Steroids and Walden Inversion. Part XVIII. The Preparation and Configuration of the Epimeric 7-Chlorocholestanes.*

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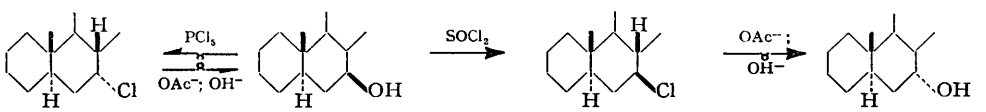
The epimeric 7-chlorocholestanes have been prepared and their configurations determined by conversion by acetolysis and alkaline hydrolysis into the appropriate cholestan-7-ols. Their behaviour in elimination reactions with pyridine, *s*-collidine, and quinoline has been examined.

IN Part I of this series (Shoppee, *J.*, 1946, 1138) the configurations of the epimeric 3-chlorocholestanes were established. The present paper describes the preparation of the epimeric 7-chlorocholestanes and an examination of their acetolysis products, whereby their configurations have been determined.

Treatment of cholestane-7β-ol (II) with phosphorus pentachloride in chloroform in the presence of calcium carbonate at 0° gave 7α-chlorocholestane (I) (55%) together with some unsaturated material; use of phosphorus pentabromide similarly furnished 7α-bromocholestane, m. p. 109°, $[\alpha]_D$ −20°. The change of sign in the specific rotation of the alcohol (II) and the products of these substitution reactions suggests that inversion of configuration at $C_{(7)}$ has occurred.



(I) M. p. 78°, [−21°] (II) M. p. 113°, [+52°] (III) M. p. 67°, [+77°] (IV) M. p. 98°, [+11°]

(Values in square brackets are $[\alpha]_D$)

Similar treatment of cholestan-7α-ol (IV) with phosphorus pentachloride afforded only unsaturated non-crystalline products. However, treatment of cholestan-7β-ol (II) with thionyl chloride in ether in the presence of calcium carbonate at 0—20° gave a small yield of 7β-chlorocholestane (III), accompanied by cholestan-7β-yl sulphite and much

* Part XVII, preceding paper.

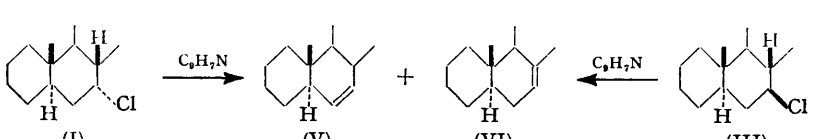
cholest-7-ene; use of thionyl chloride in absence of a solvent and of calcium carbonate first at 20° and then at 75° was more satisfactory and gave 7β-chlorocholestane (III) (59%). The correspondence of sign in the specific rotation of the alcohol (II) and the chloride (III) suggests retention of configuration at $C_{(7)}$.

Whereas the epimeric 3-chlorocholestanes were found to undergo acetolysis only at 180°, the epimeric 7-chlorocholestanes react slowly with 4M-potassium acetate in acetic acid at 140°. Acetolysis of 7α-chlorocholestane (I) gave material which, after alkaline hydrolysis, was separated chromatographically into pure cholestan-7β-ol (II) (15%) unaccompanied by the 7α-epimeride, and cholest-7-ene (78%), m. p. 83°, $[\alpha]_D$ +14°. Conversely, acetolysis of 7β-chlorocholestane (III) gave a product which, after alkaline hydrolysis, furnished pure cholestan-7α-ol (IV) (43%) unaccompanied by the 7β-epimeride, and cholest-7-ene (34%), m. p. 84°, $[\alpha]_D$ +14°.

The production of only a *single* epimeride in each acetolysis shows that a bimolecular replacement (S_N2) proceeding with inversion of configuration is solely responsible for the substitution process, and, since the configurations of the epimeric cholestan-7-ols are established, determines the configurations of the two 7-chlorocholestanes as (I) and (III) respectively.

