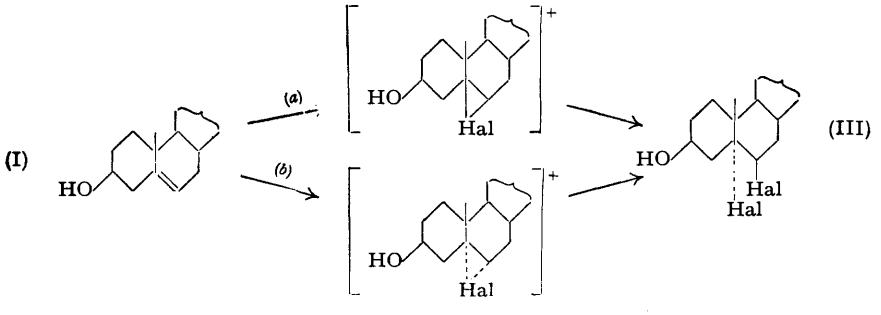
579. *The Stereochemistry of Steroids. Part V.* The Stereochemical Course of the Addition of Halogens to Cholesterol.*

By D. H. R. Barton, E. Miller, and H. T. Young.

On treatment with thionyl chloride or phosphorus pentachloride 5α-chloro-6β-hydroxycholestan-3β-yl benzoate affords cholesteryl benzoate dichloride. Similarly the corresponding 5α-bromo-compound gives 5α-bromo-6β-chlorocholestan-3β-yl benzoate. The significance of these findings is discussed (*a*) in confirming the configurations previously assigned to the cholesterol dihalides and (*b*) in demonstrating the kinetically controlled non-Markownikoff opening of the α-halonium ions postulated as intermediates in the addition of halogens to cholesterol.

The addition of molecular chlorine or bromine to cholesterol (I) affords the corresponding dichloride or dibromide (II; Hal = Cl or Br respectively). These compounds are well-characterised derivatives which have been known for many years. In Parts I and II of this series (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, 1066) it was proved that the configuration at $C_{(6)}$ was β in both cases. Accepting the well-established rule of *trans*-addition of ionic-type reagents we concluded that, of the two formal possibilities (III) and (IV), (III) correctly represented the configurations at both $C_{(5)}$ and $C_{(6)}$. Various elimination reactions provided strong support for our views. However, in a paper which appeared simultaneously with ours, Rivett and Wallis (*J. Org. Chem.*, 1950, **15**, 35) recorded the opinion that these dihalides should be represented by (IV). Their argument for the assignment of the β-configuration at $C_{(5)}$ is mechanistically weak as we have already commented (Barton and Miller, *loc. cit.*). Nevertheless we felt it desirable to obtain additional and more direct evidence on the configurations at $C_{(5)}$ in order to place our conclusions beyond doubt. As will be clear from the sequel other interesting theoretical questions were also answered by our experiments.

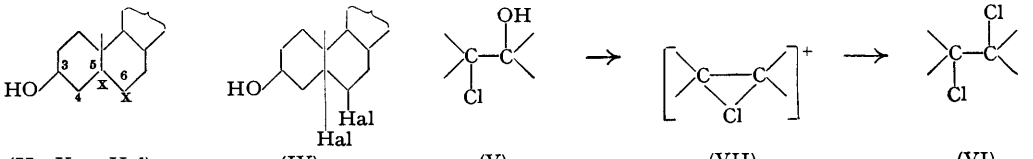
The elegant investigations by Winstein and his colleagues (series of papers in the *J. Amer. Chem. Soc.*, on " The Role of Neighbouring Groups in Replacement Reactions ") on the stereochemical course of (*inter al.*) the replacement reactions of bromohydrins, and by Lucas and Gould (*ibid.*, 1941, **63**, 2541) on the corresponding reactions of chlorohydrins, can be applied to the present problems.



Lucas and Gould demonstrated that when a chlorohydrin (V) is treated with thionyl chloride or with phosphorus pentachloride the corresponding dichloride (VI) is formed, *via* the chloronium

* Part IV, *J.*, 1951, 1048.

