789. *Steroids and Related Compounds. Part XV.* The Chlorination of Cholestan-3-one.*

By Bernard Ellis and Vladimir Petrow.

The preparation of some chlorinated derivatives of cholestan-3-one is described.

Difficulty encountered in converting an *allo*pregnan-3-one derivative into the corresponding Δ^4-unsaturated compound by the method of Rosenkranz, Mancera, Gatica, and Djerassi (*J. Amer. Chem. Soc.*, 1950, **72**, 4077) led us to study the chlorination of the model compound cholestan-3-one and the dehydrochlorination of the products. [Berreboom, Djerassi, Ginsburg, and Fieser independently report the chlorination and dehydrochlorination of cholestanone in a paper (*ibid.*, 1953, **75**, 3500) which became available to us after submission of this manuscript.]

Treatment of cholestan-3-one (I; R = R′ = R″ = H) with one equivalent of chlorine in acetic acid gave 2-chlorocholestan-3-one (I; R = Cl, R′ = R″ = H), the constitution of which was established by treatment with 2 : 4-dinitrophenylhydrazine in acetic acid, cholest-1-en-3-one 2 : 4-dinitrophenylhydrazone being obtained (see Djerassi, *ibid.*, 1949, **71**, 1003). Treatment of 2-chlorocholestan-3-one with zinc dust and acetic anhydride led to the formation of 3-acetoxycholest-2-ene (II) (Dauben, Micheli, and Eastham, *ibid.*, 1952, **74**, 3852), which passed smoothly into cholest-1-en-3-one (III; R = H) on reaction with *N*-bromosuccinimide (cf. Djerassi and Scholz, *J. Org. Chem.*, 1949, **14**, 660). In marked contrast to the behaviour of its 2-bromo-analogue, 2-chlorocholestan-3-one largely failed to react with boiling collidine and with sodium iodide in acetone and, furthermore, was recovered unchanged after treatment with chromous chloride.

Reaction of cholestan-3-one in acetic acid with two equivalents of chlorine resulted in

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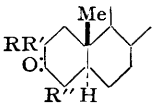
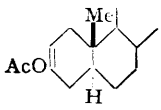
rapid separation of 2-chlorocholestan-3-one. The mother-liquors, however, contained small quantities of the desired dichloro-derivative, which was obtained in better yield by monochlorination of (I; R = Cl, R′ = R″ = H) in chloroform–acetic acid. The constitution of 2 : 2-dichlorocholestan-3-one (I; R = R′ = Cl, R″ = H) is assigned to



(I)



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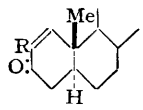

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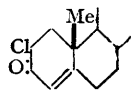

(IV)

this compound on the basis of (i) its high dextrorotation, in which respect it resembles 2 : 2-dibromo- and differs from 2 : 4-dibromo-3-oxo-steroids, and (ii) its behaviour on treatment with boiling collidine which gave a chloro-substituted cholesten-3-one differing from authentic 2-chlorocholest-4-en-3-one (IV) (see below) and is hence formulated as the isomeric 2-chlorocholest-1-en-3-one (III; R = Cl). In agreement therewith the ultraviolet absorption spectrum of the compound shows a maximum at 246·5 mμ (in *iso*propanol) indicative of an αβ-unsaturated ketone. It may be noted that Δ^1-3-oxo-steroids absorb at 230 mμ, whilst their 2-bromo-derivatives absorb at *ca.* 255 mμ (Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404; Nussbaum, Mancera, Daniels, Rosenkranz, and Djerassi, *ibid.*, 1951, **73**, 3263). The bathochromic effect of the halogen atom in (III; R = Cl or Br) consequently decreases in the order Cl < Br.

