872. *Nucleophilic Substitution of* 9α-*Bromo*-11-*keto-steroids.*

By J. S. G. Cox.

9α-Bromo-11-keto-steroids have been shown to undergo S_N2' displacement, giving 12α-substituted 11-keto-compounds with methoxide and hydroxide ions.

ALTHOUGH the preparation and reactions of α-bromo-keto-steroids have been thoroughly investigated, yet, apart from the Faworskii rearrangement,[1] the action of alkalis has received relatively little attention.[2] The opportunity of examination of such reactions in the case of 9α-bromo-11-ketones of the 5α- and 5β-pregnane series presented itself during studies directed towards the synthesis of the corresponding 9α-methyl compounds.[3]

Alkaline methanolysis of 3α,20β-dibenzoyloxy-9α-bromo-5β-pregnan-11-one [4,*] (I) caused, in addition to the expected ester hydrolysis, the replacement of bromine by methoxyl. The presence of the methoxyl group and the absence of bromine were shown by analysis and confirmed by the infrared spectrum, peaks at 2820 (sh) and 1095 cm.$^{-1}$ being characteristic of the methoxyl group.[5] Acetylation with acetic anhydride–pyridine gave the methoxy-diacetate (IIb).

The nuclear magnetic resonance spectra of 3α,20β-diacetoxy-5β-pregnan-11-one [6] (IIa) and the derived 12-methoxy-compound (IIb) located the methoxyl group unambiguously in position 12. The sharp peak at 121 cycles/sec. ascribed [7] to the two protons

* For position 20, β is used in Plattner's sense.

[1] (*a*) For general review of the Faworskii rearrangement see Jacquier, *Bull. Soc. chim. France*, 1950, D 35; cf. Wendler, Graber, and Hazen, *Tetrahedron*, 1958, **3**, 144; Evans, de Paulet, Shoppee, and Winternitz, *J.*, 1957, 1451; (*b*) Loftfield, *J. Amer. Chem. Soc.*, 1951, **73**, 4707.

[2] Stevens and Farkas, *J. Amer. Chem. Soc.*, 1952, **74**, 5352; Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 521.

[3] Jones, Meakins, and Stephenson, *J.*, 1958, 2156.

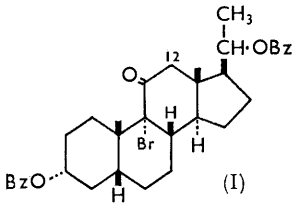
[4] Jones and Wluka, *J.*, 1959, 907.

[5] Henbest, Meakins, Nicholls, and Wagland, *J.*, 1957, 1462.

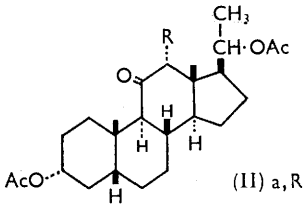
[6] Sarett, *J. Amer. Chem. Soc.*, 1948, **70**, 1690.

[7] Shoolery and Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121; Bishop, Cox, and Richards, unpublished work.

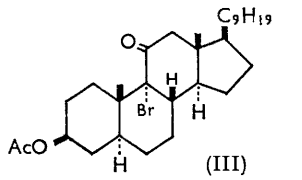
at position 12 (shifted to a lower field by the adjacent carbonyl group) in the spectrum of the ketone (IIa) was absent in the spectrum of the methoxyl derivative (IIb), showing that position 12 of the latter was substituted. The very sharp peak at 91 cycles/sec. was due to the methoxyl protons whilst the remaining 12-proton appeared as a smaller sharp peak (approx. one-third of the area of the methoxyl peak) moved to a lower field than all



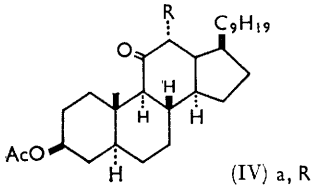
(I)



(II) a, R = H; b, R = OMe



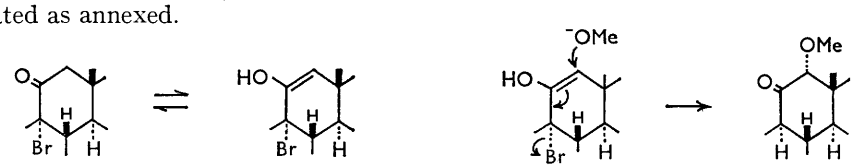
(III)



