Studies in the Steroid Series. Part LXIX. Bromination of 11-Oxo-5α-steroids.*

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Bromination of an 11-oxo-5α-steroid gave a 9α-bromo-ketone in high yield. This was converted into a Δ^8-11-ketone with collidine, and somewhat unexpectedly by lithium aluminium hydride into the 9β : 11β-epoxide and by sodium borohydride into the original ketone.

The bromination of 5α-steroids having an 11-oxo-group as the only ketonic function has not been described, although in the 5β-series Turner, Mattox, Engel, McKenzie, and Kendall (*J. Biol. Chem.*, 1946, **166**, 345; 1948, **173**, 283) reported the isolation of a 12α-bromo-11-ketone. From the considerable amount of work on cortical compounds and intermediates it is clear that bromination of 11-ketones of the 5α- or 5β-series cannot be too rapid as halogenation adjacent to other ketonic functions (*e.g.*, 3-oxo and/or 20-oxo) always occurs preferentially. In view of current interest in routes to 9-halogeno-steroids, the bromination of the simpler system, 3β-acetoxyergostan-11-one (I), has been studied.

This ketone in acetic acid at room temperature was treated with bromine (1 mol.) in the presence of hydrogen bromide, the solution being decolourized in 30—60 minutes. Isolation in the usual way gave a high yield of bromo-ketone [shown to be (II), see below]. However, on some occasions, although the bromination proceeded at about the same rate, a mixture was produced. It was considered possible that this occasional erratic course might be due to the adventitious presence or absence of substances promoting a free-radical reaction, for Kharasch, Sternfeld, and Mayo (*J. Amer. Chem. Soc.*, 1937, **59**, 1655)

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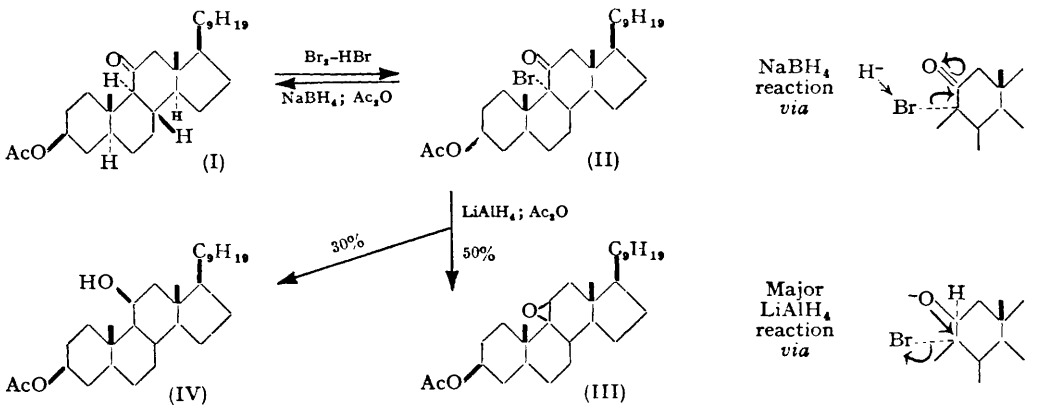
have reported that the isomerization of a bromo-ketone may be accelerated by peroxides, oxygen, or illumination. Bromination of (I) in the dark in air, in daylight in nitrogen, or in the dark in nitrogen (one experiment each) led in each case to good yields of the bromo-ketone, the rate of bromination not being appreciably altered. Finally it was found that bromination at 40° in the dark in nitrogen gave 85% yields of bromo-ketone (3 experiments), the reaction being complete in less than 5 minutes. Although further experimentation is necessary to determine more precisely the factors causing the occasional formation of mixtures in the earlier experiments, it seems likely that still closer attention to reaction conditions may often be of value in the bromination of ketones.

