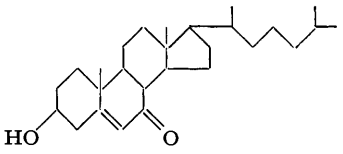
104. *Aminosteroids. Part II. Preparation of* 3 : 7-*Diketocholestene.*

By Jean Barnett, Brenda E. Ryman, and F. Smith.

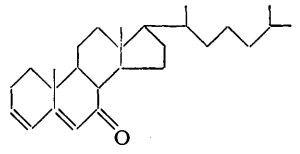
3 : 7-*Diketocholestene* has been prepared from 7-ketocholesterol. An improved method for the preparation of the latter is also described. The diketone appears to exist only in the enolic form.

The preparation of 3 : 7-*diketocholestene* was undertaken to complete a series of diketosteroids which were required as intermediates for the preparation of diaminosteroids.

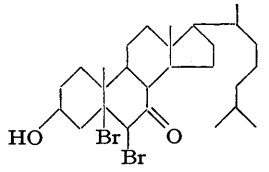
The starting material, 7-ketocholesterol (I), was prepared by Mauthner and Suida (*Monatsh.*, 1896, **17**, 579) and by Windaus (*Ber.*, 1915, **48**, 854) by hydrolysis of the acetate with boiling alcoholic potash; however this method in our hands always yielded considerable amounts of 7-ketocholestadiene (II). We have therefore made use of milder conditions, *viz.*, very dilute aqueous-alcoholic potassium carbonate solution, shaking at room temperature until hydrolysis is complete. In this way a quantitative yield of 7-ketocholesterol was obtained.



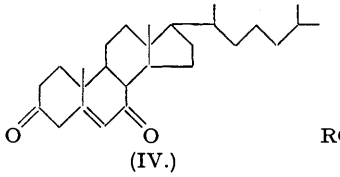
(I.)



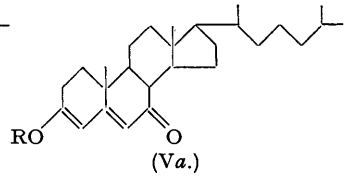
(II.)



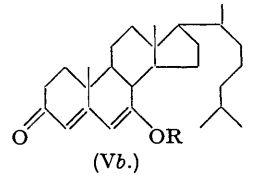
(III.)



(IV.)

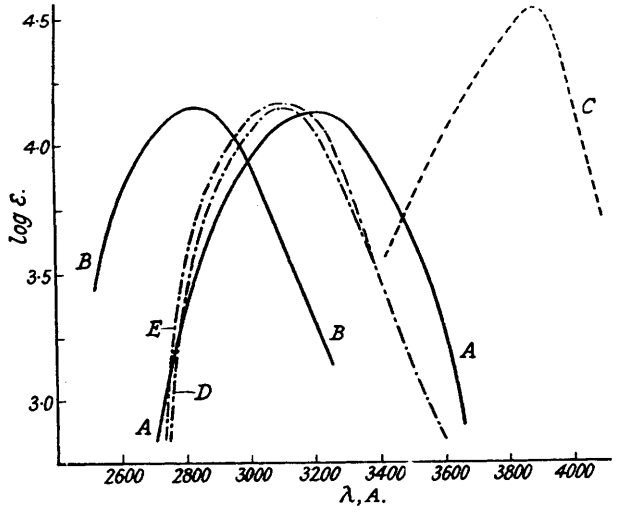


(V*a*.)



(V*b*.)

It was stated by Mauthner and Suida (*loc. cit.*) that 7-ketocholesterol did not absorb bromine. However, it was found that addition of two atoms of bromine to the ketone in carbon disulphide solution at room temperature



A. { *Enol of* 3 : 7-*diketocholestene in ethyl alcohol* (2·4 *mg.*-%).
{ *Enol acetate after making alkaline followed by reacidification* (3 *mg.*-%).
B. *Enol acetate in neutral* EtOH (3 *mg.*-%).
C. { *Enol of* 3 : 7-*diketocholestene in alkaline* EtOH (*ca.* 5 × 10^{-3} N; 0·48 *mg.*-%).
{ *Enol acetate in alkaline solution* (0·76 *mg.*-%).
D. *Methyl ether of enol in neutral or alkaline* EtOH (3 *mg.*-%).
E. *Ethyl ether of enol in neutral or alkaline* EtOH (3 *mg.*-%).