Secondary alkyl halides, *e.g.*, (I), (III), in non-aqueous media and in the absence of effective basic reagents give olefins, here cholest-7-ene, by the unimolecular elimination mechanism ($E1$); the absence of unimolecular acetolysis involving racemisation (S_N1), in which the slow halogen-ionisation stage would also be the initial stage of the elimination reaction ($E1$), suggests that the stability of the cholestan-7-yl cation is less than that of the cholestan-3-yl cation. Either the life of the cholestan-7-yl cation is too short to permit reaction with the weakly nucleophilic acetate anion, or the rate of reaction with the acetate anion may be so slow relatively to the internal depolarisation of the cation that co-ordination is completely excluded. The proportions of the epimeric chlorides involved in substitution and elimination appear to depend on the circumstance that steric retardation operates in bimolecular nucleophilic substitutions (S_N2) but not in unimolecular eliminations ($E1$) (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 186). Since 7α-chlorocholestane (I) reacts chiefly by elimination (S_N2 15%, $E1$ 78%) whereas 7β-chlorocholestane (III) reacts mainly by substitution (S_N2 43%, $E1$ 34%), the repulsive non-bonded interactions in the S_N2 linear transition states must be greater for (I) [(1 : 2-OAc;6β-H) + (1 : 2-OAc;8β-H) + (1 : 4-OAc;10β-Me)] than for (II) [(1 : 3-OAc;5α-H) + (1 : 3-OAc;9α-H) + (1 : 3-OAc;14α-H)] (cf. Barton, *Chem. and Ind.*, 1953, 664).

An examination has been made of the relative ease with which the epimeric 7-chlorocholestanes undergo dehydrohalogenation and of the products formed. Both chlorides were stable to pyridine at 116°; 7α-chlorocholestane (I) by treatment with *s*-collidine at 170° gave some unsaturated material, but 7β-chlorocholestane (III) was recovered unchanged and unaccompanied by unsaturated products. With quinoline at 238°, 7α-chlorocholestane (I) gave a mixture of cholest-6-ene (V) (25%) and cholest-7-ene (VI) (75%), m. p. 69—71°, $[\alpha]_D$ −13°, whilst 7β-chlorocholestane (III) gave a similar mixture of cholest-6-ene (V) (20%) and cholest-7-ene (VI) (80%), m. p. 70—72°, $[\alpha]_D$ −7°.



(I) (V) (VI) (III)

M. p. 86°, $[\alpha]_D$ −88° M. p. 85°, $[\alpha]_D$ +12°

It is known from the above acetolyses that the cholestan-7-yl cation, derivable equally from either chloride, expels a proton to give cholest-7-ene unaccompanied by cholest-6-ene (example of super-Saytzew orientation); the formation of cholest-6-ene from both chlorides therefore cannot occur by a unimolecular elimination ($E1$). Since the tertiary base quinoline appears to be too weak to promote a bimolecular elimination ($E2$), it seems probable that it acts here as a thermal medium. In the case of 7α-chlorocholestane

[I; 6α-H(equatorial); 7α-Cl(axial); *cis*], thermal *cis*-elimination can afford only cholest-6-ene, whereas in the case of 7β-chlorocholestane [III; 6β- or 8β-H(axial); 7β-Cl(equatorial); *cis*] can furnish both cholest-6-ene and cholest-7-ene.

Experimental

For general experimental directions see preceding paper. $[\alpha]_D$ are in $CHCl_3$; ultra-violet absorption spectra were determined in EtOH on a Unicam SP.500 spectrophotometer with corrected scale.

Cholestan-7β-ol, m. p. 113°, was prepared from cholestan-7-one by reduction with sodium–butan-1-ol, and cholestan-7α-ol, m. p. 98°, by use of lithium aluminium hydride (Cremlyn and Shoppee, preceding paper).

7α-*Chlorocholestane*.—Cholestan-7β-ol (1 g.; dried at 100°/0·01 mm.) in chloroform (60 c.c.) containing dry calcium carbonate (1·3 g.) in suspension was treated with phosphorus pentachloride (2 g.; freshly sublimed) added during 45 min. at 0° with shaking. The mixture was shaken for 2 hr. at 0°, then for 1·5 hr. at 20°, set aside for 19 hr. at 20°, poured into sodium hydrogen carbonate solution containing ice, and extracted with ether. The resultant oil (1·3 g.) contained unsaturated material, and was stirred with chromium trioxide (700 mg.) in acetic acid (35 c.c.) at 60° for 0·5 hr.; after removal of acetic acid at 35°/10 mm., the mixture was poured into 2N-sodium carbonate and extracted with ether. The product (1·15 g.) gradually crystallised and was chromatographed on neutralised aluminium oxide (30 g.) in pentane. Elution with pentane (2 × 100 c.c.) furnished an oil (570 mg.) which crystallised, and by recrystallisation from acetone gave 7α-*chlorocholestane* (55%), m. p. 76—78°, $[\alpha]_D$ −21° (*c*, 4·7) [Found (after drying at 60°/0·01 mm. for 10 hr.): Cl, 8·9. $C_{27}H_{47}Cl$ requires Cl, 8·7%], giving no colour with tetranitromethane–chloroform.

