184. *Studies in the Steroid Series. Part LXXII.* The Bromination of 11-Oxo-5β-steroids.*

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Bromination of 11-ketones (I) of the 5β-pregnane series gives 12α-bromo-compounds. From the $\Delta^{9(11)}$-enol acetates (II), however, by bromination in the presence of hydrogen bromide acceptors, 9α-bromo-ketones can be prepared; treatment with pyridine converts them into the desired Δ^{8}-11-ketones (V).

In connection with attempts to prepare 9-methylated steroids [1] suitable for conversion either into compounds related to the pentacyclic triterpenes or into analogues of steroid hormones, it was desired to obtain 7 : 8- or 8 : 9-ethylenic 11-ketones of the 5β- or 5α-pregnane (*allo*pregnane) series. Bromination of an 11-ketone belonging to the 5α-steroid series (*i.e.*, 3β-acetoxyergostan-11-one) results in the formation of the 9α-bromo-ketone in good yield,[2] the position of substitution being in accord with the tendency of 11-ketones of this series to enolise towards $C_{(9)}$, *e.g.*, acetylation giving 9 : 11-unsaturated 11-acetates. 11-Ketones of the 5β-series, on the other hand, have been reported to give 12α-bromo-compounds [3] despite the fact that enol acetylation proceeds as in the 5α-series.[4]

(Tertiary bromo)-ketones are converted by hydrogen bromide into the secondary isomers [5] and it has been established that a 9α-bromo-11-ketone in the ergostane series also behaves in this way.[2,6] The isolation [3] of the 12α-bromo-compound of the 5β-pregnane type might well be due to the ready isomerisation of an initial 9-bromo-compound (the yield quoted was only 40%). Of course with the *cis*-AB-junction it is also possible that isomerisation might be facilitated, or bromination prevented, by the greater steric compression on a 9α-bromine atom.

Bromination of 3α : 20β-diacetoxy-5β-pregnan-11-one (Ia) under normal conditions, *i.e.*, at 50° in acetic acid under nitrogen in the dark (cf. ref. 2), gave the 12α-bromo-ketone (IV) in 70% yield. Its structure was proved by its stability to both bases and hydrogen bromide while the absence of any appreciable shift in the infrared carbonyl stretching frequency, and the ultraviolet absorption maximum at *ca.* 3200 Å (Δλ 230 Å), are in agreement with a 12α-configuration.[7] The optical rotatory dispersion † and molecular rotation differences also lead to the same conclusion.

The enol acetate (IIa) was prepared in 80% yield by treatment of the ketone (Ia) with acetic anhydride and toluene-*p*-sulphonic acid. Bromination in acetic acid gave again the 12-bromo-compound (IV), but by adding sodium acetate to the reaction medium or, better, by using pyridine [8] in acetic acid (10%) as solvent, the 9α-bromo-isomer (IIIa) was obtained in high yield. Its structure was proved by (*a*) its light absorption and optical rotatory dispersion,† indicating also axial conformation of the bromine atom, (*b*) its conversion with hydrogen bromide into the isomeric 12α-bromo-ketone (IV), and (*c*) its easy dehydrobromination with boiling pyridine to the Δ^{8}-11-ketone (Va).

An attempt to obtain chemical proof of the configuration of the 9-bromine atom in (IIIa) by the Fieser method [9] was frustrated by the production, on lithium aluminium

