Bromination of 2-Oxo-5β-steroids

Yasuo SATOH, Akira HORIUCHI, Tadaaki MATSUKURA and Akira HAGITANI

Department of Chemistry, College of Science, St. Paul's University (Rikkyo Daigaku), Nishi-Ikebukuro, Toshima-ku, Tokyo

(Received September 20, 1968)

In the bromination of any given keto-steriod, Corey has proposed a means of predicting the configuration of bromine in the product.[1] The bromination of keto-5α-steroids which possess a carbonyl group on each position in ring A has been thoroughly investigated,[2] and the configuration of the brominated product in every case was in agreement with Corey's prediction. In the case of the bromination of keto-5β-steroids, however, only that of the 3-oxo derivative has been reported.[3]

The authors wish to report on the bromination of 2-oxo-5β-steroids and on the relation between these products and Corey's prediction.

5β-Chlestan-2-one[4] (4.24 g) was dissolved in acetic acid (100 m*l*) and a few drops of 49% hydrogen bromide were added, followed by addition of bromine (1.75 g) in acetic acid (10 m*l*) with stirring for 25 min at 18°C. The reaction mixture was cooled and then the crystals formed were collected. The crystals were dissolved in ether and the ethereal solution was washed, dried and evaporated. Crystallization of the residue from methanol-ether gave needles (3.82 g), mp 128—130°C. IR (KBr disk): 1714 ($\nu_{C=O}$) and 668 cm^{-1} (ν_{C-Br}). NMR (in $CDCl_3$) τ: 4.32 (singlet, one proton). ORD (*c* 0.52, Di) at 26°C: $[\alpha]_{589}$ +9.6°, $[\alpha]_{400}$ +421°, $[\alpha]_{336}$ +2187° (peak), $[\alpha]_{314}$ 0°, $[\alpha]_{288}$ −2369° (trough). Found: C, 69.78; H, 9.80%. Calcd for $C_{27}H_{45}OBr$: C, 69.65; 9.74%.

The bromination of methyl 2-oxocholanate (834 mg)*1,5) was carried out using the technique as described above. The reaction mixture was taken up in ether and the ether extracts were washed, dried and evaporated. On chromatography of the residue on silica gel (50 g), elution with benzene gave an oily product (650 mg). The crystallization of this product from methanol afforded needles (81 mg), mp 138—140°C. IR (KBr disk): 1735, 1710 ($\nu_{C=O}$), 1171 (ν_{C-O-C}) and 673 cm^{-1} (ν_{C-Br}). NMR (in $CDCl_3$) τ: 5.66 (singlet, one proton) and 6.35 (singlet, three protons). ORD (*c* 0.62, Di) at 25°C: $[\alpha]_{589}$ +67.7°, $[\alpha]_{400}$ +271°, $[\alpha]_{335}$ +1394° (peak), $[\alpha]_{313}$ 0°, $[\alpha]_{289}$ −1468° (trough). Found: C, 63.33; H, 8.00%. Calcd for $C_{25}H_{39}O_3Br$: C, 64.24; H, 8.41%. An oily product from the mother liquor was identical with the above crystals in IR- and NMR-spectra.

These compounds are 1β-bromo-2-oxo-5β-steroids, not 1α- or 3-bromo isomers. This has been confirmed by signs of the Cotton effect, Δ[A]- (+233 for 5β-cholestan-2-one and +164 for methyl 2-oxocholanate) and $\Delta\lambda_1$-values (+20 and +18 mμ, respectively) in ORD, by the shifts of C=O stretching bands (+4 and +2 cm^{-1}, respectively) in the IR spectra and by the patterns of the NMR spectra.

In connection with the above investigation, we carried out the enol acetylation of 5β-chloestan-2-one according to directions of Djerassi *et al.* described for the 5α-series.[2] The reaction product was chromatographed in petroleum ether on silica gel. Elution with benzene gave 5β-cholest-1-en-2-ol acetate, mp 103—105°C, $[\alpha]_D^{26}$ +52.0° (*c* 0.997, in $CHCl_3$), from ethanol. IR (KBr disk): 1750 ($\nu_{C=O}$), 1687 ($\nu_{C=C}$) and 1215 cm^{-1} (ν_{C-O-C}). NMR (in $CDCl_3$) τ: 4.66 (singlet, one proton) and 7.93 (singlet, three protons). It has been found, moreover, that bromination of this enol acetate with bromine in acetic acid gave the same product as described above for 5β-cholestan-2-one.

From these results, we may conclude that the enolization of the 2-oxo-5β-steroids occurs in the direction of C_1, not C_3, and that the bromination of these ketones forms the 1β-bromo-2-oxo derivatives. The configuration of these bromoketones is consistent with Corey's prediction for the 2-oxo-5β-steroids.[1]

Further details will be published later.

1) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); **76**, 175 (1954).
2) C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco (1963), p. 179.
3) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); L. F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953); C. W. Shoppee, A. B. Devine, and R. E. Lack, *J. Chem. Soc.*, **1965**, 6458.
4) M. Tomoeda and T. Koga, *Tetrahedron Letters*, **1965**, 3231.
*1 ORD (*c* 0.59, Di) at 26°C: $[\alpha]_{317}$ −273° (trough), $[\alpha]_{307}$ −166° (shoulder), $[\alpha]_{275}$ +509° (peak).
5) This compound, not yet given in literature, will be reported at the Sendai Meeting of the Chemical Society of Japan, October, 1968.