(IV) a, R = OAc; b, R = OEt

the other ring protons since it was attached to a carbon atom carrying an oxygen substituent. This nucleophilic displacement of bromine is not confined to the 5β-pregnane series. Treatment of 3β-acetoxy-9α-bromo-ergostan-11-one [8] with aqueous-ethanolic potassium hydroxide gave a non-crystalline product which was separated (after acetylation with acetic anhydride–pyridine) by chromatography on alumina into the 12α-acetoxy- (IVa) and the 12-ethoxy-analogue (IVb) of 3β-acetoxyergostan-11-one. The presence of the 12-acetoxy-group adjacent to the 11-carbonyl group in compound (IVa) was clearly seen from the infrared data, peaks at 1753, 1734, 1238, and 1221 cm.$^{-1}$ being in excellent agreement with the values for similar compounds.[9] These frequency displacements are thought to be attributable to dicarbonyl interactions and, as expected, the 12-ethoxy-compound (IVb) in which such interactions are not possible, shows a normal 11-carbonyl band at 1711 cm.$^{-1}$, in addition to the strong ether band at 1102 cm.$^{-1}$.

These displacements provide further examples of S_N2' reactions in the steroid series, previous examples being reported by Fieser and others.[10] The tertiary and axial nature of the 9-bromine atom, being ideal for displacement, greatly facilitates the reaction whilst the possible competing S_N2 reaction is suppressed by steric factors, *i.e.*, necessitating inversion of the B/C ring junction. Mechanistically, the course of the reaction may be illustrated as annexed.



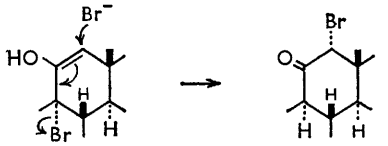
An alternative mechanism, namely, initial attack by methoxide leading to epoxide formation, subsequent cleavage also by OMe^- giving the α-methoxy-ketone, was eliminated by the nuclear magnetic resonance data since position 12 is shown to be substituted.

Normally in S_N2' reactions the reaction gives double inversion, the new group entering

[8] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.
[9] Dickson and Page, *J.*, 1955, 447.
[10] Fieser and Romero, *J. Amer. Chem. Soc.*, 1953, **75**, 4716; Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *ibid.*, p. 4712; Herran, Rosenkranz, and Sondheimer, *Chem. and Ind.*, 1953, 824; Ireland, Wrigley, and Young, *J. Amer. Chem. Soc.*, 1959, **81**, 2818.

from the same side of the molecule as the group which is displaced.[11] Since in this series of reactions epimerisation at position 12 may take place under alkaline conditions, the reaction is probably thermodynamically controlled. However, the configuration of the acetoxy-group (12α axial) in compound (IVa) follows from the optical rotatory dispersion curve in methanol (kindly determined by Dr. W. Klyne), the results being in excellent agreement with those reported by Djerassi *et al.*[12,*]

In all these reactions it is remarkable that no elimination (E_2) occurs in spite of the ready dehydrobromination of these α-bromo-ketones with bases such as pyridine.[4,8] (Tertiary bromo)-ketones are readily converted by hydrogen bromide into the secondary isomers.[13] In certain cases, *e.g.*, 9α-bromo-11-ketones, this rearrangement could proceed by a similar S_N2' mechanism, acid-catalysed enolisation of the ketone, followed by nucleophilic attack by bromide ion, being the necessary steps, *e.g.*:



The reaction may be thought of as a double inversion involving the two ends of the allylic system, thus giving the correct stereochemistry for the incoming group, *e.g.*, 9α-bromo-11-ketones ⟶ 12α-bromo-11-ketones.[8,4]

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were measured for $CHCl_3$ solutions at room temperature, infrared spectra (unless otherwise specified) for CS_2 and ultraviolet absorption spectra for EtOH 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°.

Nuclear Magnetic Resonance Spectra.—Spectra were obtained at 29·92 megacycles/sec. in a magnetic field of ~7000 gauss. The compounds were studied in ~0·2M-solution in " AnalaR " chloroform.