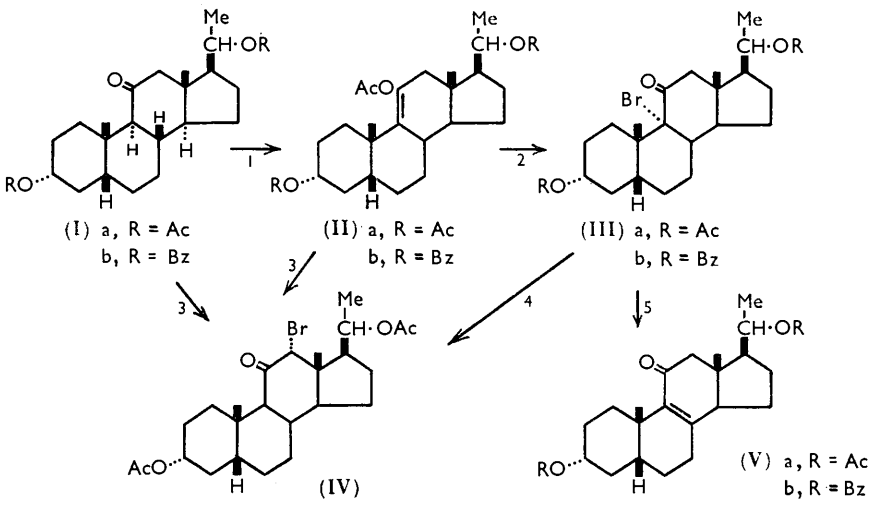
* Part LXXI, *J.*, 1958, 2156.

† We are much indebted to Professor C. Djerassi for these measurements.

[1] Cf. Jones, Meakins, and Stephenson, *J.*, 1958, 2156.
[2] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.
[3] Turner, Mattox, Engel, McKenzie, and Kendall, *J. Biol. Chem.*, 1946, **166**, 345; 1948, **173**, 283.
[4] Hirschmann and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 2361.
[5] Heilbron, Jones, and Spring, *J.*, 1937, 801.
[6] Wrigley, Ph.D. thesis, Manchester, 1956.
[7] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828; Cookson, *J.*, 1954, 282.
[8] Cf. Corey and Ursprung, *J. Amer. Chem. Soc.*, 1956, **78**, 5041.
[9] Fieser and Ettore, *J. Amer. Chem. Soc.*, 1953, **75**, 1700; Fieser and Dominguez, *ibid.*, p. 1704.

hydride reduction (followed by acetylation), of bromine-free compounds, the ketone (Ia), and the related 11β-alcohol. Sodium borohydride reduction of the related 9α-bromo-ketone in the ergostane series proceeded in a similar manner.[2] With the 12α-bromo-ketone (IV) on the other hand, reduction yielded the expected bromohydrin and this with base gave the 11β : 12β-epoxide.

Although the study so far had been entirely with the diacetate series, it had been realised that it would be preferable to carry out the methylation step on a dibenzoate since *O*-methylation is virtually non-existent with these esters.[10] Under very mild conditions, with dilute methanolic sodium carbonate, it was possible to convert the diacetate into the keto-diol (V; R = H) (characterised by oxidation to 5β-pregn-8-ene-3 : 11 : 20-trione) but this hydrolysis was accompanied by appreciable inversion at $C_{(14)}$.[11] This necessitated



Reagents: 1, Ac_2O–*p*-$C_6H_4Me{\cdot}SO_3H$. 2, Br–C_5H_5N–AcOH. 3, Br–AcOH. 4, HBr–AcOH. 5, C_5H_5N.

repetition of the (I)—(V) sequence of reactions in the dibenzoate series; results very similar to those already described were obtained. The absence of any significant amount of ester interchange during the preparation of the enol acetate in the dibenzoate series is noteworthy.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were measured for chloroform solutions at room temperature. Infrared spectra, unless otherwise specified, were recorded for carbon disulphide and ultraviolet absorption spectra for ethanol solutions. Usually the alumina used for chromatography was prepared by deactivating Peter Spence's Grade " H " alumina with 5% of 10% acetic acid. Light petroleum refers to the fraction of b. p. 60—80°.

