

The Conformation of 4,4-Dimethyl-steroids—an X-Ray Crystallographic Investigation

By G. FERGUSON,^{a,b} E. W. MACAULAY,^{b,c} J. M. MIDGLEY,^d J. M. ROBERTSON,^b and W. B. WHALLEY^{d*}

[^a Chemistry Department, University of Guelph, Guelph, Ontario, Canada (present address); ^b Chemistry Department, University of Glasgow, Glasgow W.2; ^c National Research Council, Ottawa 7, Ontario, Canada (present address); ^d The School of Pharmacy, The University, 29-39 Brunswick Square, London, W.C.1]

Summary Crystal structure analyses of the 17 β -iodoacetates of 17 β -hydroxy-4,4-dimethyl-19-nor- and of 17 β -hydroxy-4,4-dimethyl-androstan-3-one are reported.

THE conformation of ring A in 4,4-dimethyl-3-oxo-steroids has given rise to much discussion.¹ With the availability² of authentic 17 β -hydroxy-4,4-dimethyl-19-nor-5 α -androstan-3-one we now record a definitive contribution to this problem. Thus crystal structure analyses of the 17 β -iodoacetates of 17 β -hydroxy-4,4-dimethyl-5 α -androstan-3-one (I; R = Me) and of the 19-nor-analogue (I; R = H) were undertaken to obtain quantitative information about the distortion produced in ring A by the steric interaction of the axial methyl substituents at C-4 and C-10.

Crystallographic data are as follows: 17 β -Iodoacetoxy-4,4-dimethyl-5 α -androstan-3-one (I; R = Me), C₂₃H₃₅O₃I. Orthorhombic, $a = 14.96$, $b = 19.53$, $c = 7.47$ Å. Space group $P2_12_12_1$. $Z = 4$.

17 β -Iodoacetoxy-4,4-dimethyl-19-nor-5 α -androstan-3-one (I; R = H), C₂₂H₃₃O₃I. Orthorhombic, $a = 11.36$, $b = 25.43$, $c = 7.52$ Å. Space group $P2_12_12_1$. $Z = 4$.

For (I; R = Me) 2089 independent reflexions were measured with a Hilger Linear Diffractometer with Mo- K_{α} radiation. For (I; R = H), 1110 independent reflexions were obtained from a Picker four circle diffractometer using Mo- K_{α} radiation. Both structures were solved by way of the heavy atom and refined by least-squares methods. R is 0.046 for (I; R = H) and 0.14 for (I; R = Me). The lower R -factor for (I; R = H) is undoubtedly due to the improved data collection system used with (I; R = H) compared with that used with (I; R = Me). In the former case the crystal used was only irradiated when required by the computer-controlled diffractometer; with (I; R = Me) the crystal was continuously irradiated throughout the data collection period with some deterioration of the sample. Average e.s.d.s. for distances, angles, and torsional angles involving carbon atoms are respectively 0.020 Å, 0.9°, and 1.3° for (I; R = H), and 0.03 Å, 1.7°, and 2.5° for (I; R = Me).

Examination of molecular models suggests that the most likely deformation in (I; R = Me) would arise from rotation about the C-4-C-5 bond so as to increase the methyl separation. The extreme effect of such a rotation would be to change the conformation of ring A from the chair form to

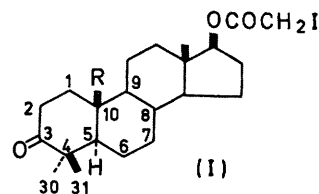
a boat. This extreme form may be rejected immediately on examination of the displacements of the atoms from the best planes through the atoms of ring A in both (I; R = Me) and (I; R = H) (Table 1). These displacements also suggest that ring A in (I; R = Me) is slightly flatter than in (I; R = H). The values of the CC-CC torsion angles (ϕ) in ring A in both steroids are in Table 2. The angles ϕ

TABLE 2.

