125. *Modified Steroid Hormones. Part I. Some 4-Bromo-3-oxo-Δ⁴-derivatives.*

By D. N. Kirk, D. K. Patel, and V. Petrow.

Bromination of some 3-oxo-Δ⁴-steroids (I) in ethylene or propylene oxide gives the corresponding 4-bromo-3-oxo-Δ⁴-steroids (II). The yields are significantly increased by passing the total bromination products through alumina. These bromo-compounds are also obtained, but in lower yields, by bromination in the presence of collidine.

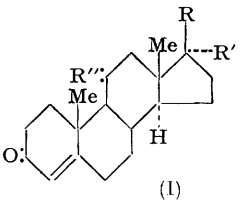
Bromination of 3-oxo-Δ⁴-steroids (I) with bromine in acetic acid–ether, or with *N*-bromosuccinimide in a suitable solvent, leads generally to allylic bromination with formation of the corresponding 6-bromo- and 2 : 6-dibromo-3-oxo-Δ⁴-steroids.[1] We now find that, by carrying out the bromination in the presence of a proton acceptor, allylic bromination is suppressed and 4-bromo-3-oxo-Δ⁴-steroids (II) are obtained.

Bromination of cholestenone (I*a*) in acetic acid–collidine led to a new monobromo-derivative which differed from authentic 2α-bromo-,[2] 6α-bromo-,[3] and 6β-bromo-cholest-4-en-3-one.[4] Its ultraviolet absorption spectrum showed a maximum at 261 mμ. The constitution of 4-bromocholest-4-en-3-one (II*a*) is consequently assigned to this compound as α-bromo-substitution into an αβ-unsaturated ketone (max. *ca.* 240 mμ) is known [5] to result in a bathochromic shift of *ca.* 23 mμ in the absorption maximum. In addition, reaction of the bromide (II*a*) with *o*-phenylenediamine in acetic acid leads to the quinoxaline derivative previously obtained from cholestane-3 : 4-dione.[6] Surprisingly, reaction of the bromide (II*a*) with lithium fluoride in dimethylformamide, with lithium chloride in collidine, or less effectively with collidine alone, leads to cholesta-4 : 6-dien-3-one. Extension of the bromination to testosterone propionate (I*b*) and to progesterone (I*c*) led to 4-bromotestosterone propionate (II*b*) and 4-bromoprogesterone (II*c*), respectively, severally characterised by their absorption maxima.

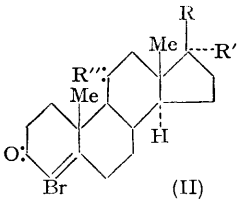
The yields of 4-bromo-steroids obtained as above ranged from 5% (II*b*) to 30% (II*c*). We therefore turned our attention to the use of proton-acceptors other than collidine in the hope of improving the yields, particularly of the testosterone derivative. By using ethylene or propylene oxide as proton acceptor, the yields of 4-bromo-3-oxo-Δ⁴-steroids (II) were substantially raised, particularly if the solutions of the total bromination products were percolated through short columns of alkaline aluminium oxide. In this way, the bromides (II*a*, *b*, and *c*) were obtained in yields exceeding 50%. The reaction was also

[1] See Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.
[2] Djerassi, *ibid.*, 1949, **71**, 1003; see Jones, Ramsay, Herling, and Dobriner, *ibid.*, 1952, **74**, 2828, for stereochemistry of 2 : 4-dibromocholestan-3-one.
[3] Barton and Miller, *ibid.*, 1950, **72**, 1066.
[4] Ruzicka, Bosshard, Fischer, and Wirz, *Helv. Chim. Acta*, 1936, **19**, 1147; see ref. 3 for stereochemistry of the bromine atom.
[5] Nussbaum, Mancera, Daniels, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3263.
[6] Butenandt, Schramm, Wolff, and Kudszus, *Ber.*, 1936, **69**, 2779; Inhoffen, *Ber.*, 1937, **70**, 1695.