3α : 20β-*Diacetoxy*-12α-*bromo*-5β-*pregnan*-11-*one* (IV).—A solution of 3α : 20β-diacetoxy-pregnan-11-one [12] (1·0 g.) in acetic acid (10 c.c.) was treated in nitrogen in the dark at 50° with a 50% w/v solution (5 drops) of hydrobromic acid in acetic acid, and with bromine (420 mg.; 1·1 mol.) in acetic acid (1·2 c.c.). The flask was then stoppered; after 50 min. the mixture was diluted with ether, and isolation in the normal manner gave the 12α-*bromo-ketone* (860 mg.) as needles (from methanol), m. p. 176—178°, $[\alpha]_D$ −4° (*c* 0·93) (Found: C, 60·3; H, 7·7; Br, 16·1. $C_{25}H_{37}O_5Br$ requires C, 60·3; H, 7·5; Br, 16·1%), $\nu_{max.}$ 1730, 1230 (acetate), 1709 cm.$^{-1}$ (carbonyl), $\lambda_{max.}$ 3190 Å (ε 150). The bromo-ketone was mainly recovered when refluxed in collidine for 7 hr., or in pyridine containing silver nitrate (10%) for 10 hr. No change in rotation

[10] Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1131.
[11] Cf. Wendler, Graber, Snoddy, and Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476. This inversion will be discussed in detail in a later publication.
[12] Sarett, *J. Amer. Chem. Soc.*, 1948, **70**, 1690.

was observed when the bromo-ketone (100 mg.) was kept for 4 days in acetic acid (5 c.c.) containing hydrobromic acid (50% in acetic acid; 15 drops), and the compound was recovered unchanged.

3α : 11 : 20β-*Triacetoxy*-5β-*pregn*-9(11)-*ene* (IIa).—(*a*) A solution of 3α : 20β-diacetoxypregnan-11-one (1·0 g.) in carbon tetrachloride (9·4 c.c.) was treated with acetic anhydride (0·6 c.c.) and 60% aqueous perchloric acid (0·03 c.c.), and kept at 15° for 15 days. The mixture was washed with ice-cold 5% sodium hydroxide solution and water and dried. Evaporation, and repeated recrystallisation of the product from acetone–light petroleum, gave needles of the *enol acetate* (400 mg.), m. p. 224—228°, $[\alpha]_D$ +90° (*c*, 1·02) (Found: C, 70·4; H, 8·65. $C_{27}H_{40}O_6$ requires C, 70·4; H, 8·75%), $\nu_{max.}$ 1733, 1235 (acetate), 1640 (C=C stretching), and 1752 (sh) and 1212 cm.$^{-1}$ (11-acetate).

(*b*) The solvent was fractionally distilled from a solution of 3α-acetoxy-20β-hydroxy-5β-pregnan-11-one (23·3 g.) and toluene-*p*-sulphonic acid (8 g.) in acetic anhydride (600 c.c.; acetic acid-free), while acetic anhydride was added periodically to keep the volume approximately constant. After 10 hr., the residual solvent was removed under reduced pressure, and methanol was added cautiously to the cooled residue. A small volume of water was added, followed by solid potassium hydrogen carbonate; the product was then isolated *via* ethyl acetate. After two recrystallisations from acetone, the enol acetate (20·3 g., 78%) was obtained as needles, m. p. 224—228°, identical with the above product.

3α : 20β-*Diacetoxy*-9α-*bromo*-5β-*pregnan*-11-*one* (IIIa).—(*a*) Bromine (5·9 g., 1·5 mol.) in acetic acid (18 c.c.) was added to a solution of the above enol acetate (11·3 g.) in 10% v/v pyridine–acetic acid (400 c.c.) in nitrogen. The flask was stoppered, and stored at 30° for 30 hr. in the dark. Sodium sulphite was added and the product was isolated in the usual manner with ether, being dried by azeotropic distillation with benzene under reduced pressure. The 9α-*bromo-ketone* separated from methanol as an amorphous solid (9·5 g.), with m. p. 152—154° when the sample was placed on the block at 140° and heated rapidly. It decomposes fairly rapidly at 100° and slowly at 20°, even in the dark. The bromo-ketone was also readily characterised by its rotation, $[\alpha]_D$ +170° (*c* 1·04), which differed appreciably from those of the enol acetate, 11-ketone, or the 12α-bromo-ketone (Found: C, 60·4; H, 7·45; Br, 15·5. $C_{25}H_{37}O_5Br$ requires C, 60·3; H, 7·5; Br, 16·1%). It had infrared peaks at 1730, 1230 (acetate), and 1709 cm.$^{-1}$ (11-ketone), and ultraviolet absorption max. 3200 Å (ε 100).

