lambda_{max.}$ 238 mμ, log ε 4·2, formed by elimination of toluene-*p*-sulphonic acid, and (*b*) an oil, $[\alpha]_D$ +70°, $\lambda_{max.}$ 211 mμ, log ε 3·41, which we regard as ψ-cholesteryl methyl ether (XI) rather than as the 5 : 7-*cyclo*cholestane derivative (IV; R = Me) on the following grounds. First, methanolysis of ψ-cholesteryl toluene-*p*-sulphonate in the absence of potassium acetate furnished the same two products; secondly, the methyl ether by treatment with hydrochloric–acetic acid at 15° failed to rearrange to ψ-cholesteryl chloride (VI) as would be expected by analogy with the ready conversion of 6β-methoxy-3 : 5-*cyclo*cholestane into cholesteryl chloride (Beynon, Heilbron, and Spring, *J.*, 1936, 907); thirdly, methylation of ψ-cholesterol with potassium and methyl iodide gave a non-crystalline methyl ether




(IX) (X) (XI) (V)

with the same physical characteristics. We have thus been unable to realise the rearrangement (III ⟶ IV); a probable contributory factor is the greater rigidity of ring B in (III), resulting from *trans*-fusion with ring C, as compared with ring A in (I). We are examining the reaction of the toluene-*p*-sulphonate (X) with other alcohols, *e.g.*, 4-bromobenzyl alcohol, in the hope of obtaining crystalline analogues of (XI) or (IV); an alternative route to compounds of type (IV) using 4-oxocholestan-7β-yl toluene-*p*-sulphonate or halides is also being explored.

We have observed that, whilst ψ-cholesteryl toluene-*p*-sulphonate (X) in pentane solution is unaltered by passage through a column of neutralised aluminium oxide, use

* Calculated as follows: [$M_D$ (cholestane-3β : 7β-diol) = +214°] − [ΔO : 3β = +2°] + [ΔE4 = +159°] = +371°; [$M_D$ (cholestane-3β : 7α-diol) = +33°] − [ΔO : 3β = +2°] + [ΔE4 = +159°] = +190° (cf. Barton and Klyne, *Chem. and Ind.*, 1948, 755).

† The contributions for ΔO : 7β and ΔO : 7α in A/B-*trans*- and A/B-*cis*-systems are averaged (7β = +103°, 7α = −69°) and added to the molecular rotation for cholest-4-ene + 248°. The contributions for ΔA : 7β and ΔA : 7α are similarly averaged (7β = +208°, 7α = −144°) and added.

of alkaline aluminium oxide leads to hydrolysis (70%) with intervention of the π-electrons of the 4 : 5-double bond and retention of configuration at $C_{(7)}$, to regenerate ψ-cholesterol (V), and to an elimination reaction (*E*1) (~12%) whereby the intermediate carbonium ion affords cholesta-4 : 6-diene (IX).

An attempt was made to prepare *epi*-ψ-cholesterol. ψ-Cholesterol was converted into the non-crystalline 4ξ : 5ξ-dibromide, which was oxidised with chromium trioxide–acetic acid; debromination with zinc–ethanol and chromatography of the product on neutralised aluminium oxide failed to afford cholest-4-en-7-one (cf. Butenandt and Schmidt-Thomé, *Ber.*, 1936, **69**, 882; Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244; Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 5421) required for reduction with lithium aluminium hydride or sodium borohydride, and furnished cholest-5-en-7-one. This conversion of an unconjugated ketone into the conjugated isomeride may have been induced by the specimen of aluminium oxide used, and may be compared with the conversion of cholest-5- into cholest-4-en-3-one (Shoppee and Summers, *J.*, 1950, 687; Birch, *ibid.*, p. 2325).

## Experimental

For general experimental directions see *J.*, 1954, 3515. $[\alpha]_D$ were determined in $CHCl_3$ and ultra-violet absorption spectra were determined with an SP. 500 Unicam spectrophotometer with corrected scale in EtOH, unless otherwise stated. Neutralised aluminium oxide was prepared according to the procedure of Reichstein and Shoppee (*Discuss. Faraday Soc.*, 1949, **7**, 305).