extended to the preparation of 4-bromo-17α-hydroxy- (II*d*) and 4-bromo-11-oxo-progesterone (II*e*) from 17α-hydroxy- (I*d*) and 11-oxo-progesterone (I*e*), respectively. *Inter alia*, the need for the alumina treatment referred to above argues for the presence in the bromination products of some 4ξ : 5ξ-dibromide which may be expected to pass into the monobromides (II) under the influence of the basic reagent.[7]



(I)



(II)

(*a*) R = C_8H_{17}, R′ = H, R″ = H_2. (*d*) R = COMe, R′ = OH, R″ = H_2.
(*b*) R = O·COPr, R′ = H, R″ = H_2. (*e*) R = COMe, R′ = H, R″ = O.
(*c*) R = COMe, R′ = H, R″ = H_2.

Experimental

Ultraviolet absorption spectra were kindly determined by Mr. M. Davies, B.Sc., for EtOH solutions. Optical rotations were measured in $CHCl_3$ solution in a 1-dm. tube.

4-Bromocholest-4-en-3-one (II*a*).—(i) Cholestenone (3 g.) in anhydrous ether (30 ml.) and collidine (10 ml.) was treated with bromine in acetic acid (30 ml. of 1·05M; 4 mols.) in the dark at 20—25° for 48 hr. Collidine hydrobromide separated. The mixture was poured into water and extracted with ether which was then successively washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate solution, and water, and dried. After removal of ether the residue was crystallised from ethanol to give *4-bromocholest-4-en-3-one*, slightly coloured needles, m. p. 113°, $[\alpha]_D^{27}$ +110° (*c* 0·472), $\lambda_{max.}$ 261—262 mμ (log ε 4·08) (Found: C, 70·3; H, 9·4; Br, 16·8. $C_{27}H_{43}OBr$ requires C, 69·9; H, 9·4; Br, 17·2%). Removal of colour was achieved by percolating a solution of the material in benzene–light petroleum (1 : 1) through a column of alumina (B.D.H., chromatography grade; 15 g.). The use of excess of bromine was necessary, otherwise lower yields were obtained.

(ii) Cholestenone (5 g.) in ethylene oxide (40 ml.) at −30° was treated with bromine in acetic acid (13·5 ml. of 0·985M) and kept at −30° in the dark for 20 hours. The product, isolated with ether as above, was percolated in benzene–light petroleum through alumina (50 g.), and the product crystallised from ethanol. *4-Bromocholestenone* formed needles, m. p. 113—114°, $[\alpha]_D^{22}$ +110° (*c* 0·472), $\lambda_{max.}$ as above (Found: Br, 18·7%), not depressed on admixture with a sample prepared as under (i).

Chromatography, on alumina, of the oily residues left after removal of the product (II*a*) failed to furnish a crystalline product.

Reaction of the bromide with silver acetate in pyridine–ether under reflux gave an oil which failed to yield a solid product on chromatography or treatment with dinitrophenylhydrazine.

The quinoxaline derivative of cholestane-3 : 4-dione was formed as pale brown plates, m. p. 205—207°, $\lambda_{max.}$ 239 (log ε 4·48) and 321 mμ (log ε 4·00) (Found: N, 5·8. Calc. for $C_{33}H_{48}N_2$: N, 5·9%) [after crystallisation from methylene chloride–ethanol (1 : 3) and from ethyl acetate], by heating the bromide (500 mg.) with *o*-phenylenediamine (125 mg.) in acetic acid (5 ml.) under reflux for 2 hr., dilution with methanol (5 ml.), and chilling (lit.,[6] m. p. 207—208°).

Cholesta-4 : 6-dien-3-one.—(i) The ketone (I*a*) (500 mg.) and lithium fluoride (110 mg.) in *NN*-dimethylformamide (5 ml.) were heated under reflux for 24 hr. The product, isolated with ether, was percolated in benzene–light petroleum (b. p. 40—60°) (1 : 1) through alumina (10 g.). Crystallisation at 0° from methanol–pentane (10 : 1) gave cholesta-4 : 6-dien-3-one, pale yellow prisms, m. p. 78°, $\lambda_{max.}$ 284 mμ (log ε 4·36) (Found: C, 84·3; H, 11·2. Calc. for $C_{27}H_{42}O$: C, 84·7; H, 11·1%); the dinitrophenylhydrazone formed dark red needles, m. p. 232°.