(*b*) When the enol acetate (500 mg.) in acetic acid (20 c.c.) containing fused sodium acetate (500 mg.) was treated with bromine (0·21 g., 1·2 mol.) for 24 hr. at 30° in the dark, the 9α-bromo-ketone was obtained in 45% yield. In the absence of sodium acetate, the 12α-bromo-isomer was isolated in 70% yield.

Isomerisation of the 9α- *into the* 12α-*Bromo-ketone* (IIIa ⟶ IV).—A solution of 3α : 20β-diacetoxy-9α-bromo-5β-pregnan-11-one (40 mg.) in acetic acid (8 c.c.) containing hydrobromic acid (50% in acetic acid; 3 drops) was kept at 15° for 2½ days, during which the rotation of the solution changed from +0·8° to +0·1°. (The 12α-bromo-ketone has an appreciable positive rotation in acetic acid, as compared with $[\alpha]_D$ −4° in chloroform.) Isolation *via* ether, and crystallisation from methanol, gave the 12α-bromo-ketone (17 mg.), m. p. and mixed m. p. 175—178°.

3α : 20β-*Diacetoxy*-5β-*pregn*-8-*en*-11-*one* (Va).—A solution of the 9α-bromo-ketone (2·52 g.) and silver nitrate (8·7 g.) in pyridine (70 c.c.) was heated under reflux for 2½ hr. (but see below). The product obtained *via* ether was dissolved in benzene and filtered through alumina (100 g.). Evaporation and crystallisation of the residue from acetone–methanol gave needles of the αβ-unsaturated *ketone* (1·15 g.), m. p. 76°, and 162—166° after resolidification. Crystallisation from acetone–light petroleum gave needles, m. p. 166—167°, $[\alpha]_D$ +128° (*c* 1·13) (Found: C, 71·9; H, 8·55. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%), $\nu_{max.}$ (in Nujol) 1724, 1250 (acetate), 1650 (αβ-unsaturated ketone), 1595 (8-ene) and 1072 cm.$^{-1}$, $\lambda_{max.}$ 2540 Å (ε 8000).

In a subsequent experiment, in which the bromo-ketone was not isolated and dehydrobromination was effected by refluxing in pyridine alone for 15 min., the enol acetate (IIa) (20·6 g.) gave 14·8 g. of conjugated ketone (Va).

3α : 20β-*Dihydroxy*-5β-*pregn*-8-*en*-11-*one* (V; R = H).—3α : 20β-Diacetoxy-5β-pregn-8-en-11-one (240 mg.) in methanol (40 c.c.) was treated with potassium carbonate (400 mg.) in water (4 c.c.), and kept for 3 days at 17°. The solution was neutralised with acetic acid, then concentrated under diminished pressure, and ether and chloroform were added. The recovered steroid was adsorbed on alumina (10 g.); benzene–ether (1 : 1) eluted partially saponified

material (105 mg.), and acetone then eluted the conjugated *keto-diol* (V; R = H; 105 mg.), which crystallised from acetone in needles, m. p. 213—219°, $[\alpha]_D$ +128° (*c* 0·76) (Found: C, 75·5; H, 9·5. $C_{21}H_{32}O_3$ requires C, 75·8; H, 9·7%), $\nu_{max.}$ (in Nujol) 3200—3300 (hydroxyl), 1654 (αβ-unsaturated ketone), and 1593 cm.$^{-1}$ (8-ene), $\lambda_{max.}$ 2540 Å (ε 8000).

The keto-diol (20 mg.), treated overnight at 20° with acetic anhydride (0·5 c.c.) and pyridine (0·5 c.c.), gave back the parent diacetate (20 mg.), m. p. (and mixed) 163—165°, $[\alpha]_D$ +128° (*c* 1·04).