readily yielded the *dibromide* (III), m. p. 124—125°. The latter on oxidation with chromic acid and subsequent debromination yielded 3 : 7-diketocholestene, m. p. 185—186°, which dissolved readily in sodium hydroxide solution and on re-acidification yielded the same product. No evidence was obtained that it existed in two forms; the stable form would appear, from all available evidence, to be the enolic form. It yielded a mono-acetate and a monomethyl ether readily. The absorption curves of these substances are shown in the figure. That of the enol itself [(A), fig.] shows a maximum at λ 3220 A. and is practically identical with that of its *methyl ether* [(D), fig.], thus affording evidence of its enolic structure. If it were a diketone (IV) rather than an enol (V*a* or V*b*), it would be expected to show absorption at about λ 2400 A. Addition of alkali to the enol caused a displacement of the band to λ 3900 A. The enol acetate [(B), fig.] shows a maximum absorption at λ 2840 A.; in alkali the band shifts to λ 3900 A. but on acidification the maximum appears at λ 3200 A. (identical with that of the enol), thus indicating extreme lability of the enolic acetyl group. The enol may have either of the structures shown in formulæ (V*a*) and (V*b*) (R = H). There is no evidence at present which favours one rather than the other. A *dioxime* was obtained without any difficulty.

Experimental.

7-Ketocholesterol (I.).—7-Ketocholesteryl acetate (50 g.) was suspended in methyl alcohol (5 l.) and a solution of potassium carbonate (16 g.) in water (300 c.c.) added. The mixture was shaken mechanically at 20° for 20 hours. The clear yellow liquid was diluted with water, concentrated under reduced pressure at 20° to small bulk, and extracted four times with ether. After having been washed three times with water the extracts were dried (Na_2SO_4) and the solvent removed by distillation. The residue was crystallised from hot methyl alcohol by addition of water until almost cloudy, m. p. (after drying in a vacuum at 50°) 159—161° (28 g.). A second crop of 14 g., m. p. 160—161°, was obtained by concentration of the mother liquors. Recrystallisation from ether–light petroleum did not change the m. p.

7-Ketocholestadiene (II).—7-Ketocholesteryl acetate (50 g.) dissolved in boiling methyl alcohol (300 c.c.) was treated with 5% methyl alcoholic sodium hydroxide (250 c.c.). The dark brown solution was refluxed for 30 minutes. After dilution with water, the cooled solution was neutralised with carbon dioxide and evaporated under reduced pressure to half bulk. After extraction with ether, the product was recrystallised from methyl alcohol, and then had m. p. 110—112°. It gave no depression with 7-ketocholestadiene, m. p. 112°. The absorption curve of this compound is shown in the figure.

5 : 6-Dibromo-7-ketocholesterol (III).—7-Ketocholesterol (42 g.) was dissolved in warm freshly redistilled carbon disulphide (300 c.c.). The solution was cooled to 20°, and a solution of bromine (9 c.c.) in carbon disulphide (20 c.c.) was added. The solution became warm after standing for a few minutes and was kept cool with running water. After 10 minutes at 20°, it was evaporated under reduced pressure in a bath at 30° to a thick syrup. This was taken up in ether (100 c.c.) and ethyl alcohol (200 c.c.) added. *5 : 6-Dibromo-7-ketocholesterol* crystallised at once as flocks of needles (21 g.), m. p. 123—124° (decomp.). Careful concentration of the mother liquor yielded a further crop (4·5 g.) but the filtrate decomposed with evolution of bromine when evaporated further under reduced pressure at 40°. Recrystallisation of the first crop from ether–absolute alcohol gave glistening needles, m. p. 124—125° (decomp.), $[\alpha]_D^{17°}$ — 5·6° (*c*, 0·88 in chloroform) (Found: C, 57·65, 57·73; H, 8·04, 8·27. $C_{27}H_{44}O_2Br_2$ requires C, 57·84; H, 7·91%). Dibromo-7-ketocholesterol is soluble in ether and carbon disulphide, but practically insoluble in alcohol and light petroleum.