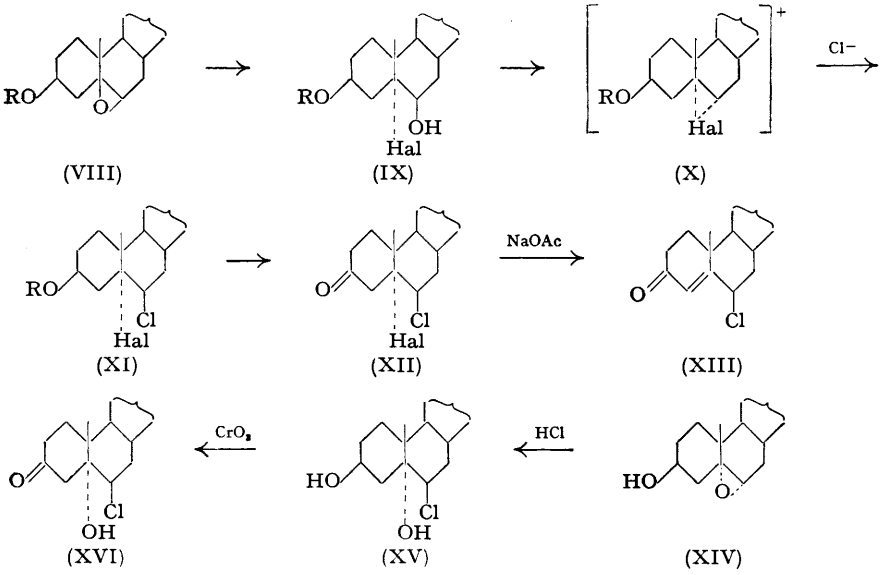
ion (VII), with complete retention * of configuration as a result of successive inversions: V → VII → VI. This important finding was applied in the cholesterol series in the following way. Cholesteryl benzoate β-oxide (VIII; R = Bz), when treated with hydrogen chloride (Spring and Swain, *J.*, 1939, 1356), gave 5α-chloro-6β-hydroxycholestan-3β-yl benzoate (IX;



(II; X = Hal) (IV) (V) (VII) (VI)

R = Bz, Hal = Cl). With both thionyl chloride and phosphorus pentachloride the latter furnished, *via* the chloronium ion (X; R = Bz, Hal = Cl), a dichloride (XI; R = Bz, Hal = Cl). This dichloride, obtained in both cases in good yield, was identified as cholesteryl benzoate dichloride. The α-configuration at $C_{(5)}$ in the latter is thus confirmed.

In principle there are two possible stereochemical routes for the formation of the cholesterol dihalides. These involve either (*a*) Markownikoff addition or (*b*) non-Markownikoff addition of Hal^- to the intermediate halonium ion. Previously (*loc. cit.*, p. 1066) we had assumed, principally from analogy with the addition reactions of iodine chloride (see Dewar, "The Electronic Theory of Organic Chemistry," Oxford Univ. Press, p. 143), that (*a*) would be the preferred path for the reaction. However in a recent review of the stereochemistry of steroids



Fieser (*Experientia*, 1950, **6**, 312) suggested that the cholesterol dihalides were formed by route (*b*). Clearly the reactions reported immediately above confirm Fieser's views in so far as the formation of cholesterol dichloride is concerned. It was of interest, therefore, to determine whether the kinetically controlled addition of bromine to cholesterol followed a route through the 5 : 6α-bromonium ion.

Treatment of cholesteryl benzoate β-oxide with aqueous hydrobromic acid gave 5α-bromo-6β-hydroxycholestan-3β-yl benzoate (IX; R = Bz, Hal = Br) which, on reaction with both thionyl chloride and phosphorus pentachloride, gave the same cholesteryl benzoate chlorobromide. The latter was shown to be 5α-bromo-6β-chlorocholestan-3β-yl benzoate (XI;

* Lucas and Gould, and also Winstein and his colleagues, worked with symmetrical olefins. Therefore, in the case of unsymmetrically substituted cyclic olefins such as cholesterol, it can only be concluded that, if one employs a *trans*-chloro- or -bromo-hydrin, the dihalide produced will likewise be *trans*. The formation of either the 5α : 6β- or of the 5β : 6α-dihalide from the 5α-halogen-6β-hydroxyhydrin would be in agreement with the previous findings.

