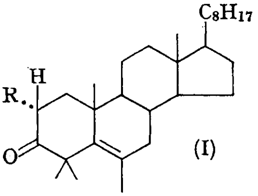
Some Exceptions to the Axial Halogeno-ketone Rule

By J. S. E. HOLKER, W. R. JONES, and M. G. R. LEEMING
(Department of Organic Chemistry, The University, Liverpool)
and G. M. HOLDER and W. B. WHALLEY
(The School of Pharmacy, The University, London, W.C.1)

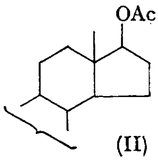
IT has been shown[1,2,3] by charge transfer and proton magnetic resonance spectroscopy that ring A in 4,4,6-trimethylcholest-5-en-3-one (I; R=H) (ν_{max} 1704 cm.$^{-1}$, λ_{max} 288 mμ) has essentially a classical boat conformation with C-3–C-10 at the stem and stern positions. It is clear that this conformation is preferred because of the non-bonded interactions between the C-4 and C-6 methyl substituents in the alternative chair conformation.

Bromination of (I; R=H) under kinetic or thermodynamically controlled conditions gave the 2α-bromo-derivative (I; R=Br) in which the halogen is clearly axially oriented (ν_{max} 1706 cm.$^{-1}$, λ_{max} 313 mμ) and ring A has a classical boat conformation[2] with C-3–C-10 at the stem and stern positions. In (I; R=H) and (I; R=Br) the C-19 methyl signal occurs at τ 9·24 and 9·25, respectively, the high-field shift being due to the C-19 methyl lying in the shielding cone of the carbonyl group.[3]

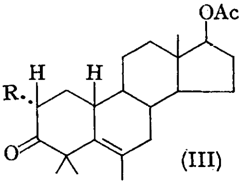
17β-Acetoxy-4,4,6-trimethylandrost-5-en-3-one (II; R=H) and its 19-nor-analogue (III; R=H) have now been prepared. Thus, analogous to (I; R=H), (II; R=H) was obtained from 6α-androst-4-en-3-one and had ν_{max} 1703 cm.$^{-1}$ and λ_{max} 287 mμ, whilst (III; R=H) (ν_{max} 1710 cm.$^{-1}$, λ_{max} 290 mμ) was prepared as follows. 4,4-Dimethyl-19-norandrost-5-en-3-one was converted into the tetrahydropyranyl ketal (IV) which was transformed into 3,3-ethylenedioxy-17β-(2'ξ-tetrahydropyranyloxy)-4,4-dimethyl-5α-androstan-6α-ol (V) by the hydroboration procedure. The corresponding ketone (VI) regenerates the alcohol (V) with borohydride and is stable to base. Wolff–Kishner reduction of (VI) and subsequent removal of the protective groups gave 4,4-dimethyl-19-norandrostan-3-one,[4] thereby establishing the stereochemistry of the precursors. Treatment of (VI) with methyl-lithium followed by dehydration of the resultant tertiary alcohol gave 4,4-6-trimethyl-19-norandrost-5-en-3-one.



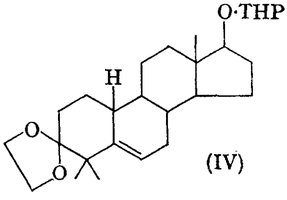
(I)



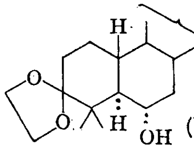
(II)



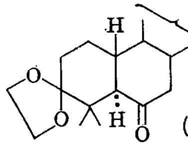
(III)



(IV)



(V)



(VI)

It is clear that in both (II; R=H) and (III; R=H) ring A exists in a boat conformation since in each ketone the non-bonded interactions between the C-4 and C-6 methyl groups are equivalent to those in (I; R=H). Further, in (III; R=H) the C-19 methyl signal occurs at high field (τ 9·24). Bromination of (II; R=H) and of (III; R=H) gave the corresponding 2α-bromo-derivatives in which spectroscopic evidence clearly shows that the halogen is axially oriented. Thus, (II; R=Br) has ν_{max} 1705 cm.$^{-1}$ and λ_{max} 316 mμ and (III; R=Br) has ν_{max} 1720 cm.$^{-1}$ and λ_{max} 316 mμ.

(I; R=H)	(I; R=Br)	(II; R=H)	(II; R=Br)	(III; R=H)	(III; R=Br)
+107°	+84°	+107°	+89°	+83°	+61°

The chemical shift (τ 9·22) of the C-19 methyl groups in (II; R=Br) and the identity of the couplings of the C-2 protons in (II; R=Br) with those[2] in (I; R=Br) clearly establish the structure of (II; R=Br). Although similar definitive evidence is not available from the n.m.r. spectrum it is clear that (III; R=Br) must be the 2α-bromo-derivative.

In the bromo-ketones (I; R=Br), (II; R=Br), and (III; R=Br), the halogen is in a negative octant and according to the axial halogeno-ketone rule[5] they should have negative Cotton effects. However, comparison of the amplitudes of the parent and bromo-ketones shows that in each case the bromo-ketones exhibit positive Cotton effects, similar to those of the parent ketones. Possible explanations of this will be discussed later.

All new compounds have the requisite spectral and analytical characteristics.

(*Received, December* 15*th*, 1966; *Com.* 999.)

---

[1] D. T. Cropp, B. B. Dewhurst, and J. S. E. Holker, *Chem. and Ind.*, 1961, 209.

[2] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, **1963**, 806.

[3] *Cf., e.g.*, B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J.-P. Pete, *Bull. Soc. Chim. France*, 1964, 3259.

[4] J. M. Midgley, W. B. Whalley, and (in part) G. F. Katekar and B. A. Lodge, *Chem. Comm.*, 1965, 169.

[5] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.*, 1957, **79**, 1506.