3 : 7-Diketocholestene, Enolic Form [(V*a*) or (V*b*), R = H].—5 : 6-Dibromo-7-ketocholesterol (22 g.), dissolved in benzene (220 c.c.), was shaken for 5 hours with a solution of chromic oxide (14·3 g.) in water (66 c.c.) and glacial acetic acid (143 c.c., distilled over chromic oxide). The benzene layer was separated, washed once with water, and then treated with glacial acetic acid (110 ml.) and zinc wool (7·7 g.). Most of the benzene was distilled off (water-bath); the residue was refluxed for one hour (bath temperature 115°). The cooled liquid was filtered through glass wool and the filtrate extracted three times with ether. The ethereal extracts were washed twice with water, then three times with dilute sodium hydroxide solution. The combined alkaline extracts were acidified with dilute sulphuric acid and the yellowish precipitate filtered off. This solid was extracted with ether (2 l.). After the ethereal solution had been dried and the solvent evaporated, the residue was crystallised from ether–light petroleum, yielding glistening rectangular leaflets, m. p. 185—186° (5·8 g.). From the mother liquor a further amount (4·8 g.) was obtained, m. p. 184—185°. The m. p. was unchanged by a further recrystallisation either from methyl alcohol or from ether–light petroleum, $[\alpha]_D^{16.5°}$ — 53° (*c*, 1·0 in chloroform) (Found: C, 81·37, 81·56; H, 10·84, 10·95. $C_{27}H_{42}O_2$ requires C, 81·34; H, 10·63%). The absorption curve for this *substance* is shown in the figure. The diketone is soluble in ethyl and methyl alcohols, acetone, and benzene, difficultly soluble in ether, and insoluble in light petroleum. The crystals darken, after exposure to light for several weeks, to a golden brown colour.

Methyl Ether [(V*a*) or (V*b*), R = Me].—3 : 7-Diketocholestene (enol form, 200 mg.) was refluxed for one hour with methyl alcohol (20 c.c.) and concentrated sulphuric acid (2 c.c.). The cooled solution, after dilution with ether, was extracted three times with water, then once with dilute sodium hydroxide solution, to remove any traces of unchanged enol. After washing once more with water, the ethereal solution was dried (Na_2SO_4) and evaporated to dryness. The residue (150 mg.) was recrystallised twice from methyl alcohol yielding the *methyl ether*, m. p. 136—137° (50 mg.) (Found: C, 81·56; H, 11·02. $C_{28}H_{44}O_2$ requires C, 81·55; H, 10·76%).

Enol Acetate [(V*a*) or (V*b*), R = COMe].—3 : 7-Diketocholestene (enol form, 50 mg.) was kept with absolute pyridine (1 c.c.) and acetic anhydride (0·5 c.c.) at 15° for 15 hours. The red solution, after dilution with iced ether, was extracted twice with ether, and the extract was washed with ice-cold dilute hydrochloric acid and then with water. The dried ethereal extract was concentrated under reduced pressure and the residue crystallised from methyl alcohol, in which it was very soluble, at 0°. The enol acetate obtained had m. p. 106—108°. Its absorption curve is shown in the figure.

3 : 7-Diketocholestene Dioxime.—3 : 7-Diketocholestene (5 g.) was dissolved in hot ethyl alcohol (150 c.c.) and treated with a solution of hydroxylamine [prepared by dissolving hydroxylamine hydrochloride (4 g.) and fused sodium acetate (6 g.) in water (5 c.c.), adding alcohol (20 c.c.) and filtering of the precipitated sodium chloride]. This solution was refluxed for 5 hours. The crystals which came out on cooling were filtered off, washed with 80% aqueous alcohol, then with absolute alcohol, and finally with ether. Yield 3·0 g., m. p. 229—230° (decomp.). A further crop (1·2 g.), obtained by concentration of the mother liquor, had m. p. 229—230°. The *dioxime* was insoluble in ether and benzene, only very slightly soluble in boiling alcohol, and rather more soluble in boiling dioxan. Recrystallisation from either boiling ethyl alcohol or dioxan gave needles, m. p. 229—230° (decomp.) (Found: C, 75·68, 75·46; H, 10·23, 10·37. $C_{27}H_{44}O_2N_2$ requires C, 75·70; H, 10·36%).

A. E. Hills Laboratories,
The University, Edgbaston, Birmingham, 15.

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