R = Bz, Hal = Br) in the following way. Reaction of cholesterol β-oxide (VIII; R = H) with aqueous hydrobromic acid afforded 5α-bromo-6β-hydroxycholestan-3β-ol (IX; R = H, Hal = Br) which with thionyl chloride gave 5α-bromo-6β-chlorocholestan-3β-yl chlorosulphinate (XI; R = Cl·SO·, Hal = Br). The last was not isolated but was decomposed by water to furnish 5α-bromo-6β-chlorocholestan-3β-ol (XI; R = H, Hal = Br). On benzoylation of this alcohol the 5α-bromo-6β-chloro-benzoate mentioned above was obtained, whilst by oxidation by chromic acid to (XII; Hal = Br) followed by dehydrobromination with sodium acetate 6β-chlorocholest-4-en-3-one (XIII) resulted. This chloro-ketone was previously obtained (Barton and Miller, *loc. cit.*; Rivett and Wallis, *loc. cit.*) (*a*) from cholesterol α-oxide (XIV) *via* the chlorohydrin (XV) and the ketone (XVI) followed by dehydration, a route which establishes the configuration at $C_{(6)}$, and (*b*) from cholesterol dichloride (XI; R = H, Hal = Cl) through the ketone (XII; Hal = Cl).

These experiments confirm Fieser's views of the stereochemical course of the formation of cholesterol dibromide, showing that the bromonium ions (X; R = Bz, Hal = Br) and (X; R = H, Hal = Br) are, from the Markownikoff point of view, opened abnormally. It would appear that the opening of the 5 : 6α-bromonium ion parallels sterically the opening of the 5 : 6-α-oxide ring.

In Part II of this series (Barton and Miller, *loc. cit.*) it was shown that ordinary cholesteryl benzoate dibromide with the 5α : 6β-configuration rearranged when kept in chloroform solution, to give the thermodynamically more stable 5β : 6α-dibromide. This rearrangement may complicate study of the reactions of 5α-bromo-6β-hydroxy-compounds. Thus when 5α-bromo-6β-hydroxycholestan-3β-yl benzoate (IX; R = Bz, Hal = Br) was treated with phosphorus tribromide on the steam-bath, 5β : 6α-dibromocoprostan-3β-yl benzoate resulted. However at room temperature ordinary (5α : 6β-)cholesteryl benzoate dibromide was produced. Following the arguments presented by Winstein (*loc. cit.*) these reactions provide confirmatory proof of the α-configuration at $C_{(5)}$ in ordinary cholesterol dibromide. It was of interest to note that 5α-bromo-6β-chlorocholestan-3β-yl benzoate showed no tendency to undergo rearrangement in chloroform at room temperature.

On treatment of cholesterol benzoate β-oxide with aqueous hydriodic acid under carefully controlled conditions (see Experimental) the corresponding iodohydrin (IX; R = Bz, Hal = I) was obtained. More prolonged treatment gave only cholesteryl benzoate. Attempts to replace the hydroxyl group of the iodohydrin by chlorine were not successful owing to the ease of elimination (of iodine chloride).

Experimental.

M. p.s are uncorrected. Unless specified, rotations (approximated to the nearest degree) were determined for the sodium D line in chloroform solution at room temperature (15—25°), the specimens having been dried *in vacuo* at 20° below their m. p.s or at 110°, whichever was the lower temperature.

Savory and Moore's alumina for chromatography was used in all cases unless specified to the contrary.

Reactions of 5α-Chloro-6β-hydroxycholestan-3β-yl Benzoate.—(i) 5α-Chloro-6β-hydroxycholestan-3β-yl benzoate (100 mg.) in dry benzene (20 ml.) was treated with phosphorus pentachloride (100 mg.), and the mixture refluxed for 30 minutes. After addition of water the mixture was refluxed for a further 10 minutes and the benzene layer separated and evaporated *in vacuo*. The residual gum was chromatographed (Birlec alumina Grade H) to give, on elution with benzene, cholesteryl benzoate dichloride (70 mg.) which, recrystallised from ethyl acetate–methanol, had $[\alpha]_D$ −20° (*c*, 2·00), m. p. 129—130°, not depressed on admixture with authentic material, m. p. 130—131°, $[\alpha]_D$ −20° (*c*, 2·28).