7α-*Bromocholestane*.—Cholestan-7β-ol (322 mg.) in chloroform (20 c.c.) containing dry calcium carbonate (1·1 g.) in suspension, by reaction with phosphorus pentabromide (2·2 g.; freshly sublimed) at −8° and subsequent treatment as above, gave a yellow oil, which was chromatographed on neutralised aluminium oxide (30 g.) in pentane. Elution with pentane (3 × 100 c.c.) gave an oil (180 mg.), which crystallised on cooling, and twice recrystallised from acetone gave 7α-*bromocholestane*, m. p. 108—109°, $[\alpha]_D$ −20° (*c*, 3·92) [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 71·6, H, 10·3. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·4%].

7β-*Chlorocholestane*.—(*a*) Cholestan-7β-ol (1·6 g.) was treated with thionyl chloride (8 c.c.; purified by distillation over quinoline, and fractionation from a small amount of linseed oil) at 20° and the mixture refluxed for 3 hr. The product was poured on ice and worked up in the usual way, to give a brown oil which was chromatographed on neutralised aluminium oxide (45 g.) in pentane. Elution with pentane (2 × 200 c.c.) gave an oil (948 mg.), which crystallised on trituration with acetone; three recrystallisations from acetone furnished 7β-chlorocholestane (59%), m. p. 66—68°, $[\alpha]_D$ +77° (*c*, 3·5) [Found (after drying at 20°/0·01 mm. for 16 hr.): Cl, 8·75. $C_{27}H_{47}Cl$ requires Cl, 8·7%].

(*b*) Cholestan-7β-ol (270 mg.) in ether (12 c.c.) was added dropwise at 0° during 20 min. to a solution of purified thionyl chloride (10 c.c.) in ether (12 c.c.) containing dry calcium carbonate (950 mg.). The mixture was shaken at 0° for 1 hr. and left at 15° for 19 hr. The reaction product, isolated in the usual way, was chromatographed on neutralised aluminium oxide (15 g.) in pentane. Elution with pentane (2 × 30 c.c.) gave a colourless oil (42 mg.), which crystallised, and by recrystallisation from acetone yielded cholest-7-ene, m. p. and mixed m. p. 84—85°. Futher elution with pentane and benzene–pentane (1 : 1) gave oils (total 215 mg.) giving a yellow colour with tetranitromethane; after oxidation of this oil as above with chromium trioxide–acetic acid at 60° for 0·5 hr., the product (166 mg.) was chromatographed on aluminium oxide (10 g.) in pentane. Elution with pentane (2 × 50 c.c.) gave 7β-chlorocholestane (30 mg.), m. p. and mixed m. p. 64—67° after recrystallisation from acetone. Elution with benzene–pentane (1 : 4, 1 : 1) gave oils (60 mg.) which solidified and by crystallisation from acetone gave *cholestan-7β-yl sulphite*, m. p. 90—94° [Found (after drying at 15°/0·02 mm. for 17 hr.): C, 80·0; H, 11·7. $C_{54}H_{94}O_3S$ requires C, 79·0; H, 11·5%].

Acetolysis of 7α-*Chlorocholestane*.—7α-Chlorocholestane (310 mg.), freshly fused potassium acetate (3·5 g.), and anhydrous acetic acid (8 c.c.) were refluxed with exclusion of moisture for 30 hr. The cooled mixture was poured into 2N-sodium carbonate (30 c.c.) and extracted with ether. The product, isolated in the usual way, was hydrolysed by refluxing 4% methanolic potassium hydroxide (30 c.c.) for 3 hr. After addition of a little water, and saturation with