*ψ-Cholesterol.* This was prepared from 7-oxocholesteryl acetate by alkaline hydrolysis, dehydration to cholesta-3 : 5-dien-7-one, and reduction thereof with sodium–propan-1-ol in 65% yield (cf. Windaus and Resau, *Ber.*, 1915, **48**, 851). It had m. p. 116°, $[\alpha]_D$ +60° (*c*, 0·81), $\lambda_{max.}$ 211 mμ, log ε 3·51, after recrystallisation from acetone–methanol and was characterised by preparation (acetic anhydride–pyridine at 15°) of the *acetate*, m. p. 63—64°, $[\alpha]_D$ +65° (*c*, 1·24), after recrystallisation from acetone–methanol [Found (after drying at 40°/0·01 mm. for 4 hr.): C, 81·0; H, 11·1. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%], and the benzoate, m. p. 156°, $[\alpha]_D$ +99°; also by preparation [3 : 5-dinitrobenzoyl chloride–benzene–pyridine at 15° (cf. Reichstein, *Helv. Chim. Acta*, 1926, **9**, 799)] of the 3 : 5-*dinitrobenzoate*, m. p. 166—167°, $[\alpha]_D$ +107° (*c*, 3·38), after two recrystallisations from acetone [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 70·2; H, 8·3. $C_{34}H_{48}O_6N_2$ requires C, 70·3; H, 8·3%], and by preparation of the *toluene*-p-*sulphonate*, m. p. 135—136° (decomp. to a red melt), $[\alpha]_D$ +21° (*c*, 1·0), after recrystallisation from acetone [Found (after drying at 90°/0·01 mm. for 3 hr.): C, 75·4; H, 9·65. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7%].

ψ-Cholesterol (172 mg.) was dissolved in amyl alcohol (30 c.c.) and sodium added to the boiling solution until no more would dissolve. After refluxing for 6 hr., the solution was cooled and, after addition of ethanol and water, evaporated under reduced pressure. The product was extracted with ether, and the extract washed with 2N-hydrochloric acid and water, dried, and evaporated. The residue was purified by chromatography on aluminium oxide (6 g.) in pentane; elution with benzene–pentane (1 : 4) yielded ψ-cholesterol (150 mg.), m. p. 116°, after recrystallisation from acetone–methanol. Similarly, ψ-cholesterol (100 mg.) after treatment with 1·2N-ethanolic sodium ethoxide at 180° for 80 hr. was recovered unchanged (90 mg.), m. p. 116° after recrystallisation from acetone–methanol.

*Cholestan-7β-ol from ψ-Cholesterol.*—ψ-Cholesterol (470 mg.), in pure ethyl acetate (25 c.c.) containing perchloric acid (60%; 0·1 c.c.), was shaken with platinum oxide (50 mg.) in hydrogen; allowing for reduction of the catalyst, 27·5 c.c. (1 mol.) were taken up in 5 min., whereafter absorption ceased. The product, obtained by filtration, washing with 2N-sodium carbonate, then with water, drying, and vacuum-evaporation, was chromatographed on aluminium oxide (15 g.) in pentane. Elution with pentane (3 × 50 c.c.) gave some uncrystallisable material, but use of benzene–pentane (1 : 9; then 1 : 4, 5 × 50 c.c.) afforded cholestan-7-β-ol (383 mg.), m. p. 115°, $[\alpha]_D$ +45° (*c*, 1·305), after recrystallisation from methanol, giving no m. p. depression with authentic cholestan-7β-ol and no colour with tetranitromethane–chloroform.