The compound (I; R = R′ = Cl, R″ = H) was unaffected by hydrogen bromide, differing in this respect from 2 : 2-dibromo-3-oxo-steroids which pass readily into 2 : 4-dibromo-ketones under similar experimental conditions. Reduction with chromous chloride furnished (I; R = Cl, R′ = R″ = H). Bromination in chloroform–acetic acid proceeded slowly over a period of days, to give a product regarded as 4-bromo-2 : 2-dichlorocholestan-3-one (I; R = R′ = Cl, R″ = Br).

Monochlorination of 2-bromocholestan-3-one (I; R = Br, R′ = R″ = H) led to the formation of a 2-bromo-2-chlorocholestan-3-one (I; R = Cl, R′ = Br, R″ = H) which showed no tendency to rearrange under the conditions employed for its preparation and passed into 2-chlorocholest-1-en-3-one (III; R = Cl) when heated with collidine. The same compound was also obtained by monobromination of 2-chlorocholestan-3-one. In this case, however, it was necessary to pour the reaction mixture into sodium acetate as soon as bromination was complete as the 2-bromo-2-chloro-ketone readily rearranged under the influence of hydrogen bromide to 4-bromo-2-chlorocholestan-3-one (I; R = Cl, R′ = H, R″ = Br). The last compound, on brief heating with collidine, passed into 2-chlorocholest-4-en-3-one (IV), which was reduced to cholest-4-en-3-one by chromous chloride.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube. Absorption spectra, measured in *iso*propyl alcohol, were kindly determined by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses Ltd. Solutions of chlorine in acetic acid were prepared immediately before use, the halogen concentration being determined volumetrically. "AnalaR" acetic acid and chloroform solvents were employed throughout.

2-Chlorocholestan-3-one.—Cholestanone (9·65 g.) in acetic acid (300 ml.) was treated at 30° with a solution of chlorine (1·87 g., equiv. to 1·05 mols.) in acetic acid (22 ml.). Decolorisation was complete within 3 min. and was immediately followed by the separation of crystals. After 1 hr. these (6·1 g.; m. p. 175—177°) were collected and the mother-liquor was concentrated to half-bulk under reduced pressure, giving a further quantity (2·2 g.; m. p. 165—167°) of crude product. Purified from chloroform–ethanol, *2-chlorocholestan-3-one* formed long silky needles, m. p. 185—186°, $[\alpha]_D^{23}$ +55·6° (*c*, 0·91) (Found: C, 77·0; H, 11·2; Cl, 8·5. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8; Cl, 8·4%). The compound was recovered unchanged after being heated under reflux with collidine for 2 hr., with sodium iodide in acetone for 6 hr., and after treatment with chromous chloride (prepared by the method of Rosenkranz *et al.*, *loc. cit.*).

Cholest-1-en-3-one 2 : 4-Dinitrophenylhydrazone.—The foregoing compound (420 mg.) in boiling acetic acid (20 ml.) was treated with 2 : 4-dinitrophenylhydrazine (218 mg.), the derivative named separating after 1 min. Crystallised from chloroform–ethanol, it formed

orange needles, m. p. 235° (Found : C, 69·7; H, 8·6; N, 10·2. Calc. for $C_{23}H_{48}O_4N_4$: C, 70·2; H, 8·6; N, 9·9%), not depressed in admixture with an authentic specimen (Djerassi, *loc. cit.*, gives m. p. 218—220°).

3-*Acetoxycholest*-2-*ene*.—Zinc dust (5·0 g.) was added in one portion to a boiling solution of 2-chlorocholestan-3-one (800 mg.) in acetic anhydride (10 ml.). After the initial vigorous reaction had subsided, the mixture was refluxed for 5 min. and the liquors were decanted into water. The crystalline material (200 mg.), which separated when the gummy product was treated with hot ethanol, was purified from chloroform–methanol, giving 3-acetoxycholest-2-ene, m. p. 90°, clearing at 96°, the melt showing a fine play of colour. No depression in m. p. was obtained in admixture with an authentic specimen prepared from cholestanone by the method of Dauben *et al.* (*loc. cit.*).