carbon dioxide, methanol was removed in a vacuum and the product extracted with ether. The residual oil (300 mg.) was chromatographed on neutralised aluminium oxide (18 g.) in pentane, 60-c.c. eluates being collected. Elution with pentane (fractions 1—3) gave an oil (236 mg.), which crystallised spontaneously, and by recrystallisation from acetone gave cholest-7-ene, m. p. and mixed m. p. 83°; benzene–pentane mixtures (fractions 4—11) gave only oils (total, 10·5 mg.), but use of benzene–pentane (1 : 1) (fractions 12—18) and benzene (fractions 19—22) gave material (total, 45 mg.), which crystallised when rubbed with acetone, and by recrystallisation from ether–methanol gave cholestan-7β-ol, m. p. and mixed m. p. 113°. Elution with ether–benzene (1 : 4) yielded only yellow oil (4 mg.). Total material eluted : 295 mg.

Acetolysis of 7β-*Chlorocholestane.*—7β-Chlorocholestane (370 mg.) was subjected to acetolysis under the conditions employed for the 7α-epimeride, and furnished a hydrolysed product which was chromatographed on neutralised aluminium oxide (25 g.) in pentane, 60-c.c. eluates being collected. Elution with pentane (fraction 1) gave an oil (114 mg.) which crystallised spontaneously, and by recrystallisation from acetone gave cholest-7-ene, m. p. 82—84°. Futher elution with pentane and benzene–pentane (1 : 9, 1 : 4) (fractions 2—8) gave oils (total 39 mg.) which failed to crystallise. Use of benzene–pentane (1 : 1) gave (fractions 9—12, 13—16, 17—20) crystalline material (86, 49, 12 mg.), which by combination and recrystallisation fram acetone gave cholestan-7α-ol, m. p. and mixed m. p. 96—98°. Elution with ether–benzene (1 : 3) gave only uncrystallisable oil (45 mg.). Total material eluted : 345 mg.

Action of Pyridine, s-*Collidine, and Quinoline.*—Both the epimeric 7-chlorocholestanes were stable to pyridine at 115° for 3 hr. and were recovered unchanged. 7α-Chlorocholestane (75 mg.) was refluxed with *s*-collidine (8 c.c.) for 3 hr.; the product, isolated in the usual way, was purified by filtration in pentane solution through neutralised aluminium oxide. After washing with pentane (200 c.c.), evaporation of the filtrate gave a colourless oil (72 mg.), which crystallised and by crystallisation from acetone gave unchanged 7α-chlorocholestane (55 mg.), m. p. and mixed m. p. 74—76°, giving no colour with tetranitromethane–chloroform. The mother-liquor on evaporation yielded a colourless oil (15 mg.), $[\alpha]_D$ +8° (*c*, 0·7), giving a yellow colour with tetranitromethane–chloroform. Similar treatment of 7β-chlorocholestane (75 mg.) furnished a colourless oil (69 mg.), which crystallised and by crystallisation from acetone gave 7β-chlorocholestane (59 mg.), m. p. and mixed m. p. 65—67°; the material in the mother-liquor gave no yellow colour with tetranitromethane–chloroform.

7α-Chlorocholestane (75 mg.) was refluxed with quinoline (8 c.c.) for 3 hr.; most of the quinoline was removed under reduced pressure, and the dark brown oil worked up in the usual manner. The product was dissolved in pentane and filtered through a column of neutralised aluminium oxide prepared in pentane. Elution with pentane (200 c.c.) gave a colourless oil (70 mg.), which crystallised on trituration with acetone. Recrystallisation from acetone–ether yielded plates (54 mg.), m. p. 67—69°, giving a negative Beilstein test and a yellow colour with tetranitromethane–chloroform; a second recrystallisation gave plates, m. p. 69—71°, $[\alpha]_D$ −13° (*c*, 1·72), consisting of an inseparable mixture of cholest-6-ene (25%) and -7-ene (75%). Similar treatment of 7β-chlorocholestane (80 mg.) gave a colourless oil (75 mg.), which crystallised and on recrystallisation from acetone yielded glistening plates (58 mg.), m. p. 65—70°, giving a negative Beilstein test and a yellow colour with tetranitromethane. A further recrystallisation from the same solvent furnished plates, m. p. 70—72°, $[\alpha]_D$ −7° (*c*, 2·17), consisting of an inseparable mixture of cholest-6-ene (20%) and -7-ene (80%).

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