The zero of reference in each spectrum was taken as the resonance position of pure benzene contained in an external capillary. The shift values of the sharp peaks in the spectrum of each steroid were determined by the audiofrequency side-band method [14] in cycles/sec. and could be reproduced to within ½ cycle/sec. The spectrometer employed for these measurements has been described by Leane *et al.*[15]

Alkaline Treatment of 3α,20β-Dibenzoyloxy-9α-bromo-5β-pregnan-11-one.—3α,20β-Dibenzoyloxy-9α-bromo-5β-pregnan-11-one (2 g.) was heated in methanolic 10% potassium hydroxide (200 c.c.) under reflux for 8 hr. Isolation of the product through chloroform and crystallisation from acetone gave *3α,20β-dihydroxy-12α-methoxy-5β-pregnan-11-one* as prisms (0·92 g.), m. p. 203—204°, $[\alpha]_D$ +39° (*c* 5·0) (Found: C, 72·8; H, 10·3; OMe, 9·3. $C_{22}H_{36}O_4$ requires C, 72·5; H, 10·0; OMe, 8·5%), $\nu_{max.}$ 3560, 2820 (sh) (OMe), 1712, and 1095 cm.$^{-1}$. Reaction with acetic anhydride–pyridine at room temperature overnight gave the *3α,20β-diacetate* as needles (from

* Comparison of optical rotatory dispersion curves (in methanol):

Me 3α,12ξ-diacetoxy-11-oxo-5β-cholenates (12α axial) [12]

Peak +5750° (335 mμ)
Trough −1590° (290 mμ) } *a* + 73

12β, equatorial

Peak +2700° (310 mμ)
Trough −75° (278 mμ) } *a* + 28

3β,12α-Diacetoxy-5α-ergostan-11-one (present work)

Peak +4550° (330 mμ)
Trough −4000° (277 mμ) } *a* + 85

[11] Stork and White, *J. Amer. Chem. Soc.*, 1953, **75**, 4119.
[12] Djerassi, Halpern, Schindler, and Tamm, *Helv. Chim. Acta*, 1958, **41**, 250.
[13] Heilbron, Jones, and Spring, *J.*, 1937, 801.
[14] Arnold and Packard, *J. Chem. Phys.*, 1951, **19**, 1608.
[15] Leane, Richards, and Schaefer, *J. Sci. Instr.*, 1959, **36**, 230.

methanol), m. p. 182—183°, $[\alpha]_D$ +97° (*c* 2·8) (Found: C, 69·8; H, 9·2. $C_{26}H_{40}O_6$ requires C, 69·6; H, 9·0%), $\nu_{max.}$ 2800 (sh) (OMe), 1740, 1710, 1238, and 1097 cm.$^{-1}$. The compound was recovered unchanged from a solution in phosphorus oxychloride–pyridine at 90° after 2 hr.

Alkaline Treatment of 3β-*Acetoxy*-9α-*bromoergostan*-11-*one*.—3β-Acetoxy-9α-bromoergostan-11-one (553 mg.) was heated in ethanolic 5% potassium hydroxide (50 c.c.) under reflux for 1 hr. Isolation of the product through ether gave an oil (410 mg.), $[\alpha]_D$ +45° (*c* 2·1). Infrared examination of this product showed complete removal of the acetoxy-group and the disappearance of C–Br bands (785 and 744 cm.$^{-1}$). Reaction with acetic anhydride–pyridine and crystallisation from methanol gave an acetate mixture, m. p. 160—166° (300 mg.) (Br absent), $[\alpha]_D$ +46° (*c* 3·1). This mixture (280 mg.) in light petroleum was chromatographed on alumina (8 g.). The column was eluted with (*a*) light petroleum–benzene (9 : 1; 100 c.c.), (*b*) light petroleum–benzene (4 : 1; 100 c.c.), and (*c*) benzene (200 c.c.). Evaporation of fractions (*a*) and (*b*) gave 3β-*acetoxy*-12α-*ethoxyergostan*-11-*one* (140 mg.) as prisms (from methanol), m. p. 152—153°, $[\alpha]_D$ +42° (*c* 2·0) (Found: C, 76·1; H, 10·4. $C_{32}H_{54}O_4$ requires C, 76·4; H, 10·8%), $\nu_{max.}$ 1736, 1711, 1240, and 1102 cm.$^{-1}$ (no OH stretching). Fraction (*c*) gave 3β,12α-*diacetoxyergostan*-11-*one* (83 mg.) as needles (from methanol), m. p. 202—204°, $[\alpha]_D$ +47° (*c* 0·7) (Found: C, 74·2; H, 9·9. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·15%), $\nu_{max.}$ 1753, 1734, 1238, and 1221 cm.$^{-1}$.

THE DYSON PERRINS LABORATORY,
UNIVERSITY OF OXFORD.

[*Received, May 19th,* 1960.]