5β-*Pregn*-8-*ene*-3 : 11 : 20-*trione*.—3α : 20β-Dihydroxy-5β-pregn-8-en-11-one (130 mg.) in acetone was oxidised with 8N-chromic acid.[13] The product was recovered *via* ether and recrystallised from methanol, to give the *trione* as needles, m. p. 195—199°, $[\alpha]_D$ +152° (*c* 1·0) (Found: C, 76·5; H, 8·85. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%), $\lambda_{max.}$ 2530 Å (ε 8000), $\nu_{max.}$ (in Nujol) 1709 (3 : 20-dione), 1650 (αβ-unsaturated ketone), and 1598 cm.$^{-1}$ (8 : 9-ene).

3α : 20β-*Dibenzoyloxy*-5β-*pregnan*-11-*one* (Ib).—3α : 20β-Dihydroxy-5β-pregnan-11-one [12] was treated with pyridine–benzoyl chloride in the usual way. The *dibenzoate* crystallised from ethyl acetate in thick prisms, m. p. 217—219°, $[\alpha]_D$ +47° (*c* 1·07) (Found: C, 77·8; H, 7·85. $C_{35}H_{42}O_5$ requires C, 77·5; H, 7·85%), $\nu_{max.}$ 1720 (benzoate and 11-ketone, not resolved) and 1270 cm.$^{-1}$ (benzoate).

11-*Acetoxy*-3α : 20β-*dibenzoyloxy*-5β-*pregn*-9(11)-*ene* (IIb).—The solvent was fractionally distilled from a solution of the keto-dibenzoate (64·9 g.) and toluene-*p*-sulphonic acid (20 g., *ca.* 1 mol.) in acetic anhydride (1·2 l.; acetic acid-free). After 4 hr., further acetic anhydride (400 c.c.) was added slowly, and after 9 hr., when the volume of the reaction mixture had been reduced to *ca.* 500 c.c., heating was discontinued. The solid which separated overnight was filtered off, washed liberally with ether, and finally with methanol, giving the *enol acetate* (59·4 g.) as needles, m. p. 236—242°. A sample recrystallised from ethyl acetate had m. p. 240—242°, $[\alpha]_D$ +56° (*c* 1·01) (Found: C, 75·9; H, 7·4. $C_{37}H_{44}O_6$ requires C, 76·0; H, 7·6%), $\nu_{max.}$ 1761, 1270 (11-acetate), 1720, 1270 (benzoate), and 1650 cm.$^{-1}$ (9 : 11-ene).

3α : 20β-*Dibenzoyloxy*-9α-*bromo*-5β-*pregnan*-11-*one* * (IIIb).—A solution of the above enol acetate dibenzoate (39·4 g.) in dry chloroform (100 c.c.) was diluted with glacial acetic acid (1 l.) and pyridine (100 c.c.). Nitrogen was bubbled into the flask for 5 min., and bromine (16·2 g.; 1·5 mol.) in acetic acid (70 c.c.) was added. The flask was stoppered, and kept at 30° in the dark for 26 hr., with periodical shaking to facilitate reaction of undissolved material. Sodium sulphite was added, and the product was isolated *via* ether. The 9α-*bromo-ketone* (32·1 g.) separated from ethyl acetate as prisms, m. p. 169—170° (sample placed on block at 160°), $[\alpha]_D$ +122° (*c*, 1·15) (Found: C, 67·7; H, 6·5; Br, 13·2. $C_{35}H_{41}O_5Br$ requires C, 67·6; H, 6·65; Br, 12·9%), $\nu_{max.}$ 1720, 1271 cm.$^{-1}$ (benzoate).

3α : 20β-*Dibenzoyloxy*-5β-*pregn*-8-*en*-11-*one* (Vb).—A solution of the 9α-bromo-ketone (5 g.) in pyridine (60 c.c.) was heated under reflux for 8 min. A large volume of ether was added, and the resulting solution was washed repeatedly with dilute hydrochloric acid. The product was then recovered in the usual manner, and recrystallised from methanol to give the conjugated *ketone* (2·9 g.) as prisms, m. p. 152—154°, $[\alpha]_D$ +18° (*c* 1·38). The compound was also obtained as needles, m. p. 132—134°, the two forms being interconvertible in solution (Found: C, 77·6; H, 7·45. $C_{35}H_{40}O_4$ requires C, 77·7; H, 7·45%); it had infrared peaks at 1719, 1265 (benzoate), and 1658 cm.$^{-1}$ (αβ-unsaturated ketone).