The major product of sodium borohydride reduction of the bromo-ketone, in methanol and in *tert.*-butanol, was (after acetylation) the starting ketone (I). It is suggested that as even unsubstituted 11-ketones are only reduced slowly by an excess of sodium borohydride (cf. Heymann and Fieser, *ibid.*, 1951, **73**, 5252; Oliveto and Hershberg, *ibid.*, 1953, **75**, 488) the nucleophilic attack by the reagent occurs alternatively at bromine to give the enolate ion of the 11-ketone.

Reduction with lithium aluminium hydride gave somewhat different results and provided proof that bromine is attached at $C_{(9)}$ in the bromo-ketone. With sufficient reagent to reduce the 11-oxo- and the 3β-acetoxy-group the 9β : 11β-epoxide (III; after reacetylation) was isolated in 50% yield; this appears to arise by hydride attack on the carbonyl group at $C_{(11)}$ followed by displacement of bromide ion. The epoxide was accompanied by some 30% of 3β-acetoxyergostan-11β-ol (IV) : this could have been formed by further reduction of the 9β : 11β-epoxide, but it is more likely that debromination (as observed with sodium borohydride) is occurring as a competing reaction, the 11-ketone being relatively rapidly reduced to the 11β-ol. Authentic 9β : 11β-epoxide was prepared by conversion of the appropriate Δ^9-compound (*J.*, 1954, 731) into the 9α-bromo-11β-hydroxy-steroid followed by dehydrobromination with potassium *tert.*-butoxide. As Fried and Sabo (*J. Amer. Chem. Soc.*, 1953, **75**, 2273) have reported, the yield of bromohydrin is greatly improved by using perchloric instead of sulphuric acid.



Further indication of the $C_{(9)}$-location of the bromine atom was provided by dehydrobromination by collidine or by silver nitrate in pyridine (pyridine alone was ineffective), the known, conjugated Δ^8-11-ketone (*J.*, 1953, 2921) then being formed. An α-configuration is assigned for the 9-bromine substituent from its method of formation; the lack of appreciable shift of the carbonyl stretching frequency is in agreement with this.

Tertiary bromo-ketones can usually be isomerized to more stable secondary bromo-compounds (cf. Heilbron, Jackson, Jones, and Spring, *J.*, 1937, 801; 1938, 102; Inhoffen and Zühlsdorff, *Ber.*, 1943, **76**, 233). Preliminary experiments have shown that hydrogen bromide will convert the bromo-ketone (II) into an isomer which appears to be the 12α-bromo-compound; a more detailed study of this reaction is being made. The formation of the 9-bromo-compound from the ergostanone (I) is in accord with the known direction of enolization of 11-ketones of the 5α-series, Δ^9-11-acetates being formed on

acetylation. Δ^9-11-Acetates are also formed from 11-ketones in the 5β-series, and the isolation of a 12-bromo-ketone by Turner *et al.* (*loc. cit.*) may be due to the greater steric crowding associated with bromination at $C_{(9)}$ in the 5β-series, which may result in bromination at $C_{(12)}$ or in ready rearrangement of bromine from $C_{(9)}$ to $C_{(12)}$.