*ψ-Cholesteryl Chloride.*—(*a*) ψ-Cholesterol (1·5 g.; dried by azeotropic distillation with benzene) was treated with freshly sublimed phosphorus pentachloride (3·5 g.) in chloroform (70 c.c.) in the presence of calcium carbonate (2·2 g.) during 45 min. at 0°. The mixture was shaken for 2 hr. at 0°, then for a further 1·5 hr. at 15°, and set aside overnight. The usual

working up gave a yellow oil (1·6 g.), which was chromatographed on neutralised aluminium oxide (40 g.) in pentane; elution with pentane (4 × 250 c.c.) yielded *ψ-cholesteryl chloride* (1·36 g.), $[\alpha]_D$ +71° (*c*, 1·97), $\lambda_{max.}$ 212 mμ, log ε 3·44 in $Et_2O$ (Found: Cl, 8·0. $C_{27}H_{45}Cl$ requires Cl, 8·7%), as a colourless oil which did not crystallise. A second preparation showed the same physical constants. The chloride (1·35 g.) was hydrogenated with platinum oxide in ethyl acetate containing one drop of 60% perchloric acid; after absorption ceased, the catalyst was filtered off, ethyl acetate largely removed in a vacuum, and the residue worked up in the usual way. The product was chromatographed on neutralised aluminium oxide (40 g.) in pentane; elution with pentane (2 × 200 c.c.) furnished a product consisting essentially of 7β-*chlorocholestane* (965 mg.) as a colourless oil,* $[\alpha]_D$ +71° (*c*, 4·82) (Found: Cl, 7·9. $C_{27}H_{47}Cl$ requires 8·7%) giving no colour with tetranitromethane. Further elution with pentane (2 × 100 c.c.) gave (i) a colourless oil (140 mg.), which gave no colour with tetranitromethane and partially crystallised on prolonged cooling to give, after drainage on porous porcelain and two recrystallisations from acetone, a small quantity of an incompletely pure *dichloro-compound*, m. p. 88—90°, $[\alpha]_D$ +103° (*c*, 3·12) (Found: Cl, 18·9. $C_{27}H_{46}Cl_2$ requires Cl, 16·1%), and (ii) a colourless unsaturated oil (77 mg.) giving a strong yellow colour with tetranitromethane. The specimen of 7β-chlorocholestane (785 mg.) was heated with freshly fused potassium acetate (7·5 g.) in acetic acid (15 c.c.) with exclusion of moisture for 48 hr. The cooled mixture was poured into 2N-sodium carbonate (50 c.c.), and the product, isolated in the usual way, refluxed with 4% methanolic potassium hydroxide (60 c.c.) for 1 hr. After addition of a little water, passage of carbon dioxide, and evaporation in a vacuum, the hydrolysis product was worked up in the usual way, and the resultant oil (756 mg.) chromatographed on neutralised aluminium oxide (21 g.) in pentane. Elution with pentane (4 × 75 c.c.) gave an oil (302 mg.), $[\alpha]_D$ +26°, which solidified and yielded cholest-7-ene, m. p. 81—83°, $[\alpha]_D$ +14° (*c*, 1·45), after three recrystallisations from acetone; elution with benzene–pentane (1 : 1; 8 × 75 c.c.) gave cholestan-7α-ol (91 mg.), m. p. and mixed m. p. 97—98°, $[\alpha]_D$ +6° (*c*, 1·07), after recrystallisation from acetone. Further elution with benzene–pentane, benzene, and ether–benzene failed to furnish cholestan-7β-ol and gave only uncrystallisable yellow oils (111 mg.).

(*b*) *ψ*-Cholesterol (350 mg.) was refluxed with thionyl chloride (2·5 c.c.) with exclusion of moisture for 3 hr.; the cooled mixture was poured into ice-water and worked up in the usual way, to give an oil (380 mg.) which was chromatographed on neutralised aluminium oxide (20 g.) prepared in pentane. Elution with pentane (2 × 200 c.c.) gave an oil (50 mg.) consisting largely of *ψ*-cholesteryl chloride, $[\alpha]_D$ +54° (*c*, 2·69), $\lambda_{max.}$ 211 mμ, log ε 3·27 in $Et_2O$; elution with benzene–pentane (1 : 4, 3 × 200 c.c.) gave *ψ*-cholesterol (320 mg.), m. p. and mixed m. p. 116° after two recrystallisations from acetone.