Cholest-1-*en*-3-*one*.—*N*-Bromosuccinimide (1·0 g.) was added to 3-acetoxycholest-2-ene (2·1 g.) in carbon tetrachloride (40 ml.), and the mixture refluxed for 5 min. The brown gum obtained on removal of succinimide followed by evaporation of the solvent *in vacuo* was chromatographed on B.D.H. alumina (10 × 3·5 cm.) made up in light petroleum (b. p. 40—60°). Elution with the same solvent gave traces of unchanged enol acetate. Further elution with light petroleum–ether (1 : 1) furnished a solid (1 g.) which crystallised from aqueous ethanol in plates, m. p. 97—98°, not depressed in admixture with an authentic specimen of cholest-1-en-3-one. The identity of the product was confirmed by the preparation of the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235°.

2 : 2-*Dichlorocholestan*-3-*one*.—(i) Cholestanone (960 mg.) in acetic acid (40 ml.) was treated at 30° with a solution of chlorine (0·39 g., equiv. to 2·2 mols.) in acetic acid (4·4 ml.). After 3 min. feathery needles (230 mg.; m. p. 177—180°) of 2-chlorocholestan-3-one began to separate and they were collected 15 min. later. Thereafter the mother-liquors deposited a dense, microcrystalline solid (120 mg.), m. p. 144—146°, which was recrystallised from ethanol, giving 2 : 2-*dichlorocholestan*-3-*one*, hard needles, m. p. 151—152°, $[\alpha]_D^{22}$ +115° (*c*, 1·1) (Found : C, 71·7; H, 9·9; Cl, 15·0. $C_{27}H_{44}OCl_2$ requires C, 71·2; H, 9·7; Cl, 15·6%).

(ii) 2-Chlorocholestan-3-one (4·2 g.) in a mixture of chloroform (60 ml.) and acetic acid (60 ml.) was treated at 20° with a solution of chlorine (0·78 g.; equiv. to 1·1 mols.) in acetic acid (8 ml.). Absorption of chlorine proceeded slowly, the mixture becoming colourless after 3 hr. The chloroform layer obtained on addition of water was washed till neutral and dried, and the solvent removed *in vacuo*. The solids (3·4 g.; m. p. 138—141°) obtained on trituration of the residue with cold acetic acid (15 ml.) crystallised from acetone, giving hard needles (2·0 g.) of 2 : 2-dichlorocholestan-3-one, m. p. 150—152°, not depressed in admixture with a specimen prepared by method (i).

The optical rotation of the compound in chloroform–acetic acid containing hydrogen bromide remained substantially unchanged during 22 hr.

When the dichloro-ketone (100 mg.) in acetone (30 ml.) was treated under carbon dioxide with chromous chloride solution (5 ml.; prep. by the method of Rosenkranz *et al.*, *loc. cit.*), there was obtained 2-chlorocholestan-3-one, identified by m. p. and mixed m. p.

2-*Chlorocholest*-1-*en*-3-*one*.—2 : 2-Dichlorocholestan-3-one (1·5 g.) was heated under reflux with collidine (8 ml.) for 10 min. The product, isolated with ether, was chromatographed on B.D.H. alumina (9 × 3 cm.) made up in light petroleum (b. p. 40—60°). Elution with light petroleum–ether (4 : 1) gave crystalline fractions which were combined and purified from methanol. 2-*Chlorocholest*-1-*en*-3-*one* (300 mg.) separated in needles, m. p. 109—110°, $[\alpha]_D^{23}$ +45° (*c*, 1·0) (Found : C, 77·0; H, 10·4; Cl, 8·7. $C_{27}H_{43}OCl$ requires C, 77·4; H, 10·4; Cl, 8·4%). Ultra-violet absorption maximum : $E_{1\,cm.}^{1\%}$ (246·5 mμ) = 242.

