150.   *An Investigation by Proton Magnetic Resonance of the Conformation of Ring* A *in Some 2-Bromo-3-oxo-steroids.*

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From the coupling constants between the 1- and the 2-protons observed in the proton magnetic resonance spectra of five 2-bromo-3-oxo-steroids (I), (II), (IV), (VI), and (VII) the conformations of ring A are deduced by application of the Karplus equation. The values of the Karplus coefficients calculated for the $\cdot CO\cdot CHBr\cdot CH_2\cdot C\lessgtr$ fragment are 12·4 and 14·3 c./sec. Large variations in the 2-proton chemical shifts are observed and a possible explanation of these is given in terms of 1,3-diaxial interactions.

ONE of the most significant new advances in proton magnetic resonance spectroscopy has been the determination of conformations in cyclic systems by use of the relation derived theoretically by Karplus: [1]

$$J = k_1 \cos^2 \phi - c; \qquad 0° \leqslant \phi \leqslant 90°$$
$$J = k_2 \cos^2 \phi - c; \qquad 90° \leqslant \phi \leqslant 180° \qquad \Big\} \qquad (1)$$

in which the coupling constant (J) of a $\gtrless CH–CH\lessgtr$ fragment is related to the dihedral angle (ϕ) between the relevant CH bonds. Although this relation has been verified experimentally by a number of investigators [2-4] it has been shown that the theoretically derived values for the coefficients k_1, k_2, and c (8·5, 9·5, and 0·28 c./sec., respectively) should be replaced by other values which vary with the nature of the substituents on the $\gtrless CH–CH\lessgtr$ fragment.[2,3,5-8] It is found experimentally that k_1 and k_2 vary from approximately 8 to 16 c./sec., with k_2 always the greater, while the only accurate determination [3] of c, so far, gives a value of 0. On the assumptions that chemically similar $\gtrless CH–CH\lessgtr$ fragments in different molecules give identical values of k_1 and k_2 and, further, that c always approximates to zero, it is possible to determine values for k_1, k_2 and the dihedral angle ϕ. This technique has been widely used in studying the conformations of both five-[2,3,9] and six-membered [7,8] rings.

(I: X = Br, Y = H)
(II: X = H, Y = Br)

(III: R = X = H)
(IV: R = H, X = Br)
(V: R = Me, X = H)
(VI: R = Me, X = Br)

(VII)
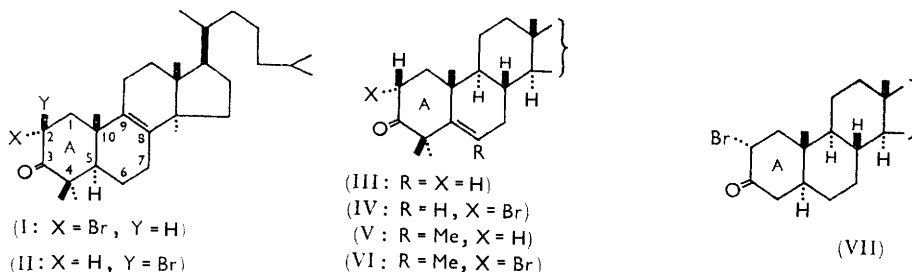
It seemed to us that application of this method to steroidal α-bromo-ketones would be valuable since (a) it would provide a check on conformational deductions made by other methods, and (b) accurate values of the parameters k_1 and k_2 for the fragment

[1] Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[2] Abraham and McLauchlan, *Mol. Phys.*, 1962, **5**, 195.
[3] Abraham and McLauchlan, *Mol. Phys.*, 1962, **5**, 513.
[4] Conroy, " Advances in Organic Chemistry," Interscience, Publ., Inc., New York, 1960, Vol. II, p. 311.
[5] Lemieux, Kullnig, Bernstein, and Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6098.
[6] Sheppard and Turner, *Proc. Roy. Soc.*, 1959, *A*, **252**, 506.
[7] Musher, *J. Chem. Phys.*, 1961, **34**, 594.
[8] Williamson and Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623.
[9] Abraham, Hall, Hough, and McLauchlan, *J.*, 1962, 3699.

–CO·CHBr·CH₂·C⤚ could be determined and subsequently applied to α-bromo-ketones of unknown conformation.