(ii) 5α-Chloro-6β-hydroxycholestan-3β-yl benzoate (50 mg.) was treated with pure thionyl chloride (0·5 ml.) and kept at room temperature for 48 hours. The excess of thionyl chloride was removed *in vacuo* and the residue chromatographed over alumina. Elution with 40% benzene–light petroleum (b. p. 40—60°) afforded cholesteryl benzoate dichloride (60%) which, recrystallised from ethyl acetate–methanol, had $[\alpha]_D$ −25° (*c*, 2·48), m. p. 130—131°, undepressed on admixture with authentic material (see above).

(iii) 5α-Chloro-6β-hydroxycholestan-3β-yl benzoate (100 mg.) was treated with dry pyridine (2 ml.) and pure thionyl chloride (1 ml.) according to the experimental procedure of Lucas and Gould (*loc. cit.*). After working up, chromatography (eluant, 50% benzene–light petroleum (b.p. 40—60°) afforded cholesteryl benzoate dichloride (15%), which, recrystallised from ethyl acetate–methanol, had m. p. 125—127°, not depressed on admixture with authentic material.

5α-Bromo-6β-hydroxycholestan-3β-yl Benzoate.—Cholesteryl benzoate β-oxide (400 mg.) in chloroform (25 ml.) was shaken with 48% aqueous hydrobromic acid (10 ml.) for 10 minutes. After the chloroform layer had been washed with dilute sodium sulphite solution and then with water, evaporation *in vacuo* afforded *5α-bromo-6β-hydroxycholestan-3β-yl benzoate*; recrystallised from ethyl acetate–methanol, this had m. p. 173—174°, $[\alpha]_D$ −22° (*c*, 3·28) (Found: Br, 14·9. $C_{34}H_{51}O_3Br$ requires Br, 13·6%).

(*a*) Treatment of this bromohydrin (400 mg.) with pure thionyl chloride (5 ml.) overnight, followed by removal of the excess of thionyl chloride *in vacuo* and chromatography over alumina (eluant, 50% benzene–light petroleum (b.p. 40—60°) afforded *5α-bromo-6β-chlorocholestan-3β-yl benzoate* (90%) which, recrystallised from ethyl acetate–methanol, had m. p. 124—125° (decomp.), $[\alpha]_D$ −35° (*c*, 1·79) (Found: Cl + Br, 19·45. $C_{34}H_{50}O_2ClBr$ requires Cl + Br, 19·45%). The rotation was unchanged during 8 days at room temperature.

(*b*) Treatment of the bromohydrin (100 mg.) in dry benzene (10 ml.) with phosphorus pentachloride (100 mg.) and refluxing for 15 minutes afforded, after working up as in experiment (i) above, the foregoing chloro-bromide (60%), m. p. 124—125°, undepressed in m. p. on admixture.

(*c*) Treatment of the bromohydrin (100 mg.) with phosphorus tribromide (0·5 ml.) at room temperature overnight afforded, after purification by chromatography (eluant, 50% benzene–light petroleum (b.p. 40—60°), cholesteryl benzoate dibromide (15%), m. p. 132—134° (decomp.) (from ethyl acetate–methanol) not depressed on admixture with authentic material, m. p. 135° (decomp.). This procedure, but with heating on the steam for 2 hours instead of storage at room temperature, gave the stereoisomeric 5β : 6α-dibromocoprostan-3β-yl benzoate, m. p. 163—164° (decomp.), undepressed on admixture with authentic material of the same m. p.