4-*Bromo*-2 : 2-*dichlorocholestan*-3-*one*.—2 : 2-Dichlorocholestan-3-one (1·84 g.) in a mixture of chloroform (40 ml.) and acetic acid (40 ml.) was treated with bromine (0·7 g., equiv. to 1·1 mols.) in acetic acid (10 ml.), absorption being complete after 3 days. The product was crystallised from ethanol and then from acetone–methanol, giving small hard prisms (950 mg.) of 4-*bromo*-2 : 2-*dichlorocholestan*-3-*one*, m. p. 109—110°, $[\alpha]_D^{21}$ +61·5° (*c*, 1·86) (Found : C, 60·9; H, 8·3. $C_{27}H_{43}OCl_2Br$ requires C, 60·7; H, 8·1%).

2-*Bromo*-2-*chlorocholestan*-3-*one*.—(i) 2-Bromocholestan-3-one (2·85 g.) in chloroform (30 ml.) and acetic acid (30 ml.) was treated with chlorine (480 mg., equiv. to 1·1 mols.) in acetic acid (6 ml.), absorption being complete in 1½ hr. The optical activity of the mixture did not change appreciably during a further 2½ hr. The gummy product was triturated with methanol (30 ml.) and the solids obtained were purified from ethyl acetate–methanol. 2-*Bromo*-2-*chlorocholestan*-3-*one* (1·2 g.) separated in hard needles, m. p. 147—148°, $[\alpha]_D^{21}$ +112·5° (*c*, 1·45) (Found : C, 64·7; H, 8·8. $C_{27}H_{44}OClBr$ requires C, 64·9; H, 8·9%).

(ii) 2-Chlorocholestan-3-one (4·2 g.) in chloroform (60 ml.) and acetic acid (60 ml.) was treated with bromine (1·76 g.; equiv. to 1·1 mols.) in acetic acid (10 ml.). Absorption was complete after 35 min., whereafter the mixture was poured into excess of aqueous sodium acetate and the product isolated in the usual way. Thrice crystallised from ethyl acetate, the bromochloro-ketone (2·0 g.) formed thick prisms, m. p. 145—147°, not depressed in admixture with a sample prepared by method (i) above.

The compound was converted into 2-chlorocholestan-3-one in warm acetone. When it (1 g.) was heated under reflux with collidine (5 ml.) for 3 min. and the product crystallised from methanol, there was obtained 2-chlorocholest-1-en-3-one (400 mg.), identified by m. p. and mixed m. p.

4-Bromo-2-chlorocholestan-3-one.—2-Chlorocholestan-3-one (3·1 g.) in chloroform (50 ml.) and acetic acid (50 ml.) was treated with bromine (1·25 g., equiv. to 1·05 mols.) in acetic acid (10 ml.), absorption being complete after 1 hr. Thereafter the optical activity decreased, reaching a constant value in 18 hr. The product was crystallised directly from aqueous acetone, giving *4-bromo-2-chlorocholestan-3-one* (2·2 g.), silvery plates, m. p. 199—200° (decomp.), $[\alpha]_D^{22}$ +3·5° (*c*, 2·24) (Found: C, 64·5; H, 8·8. $C_{27}H_{44}OClBr$ requires C, 64·9; H, 8·9%).

2-Chlorocholest-4-en-3-one.—The foregoing compound (2·6 g.) was refluxed with collidine (8 ml.) for 5 min. The *product* slowly crystallised from methanol in fine needles (900 mg.), 97—98°, $[\alpha]_D^{22}$ +87° (*c*, 0·55) (Found: C, 77·5; H, 10·6; Cl, 8·0. $C_{27}H_{43}OCl$ requires C, 77·4; H, 10·35; Cl, 8·5%). Ultra-violet absorption maximum: $E_{1\,cm.}^{1\%}$ (243 mμ) = 378.

When the foregoing compound (600 mg.) in acetone (50 ml.) was treated under carbon dioxide with chromous chloride solution (10 ml.) for 10 min. and the product isolated with ether, cholest-4-en-3-one (240 mg.) was obtained, having m. p. 79—80° (from aqueous methanol), not depressed in admixture with an authentic specimen.

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