Torsional angles ϕ (A-B). ϕ (A-B) is the dihedral angle about the A-B bond and the other two atoms required to define the angle are those bonded by A and B in the ring

Bond	(I; R = Me)	(I; R = H)
C-1-C-2	-50.8	-54.9
C-2-C-3	+48.5	+56.8
C-3-C-4	-47.0	-54.7
C-4-C-5	+46.6	+50.4
C-5-C-10	-50.8	-51.9
C-10-C-1	+52.6	+52.8

(5-10) and ϕ (10-1) compare very favourably in both, suggesting that the environment at C-10 is the same in these steroids and that the 1-3 interaction of the axial methyl groups at C-4 and C-10 is not relieved by displacement of C-19. The differences in the remaining torsion angles arise from rotation about the C-4-C-5 bond which results in a closing of the torsional angles in the more flexible portions of the ring.



Further evidence for the rotation about C-4-C-5 is found in (i) the reduction of the distance of C-3 from the plane defined by C-1-C-2-C-4-C-5 to 0.51 Å in (I; R = Me) as compared with 0.63 Å in (I; R = H), (ii) the increase in the methyl-methyl separation from the normal 1-3 transannular distance of 2.52 Å to 3.29 Å in (I; R = Me), (iii) the increase in the intramolecular distances C-31...C-2 and C-31...C-10 [3.25 Å and 3.40 Å, respectively, in (I; R = Me) compared with 3.08 Å and 3.21 Å, respectively, in (I; R = H)], and (iv) the difference in the values for the torsional angle ϕ [0(1)-3-4-30] which is 17.1° in (I; R = Me) and 2.9° in (I; R = H).

Displacement of the axial methyl group, C-31, in (I; R = Me) by such a mechanism as outlined above would lead to increased interaction between C-31 and the methylene group C-6 of ring B. This is overcome by distortion of the angle C-5-C-4-C-31 to 116.5° compared with 113.5° (in I; R = H) in such a manner as to increase the C-31-C-6

TABLE 1.

Displacements (Å) of the atoms of ring A from the best plane through them (a) in (I; R = Me) and (b) in (I; R = H)

Atom	(a)	(b)
C-1	0.215	0.215
C-2	-0.185	-0.227
C-3	0.176	0.234
C-4	-0.189	-0.231
C-5	0.220	0.215
C-10	-0.237	-0.216

distance to 3.29 Å (3.11 Å in I; R = H). Rings b and c adopt normal chair conformations.

A most striking and unexpected observation which demonstrates most clearly the reality of "conformational transmission"³ is that ring d adopts different conformations in the two compounds. Thus in (I; R = Me) it adopts a half-chair conformation which is distorted towards a C-13 envelope while in (I; R = H) it adopts a half-chair conformation distorted towards a C-14 envelope. These distortions are apparent in the displacements of C-13 and C-14 from the plane through C-15 C-16 C-17 [+ 0.339 Å and -0.427 Å, respectively, in (I; R = Me) and +0.451 Å and -0.302 Å, respectively, in (I; R = H)].

The skeleton of the perhydrophenanthrene skeleton in

both molecules is slightly convex towards the β -side and reflects the molecular overcrowding arising from the β -methyl substituents.

Although the conformation of the steroids in solution need not necessarily be identical with that exhibited in the crystal state, general considerations, together with the temperature-independence of the n.m.r. spectra of (I; R = Me) and (I; R = H), indicate with a very high degree of probability, that the conformation of (I; R = Me) and of (I; R = H) in solution is the same as, or at least very similar to, the conformations obtained in the crystal. The implications of these observations will be discussed in detail elsewhere.

(Received, May 5th, 1970; Com. 678.)

¹ D. L. Robinson and D. W. Theobald, *Quart. Rev.*, 1967, **21**, 314.

² J. M. Midgley, W. B. Whalley, and (in part) G. F. Katekar, and B. A. Lodge, *Chem. Comm.*, 1965, 169.

³ D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1960, 1297.