5α-Bromo-6β-hydroxycholestan-3β-ol.—Cholesterol β-oxide (300 mg.) was shaken with chloroform–48% aqueous hydrobromic acid (20 ml. each). There was a copious precipitate of the bromohydrin in the chloroform layer. Working up as in the similar preparation given above furnished an almost quantitative yield of *5α-bromo-6β-hydroxycholestan-3β-ol* which, recrystallised from methanol–light petroleum (b. p. 40—60°), had m. p. about 128° (decomp.), $[\alpha]_D$ −38° (*c*, 0·98) (Found: Br, 16·4. $C_{27}H_{47}O_2Br$ requires Br, 16·55%).

Treatment of this bromohydrin (500 mg.) with pure thionyl chloride (5 ml.) at room temperature for 2 days, followed by removal of the excess of thionyl chloride *in vacuo*, gave a gummy residue (presumably of the chlorosulphinate). This was digested with aqueous methanol. The insoluble matter was recrystallised from methyl alcohol and the first two crops of resinous material rejected. Further concentration gave a third crop, m. p. 139—142° (decomp.). This was chromatographed over alumina. Elution with benzene gave a small amount of resinous material, but elution with 5% methanol–ether afforded crystalline *5α-bromo-6β-chlorocholestan-3β-ol* (120 mg.), m. p. 146—147° (decomp.) (bath preheated to 60°) (from methanol), $[\alpha]_D$ −47° (*c*, 1·91) (Found: Cl + Br, 23·2. $C_{27}H_{46}OClBr$ requires Cl + Br, 23·0%). When this chlorobromide (30 mg.) reacted with benzoyl chloride (0·5 ml.) in dry pyridine (5 ml.) at room temperature for 1 hour it gave 5α-bromo-6β-chlorocholestan-3β-yl benzoate which, recrystallised from ethyl acetate–methanol, had m. p. 125—126° undepressed on admixture with the benzoate of m. p. 124—125°, prepared as described above.

5α-Bromo-6β-chlorocholestan-3β-ol (200 mg.) in "AnalaR" acetic acid (25 ml.) was oxidised by chromium trioxide (60 mg.) in water (2 drops) at 40°, the solution being heated for 1 hour. Extraction with ether and working up in the usual way afforded a crystalline residue, presumably 5α-bromo-6β-chlorocholestan-3-one. The latter was refluxed with anhydrous sodium acetate (220 mg.) in ethanol (10 ml.) for 30 minutes. Addition of water gave crude 6β-chlorocholest-4-en-3-one (120 mg.). After filtration through alumina this was recrystallised slowly from ethyl acetate to give 6β-chlorocholest-4-en-3-one, m. p. 129° (Found: Cl, 8·55. Calc. for $C_{27}H_{43}OCl$: Cl, 8·45%), undepressed on admixture with authentic material, m. p. 129—130° (Barton and Miller, *loc. cit.*) but depressed by 30° on admixture with authentic 6α-chlorocholest-4-en-3-one.

6β-Hydroxy-5α-iodocholestan-3β-yl Benzoate.—Cholesterol β-oxide (500 mg.) in chloroform (50 ml.) was cooled to −20° and mixed slowly with 55% aqueous hydriodic acid (25 ml.), the temperature being kept at −20°. The two-phase system was stirred at this temperature for 2 hours and then poured into excess of aqueous sodium hydrogen carbonate. After being washed with sodium sulphite solution and then with water the chloroform layer was evaporated *in vacuo*, to furnish in almost quantitative yield *6β-hydroxy-5α-iodocholestan-3β-yl benzoate*; recrystallised cautiously from ethyl acetate–methanol, this had m. p. about 105° (vigorous decomp.) (Found: I, 19·85. $C_{34}H_{51}O_3I$ requires, I, 20·0%).

Shaking 100-mg. portions of cholesteryl benzoate β-oxide in chloroform (20 ml.) with concentrated aqueous hydriodic acid at room temperature for 5—15 minutes and working up as above gave cholesteryl benzoate, m. p. 148—149°, undepressed on admixture with an authentic specimen. The identity was confirmed by hydrolysis to cholesterol.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and the Chemical Society for financial assistance.

DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY,
CAMBRIDGE, 38, MASS., U.S.A.

BIRKBECK COLLEGE, LONDON, W.C.1.

[*Received, June 18th*, 1951.