(ii) Cholesta-4 : 6-dien-3-one, m. p. 78°, $\lambda_{max.}$ 284 mμ (log ε 4·36) was obtained by heating the ketone (I*a*) with lithium chloride–collidine under reflux for 2 hr. Heating with collidine alone gave impure cholesta-4 : 6-dien-3-one.

[7] Cf. Bremer, Congress Handbook, XIVth Intern. Congr. of Pure and Applied Chem., p. 162.

4-*Bromotestosterone Propionate* (II*b*).—(i) Testosterone propionate (1 g.) in ether (20 ml.) and collidine (2 ml.) was treated with bromine in acetic acid (3·0 ml.; 0·98M) at 20—25° for 72 hr. in the dark. Isolation with ether gave an intractable oil which was fractionated by chromatography on alumina (10 g.) in benzene–light petroleum, then crystallised from methanol. 4-*Bromotestosterone propionate* formed needles, m. p. 140—142°, $[\alpha]_D^{25}$ +118° (*c* 0·42), $\lambda_{max.}$ 261 mμ (log ε 4·09) (Found: C, 62·0; H, 7·6; Br, 19·3. $C_{22}H_{31}O_3Br$ requires C, 62·5; H, 7·4; Br, 18·9%).

(ii) Bromination of testosterone propionate (1 g.) in ethylene oxide, followed by percolation of the product in benzene–light petroleum through alumina (10 g.) and crystallisation from methanol, gave 4-bromotestosterone propionate, m. p. 140—142°, $[\alpha]_D^{27}$ +117° (*c* 0·655), $\lambda_{max.}$ 261 mμ (log ε 4·09) (Found: Br, 18·4%), not depressed in admixture with a sample prepared as under (i).

4-*Bromoprogesterone* (II*c*).—(i) Bromination of progesterone in the presence of collidine, followed by direct crystallisation of the product, furnished 4-*bromoprogesterone*, needles (from methanol), m. p. 192—193°, $[\alpha]_D^{25}$ +185° (*c* 0·8), $\lambda_{max.}$ 261 mμ (log ε 4·07) (Found: C, 63·5; H, 7·4; Br, 19·5. $C_{21}H_{29}O_2Br$ requires C, 64·1; H, 7·4; Br, 20·3%).

(ii) Bromination of progesterone (1 g.) in ethylene oxide, followed by percolation in benzene–light petroleum through alumina (10 g.), gave 4-*bromoprogesterone*, m. p. 193—193·5°, $[\alpha]_D^{25}$ +185° (*c* 0·80), $\lambda_{max.}$ 261 mμ (log ε 4·07) (Found: Br, 20·0%), not depressed in admixture with a sample prepared as under (i). Bromination in propylene oxide gave nearly identical results.

4-*Bromo*-17α-*hydroxyprogesterone* (II*d*), prepared by bromination of the ketone (I*d*) in ethylene oxide, formed a microcrystalline powder, m. p. 176°, $\lambda_{max.}$ 259 mμ (log ε 4·04) (Found: Br, 19·1. $C_{21}H_{29}O_3Br$ requires Br, 19·5%), after crystallisation from acetone–hexane (1 : 1).

4-*Bromo*-11-*oxoprogesterone* (II*e*) formed a microcrystalline powder, m. p. 146°, λ_{max} 258—259 mμ (log ε 4·00) (Found: C, 61·7; H, 6·8; Br, 20·0. $C_{21}H_{27}O_3Br$ requires C, 61·9; H, 6·7; Br, 19·6%), after crystallisation from acetone–hexane.

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CHEMICAL RESEARCH LABORATORIES,
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