Lithium Aluminium Hydride Reduction of the 12α-*Bromo-ketone*.—A solution of the 12α-bromo-ketone (0·50 g.) in dry ether (25 c.c.) and lithium aluminium hydride (53 mg., 1·38 mol.) were heated under reflux for 1 hr. The steroid was isolated *via* ether, acetylated, and then chromatographed on alumina (45 g.). Benzene–light petroleum (2 : 1) eluted starting material (120 mg.); benzene–ether (10 : 1) eluted 3α : 20β-*diacetoxy*-12α-*bromo*-5β-*pregnan*-11β-*ol* (270 mg.), which crystallised from methanol as plates, m. p. 204—207°, $[\alpha]_D$ +91° (*c* 1·03) (Found: C, 60·1; H, 8·0; Br, 16·4. $C_{25}H_{39}O_5Br$ requires C, 60·1; H, 7·9; Br, 16·0%), $\nu_{max.}$ (in Nujol) 3500 (hydroxyl), 1733 and 1235 cm.$^{-1}$ (acetate).

3α : 20β-*Diacetoxy*-11β : 12β-*epoxy*-5β-*pregnane*.—A solution of the bromohydrin (130 mg.) in *tert.*-butyl alcohol (10 c.c.) was treated with M-potassium *tert.*-butoxide (2 c.c.) in *tert.*-butyl alcohol. The solution was kept at 55° for 15 min.; the steroid was recovered *via* ether and reacetylated at room temperature. The product in benzene was passed down a column of

* This experiment was carried out by Dr. J. S. G. Cox.

[13] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.

alumina (5 g.), then crystallised from methanol to give the 11β : 12β-*epoxide* as plates, m. p. 159—160°, $[\alpha]_D$ +74° (*c* 1·14) (Found: C, 71·8; H, 8·8. $C_{25}H_{38}O_5$ requires C, 71·75; H, 9·1%), $\nu_{max.}$ 1737 and 1237 cm.$^{-1}$ (acetate), but no hydroxyl band.

Lithium Aluminium Hydride Reduction of the 9α-*Bromo-ketone* (IIIa).—A solution of the ketone (IIIa) (620 mg.) in anhydrous ether (30 c.c.) was heated under reflux for 1 hr. with lithium aluminium hydride (66 mg., 1·38 mol.). The steroid was isolated *via* ether, acetylated, and chromatographed on alumina (55 g.). Benzene–light petroleum (2 : 1) eluted starting material (50 mg.); further elution with the same solvent and with benzene gave the parent 11-keto-diacetate (215 mg.), needles (from methanol), m. p. (and mixed) 160—161°; finally benzene–ether (10 : 1) eluted 3α : 20β-*diacetoxy*-5β-*pregnan*-11β-*ol* (230 mg.), plates (from methanol), m. p. 171—172°, $[\alpha]_D$ +69° (*c* 1·25), $[\alpha]_D$ +89° (*c* 1·07; in acetone) (Found: C, 71·4; H, 9·35. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%). This 11β-hydroxy-compound was identical with that obtained by reduction of the 11-keto-diacetate with sodium borohydride by the method of Oliveto and Hershberg.[14] It had infrared peaks (in Nujol) at 3500 (hydroxyl), 1737 and 1235 cm.$^{-1}$ (acetate).

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[14] Oliveto and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 488. Dr. Hershberg has very kindly informed us that the constants originally quoted for 3α : 20β-diacetoxy-5β-pregnan-11β-ol (m. p. 119—120°, $[\alpha]_D$ +68° in acetone) have not been confirmed on repetition of the preparation. He now finds m. p. 165—170°, $[\alpha]_D$ +69° (in dioxan), similar to the values indicated above.