*Methanolysis of ψ-Cholesteryl Toluene*-p-*Sulphonate.*—(a) *In presence of potassium acetate.* *ψ*-Cholesteryl toluene-*p*-sulphonate (1 g.) was refluxed with anhydrous potassium acetate (2·8 g.) in methanol (240 c.c.) for 6 hr.; methanol (*ca.* 200 c.c.) was removed under reduced pressure, water added, and the product extracted with ether. The ethereal extract was washed with water, dried, and evaporated completely to yield an oil (760 mg.). Chromatography on aluminium oxide (40 g.) prepared in pentane, and elution with pentane (75 c.c.) gave cholesta-4 : 6-diene, m. p. and mixed m. p. 89—90°, $[\alpha]_D$ +3° (*c*, 1·11), $\lambda_{max.}$ 239 mμ, log ε 4·2 (cf. Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 107). Further elution with pentane (5 × 75 c.c.) gave a colourless oil (605 mg.); this was rechromatographed and split into numerous fractions whose ultra-violet absorption spectra were examined. Those fractions with $\lambda_{max.}$ 210 mμ were combined and distilled (short path) at 110°/0·003 mm.; the distillate failed to crystallise, but a solution in acetone–methanol at −80° yielded crystals, which melted between 0° and 10°. 7β-*Methoxycholest*-4-*ene* (*ψ-cholesteryl methyl ether*) had $[\alpha]_D$ +70° (*c*, 2·48), $\lambda_{max.}$ 211 mμ, log ε 3·39 (Found: C, 83·6; H, 12·0. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%), and gave a lilac colour in the Rosenheim test only on standing; treatment with concentrated hydrochloric (or hydrobromic) acid in acetic acid at 15° for 40 hr. gave an amorphous product, which was separated by chromatography on aluminium oxide in pentane into seven non-crystalline fractions all giving a negative Beilstein test.

(b) *ψ*-Cholesteryl toluene-*p*-sulphonate (245 mg.) was refluxed with methanol (68 c.c.) for 2½ hr.; the product was an oil with physical constants closely similar to those recorded above for *ψ*-cholesteryl methyl ether.

* Only subsequently was 7β-chlorocholestane obtained crystalline, m. p. 65—68°, $[\alpha]_D$ +77° (cf. Cremlyn and Shoppee, following paper).

(c) ψ-Cholesterol (890 mg.) was refluxed with potassium (500 mg.) in benzene (40 c.c.) for 1 hr.; methyl iodide (20 c.c.) was added and refluxing continued for 3 hr. After cooling, methanol was added to destroy excess of potassium, and the solvents and methyl iodide were removed under reduced pressure; extraction of the residue with pentane and evaporation of the extract gave an oil (880 mg.), which by chromatography gave 7β-methoxycholest-4-ene [700 mg.) as an oil, $[\alpha]_D$ +70° (*c*, 4·18), $\lambda_{max.}$ 211 mμ, log ε 3·41, giving a lilac colour in the Rosenheim test only on standing.

*Action of Aluminium Oxide on ψ-Cholesteryl Toluene*-p-*Sulphonate*.—The toluene-*p*-sulphonate was recovered unchanged after chromatography on neutralised aluminium oxide in pentane. When the toluene-*p*-sulphonate (170 mg.) was introduced on to a column of aluminium oxide (Spence type H, 200 mesh, activity ~II on the scale of Brockmann and Schodder, *Ber.*, 1941, **74**, 73; 8 g.) and eluted with pentane (4 × 100 c.c.), cholesta-4 : 6-diene (20 mg.), m. p. 88—90°, $[\alpha]_D$ +4° (*c*, 1·1) (Eck and Hollingsworth, *loc. cit.*), was obtained; further elution with benzene–pentane (1 : 1; 4 × 100 c.c.) gave ψ-cholesterol (122 mg.), m. p. and mixed m. p. 116—117° after recrystallisation from acetone–methanol.

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