Experimental

M. p.s were recorded on a Kofler block and are corrected. Rotations were determined in chloroform solutions.

3β-*Acetoxy*-9α-*bromoergostan*-11-*one* (II).—A solution of 3β-acetoxyergostan-11-one (2·8 g.) in acetic acid (18 c.c.) was treated successively with hydrobromic acid (50% in acetic acid; 5 drops) and bromine (0·32 c.c.; 1·1 mol.) in acetic acid (3·2 c.c.), whereafter the solution was heated at 40° until the bromine colour was discharged. These operations were performed with nitrogen bubbling through the solution, and the reaction vessel shielded from light. Much of the bromo-compound crystallized when the mixture cooled, but the total product was isolated *via* ether. Crystallization from methanol–acetone gave fairly pure product (3·05 g.); further crystallization afforded the pure *bromo-ketone* as plates, m. p. 161—163°, $[\alpha]_D$ +128° (Found: C, 66·95; H, 9·4; Br, 14·6. $C_{30}H_{49}O_3Br$ requires C, 67·0; H, 9·25; Br, 14·9%). Infrared spectrum (in CS_2) = peaks at 1735, 1245 (acetate), and 1710 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-9β : 11β-*epoxyergostane* (III).—(*a*) An ether solution (20 c.c.) of the bromo-ketone (376 mg.) and lithium aluminium hydride (22 mg.; 0·83 mol.) was heated under reflux for 1 hr. The product was isolated with ether, acetylated, and chromatographed on deactivated alumina (30 g.). Elution with light petroleum–benzene (10 : 1) gave 3β-*acetoxy*-9β : 11β-*epoxyergostane* (150 mg.), m. p. 114—115° (from acetone–methanol), $[\alpha]_D$ +23° (Found: C, 78·35; H, 11·05. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Infrared spectrum: no hydroxyl band. Elution with light petroleum–benzene (1 : 1) gave 3β-acetoxyergostan-11β-ol (80 mg.), m. p. and mixed m. p. 133—134° (from methanol), $[\alpha]_D$ +28°.

(*b*) A solution of 3β-acetoxy-9α-bromoergostan-11β-ol (225 mg.) in *tert.*-butanol (20 c.c.) was treated with M-potassium *tert.*-butoxide (2 c.c.) solution in *tert.*-butanol. The solution was kept at 50° for 15 min.; the steroid was isolated with ether, acetylated, and crystallized from methanol–acetone to yield the 9β : 11β-epoxide (120 mg.), m. p. and mixed m. p. 113—115°.

3β-*Acetoxy*-9α-*bromoergostan*-11β-*ol*.—A solution of 3β-acetoxyergost-9-ene (1·13 g.) in ether (30 c.c.) and acetone (100 c.c.) containing water (9 c.c.) and N-perchloric acid (1 c.c.) was added to a solution of *N*-bromosuccinimide (700 mg.) in acetone (50 c.c.). The mixture was kept at 0° for 4 hr., then sodium sulphite solution was added followed by sodium carbonate solution until the solution was alkaline. Addition of water (500 c.c.) precipitated the product, which when crystallized from aqueous acetone afforded the *bromohydrin* (1 g.; m. p. 159—162°), $[\alpha]_D$ +28° (Found: C, 67·2; H, 9·7. $C_{30}H_{51}O_3Br$ requires C, 66·8; H, 9·45%). Infrared spectrum (in CCl_4): peaks at 3620 (hydroxyl), 1730, and 1245 cm.$^{-1}$ (acetate).

Sodium Borohydride Reduction of the Bromo-ketone (II).—The hydride (450 mg.) was added to a solution of the bromo-ketone (1 g.) in methanol (150 c.c.), the mixture then being heated under reflux for 12 hr. The steroid was isolated with ether, acetylated, and chromatographed on deactivated alumina (50 g.). Elution with light petroleum–benzene (10 : 1) gave 3β-acetoxyergostan-11-one (400 mg.), m. p. and mixed m. p. 138—139°, $[\alpha]_D$ +34°. Elution with light petroleum–benzene (1 : 1) yielded 3β-acetoxyergostan-11β-ol (60 mg.), m. p. and mixed m. p. 132—133°.

An identical experiment with *tert.*-butanol instead of methanol afforded the same products, the ketone : 11β-alcohol ratio being slightly lower.

3β-*Acetoxyergost*-8-*en*-11-*one from the Bromo-ketone* (II).—A solution of the bromo-ketone (500 mg.) in collidine (25 c.c.) was heated under reflux for 2 hr. in nitrogen. Isolation with ether and crystallization from methanol gave the conjugated ketone (300 mg.) as needles, m. p. 135—137°, $[\alpha]_D$ +116°. Light absorption (in EtOH): $\lambda_{max.}$ 2540 Å; $\varepsilon_{max.}$ 10,000. When a solution of the bromo-compound (750 mg.) in pyridine (20 c.c.) containing silver nitrate (2·5 g.) was heated under reflux for 5 hr., a good yield of the conjugated ketone was also obtained.

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