The methods which have been used previously to determine conformation in steroidal α-bromo-ketones have been essentially of two types. In the first a study of the chemistry of the compound has led to the configuration of the halogen atom,[10] and infrared [11] and ultraviolet [12] spectral studies have indicated its axial or equatorial nature. Hence the conformation of the carbonyl-containing ring has been deduced. In this way the structures of 2α- and 2β-bromolanost-8-en-3-one (I) and (II) and their saturated analogues have been demonstrated. Since in all four compounds the halogen is equatorial, it can be deduced that ring A has chair conformations in the two 2α-bromo-compounds and boat conformations in the two 2β-bromo-compounds.[13] The second method used to determine both configurations and conformations of α-bromo-ketones depends on the application of the axial halogeno-ketone rule,[14] or more general octant rule,[15] to the optical rotatory dispersion curves of the compounds. By this method the kinetically controlled bromination product from 2α-methylcholestan-3-one has been shown to be the 2α-bromo-2β-methyl compound in which ring A has a boat conformation.[16] A combination of the two methods has been used [17] to show that the bromination product from 4,4-dimethylcholest-5-en-3-one (III) is the 2α-bromo-isomer (IV) in which the halogen is axial in a boat ring A. By application of the proton magnetic resonance method it was hoped to define more closely the shape of the flexible boat conformation in some of the above compounds, and also to obtain evidence of any conformational distortion in the compounds examined.

EXPERIMENTAL

2α- and 2β-Bromolanost-8-en-3-one [13] (I) and (II), 2α-bromo-4,4-dimethylcholest-5-en-3-one [17] (IV), and 2α-bromocholestan-3-one [10] (VII) were prepared as described in the literature. 4,4,6-Trimethylcholest-5-en-3-one (V) was prepared [13] by methylation of 6α-methylcholest-4-en-3-one [19] with methyl iodide and potassium t-butoxide under the usual conditions.[20] Direct bromination of this ketone, or bromination of its enol acetate under kinetically controlled conditions, as described by Villotti, Ringold, and Djerassi,[21] gave the same monobromo-derivative.[18]

The proton magnetic resonance spectra of these bromo-steroids were measured with a Varian A60 spectrometer for solutions (*ca.* 200 mg./ml.) in deuterochloroform. Tetramethylsilane was used as the internal reference and chemical shifts (see Table 1) are given on the τ scale.

The 2-proton and those of the 1-methylene group in the bromo-ketones gave rise to ABX-type spectra.[22] In all spectra, quartet patterns at 4·9—5·7 and *ca.* 7·3 τ were attributed to the X proton at position 2 and one of those at position 1, respectively, providing enough information for a complete analysis of the ABX spectrum. Further, in compounds (II), (IV) and (VI) at least three lines due to the other 1-proton could be picked out from the large signal due to the remaining ring protons, giving a more refined basis for the spectral analysis. The normal procedure [22] permitted full analysis of the spectra in a straightforward way, proton B being defined as the high-field part of the AB pair. The results given in Table 1 are estimated to be accurate to ±0·1 c./sec. for compounds (II), (IV), and (VI) and ±0·2 c./sec. for (I) and

[10] Fieser and Ettorre, *J. Amer. Chem. Soc.*, 1953, **75**, 1700; Fieser and Dominguez, *ibid.*, p. 1704; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837.
[11] Jones, Ramsey, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[12] Cookson, *J.*, 1954, 282.
[13] Barton, Lewis, and McGhie, *J.*, 1957, 2907.
[14] Djerassi and Klyne, *J. Amer. Chem. Soc.*, 1957, **79**, 1506.
[15] Moffitt, Woodward, Moscowitz, Klyne, and Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[16] Djerassi, Finch, Cookson, and Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488.
[17] Cropp, Dewhurst, and Holker, *Chem. and Ind.*, 1961, 209; Dewhurst, Holker, Leblache-Combier, and Levisalles, *ibid.*, p. 1667.
[18] Holker and Leeming, unpublished work.
[19] Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 5362.
[20] Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1132.
[21] Villotti, Ringold, and Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5693.
[22] Bernstein, Pople, and Schneider, *Canad. J. Chem.*, 1957, **35**, 65.

TABLE 1.

Chemical shifts and coupling constants in the proton magnetic resonance spectra of some 2-bromo-3-oxo-steroids.

	τ values of protons at			Coupling constants (c./sec.)		
	posn. 2	posn. 1 (α, β)				
Compound	X	A	B	J_{AX}	J_{BX}	J_{AB}
2α-Bromolanost-8-en-3-one [13] (I)	4·88	7·32	—	5·7	13·4	13·1
2β-Bromolanost-8-en-3-one [13] (II)	4·92	7·26	7·81	11·1	8·1	13·4
2α-Bromo-4,4-dimethylcholest-5-en-3-one [17] (IV) ...	5·46	7·33	7·93	7·6	12·4	13·6
2α-Bromo-4,4,6-trimethylcholest-5-en-3-one [18] (VI)	5·63	7·34	7·93	8·0	12·4	13·6
2α-Bromocholestan-3-one [10] (VII)	5·30	7·31	—	6·0	13·2	13·0

(VII). In these compounds the first-order splittings are within 0·2 c./sec. of the actual coupling constants, but it must be emphasised that such splittings may be considerably in error for other types of $>$CH–CH$_2$– fragment, in which the chemical shift difference between the A and the B proton may be much smaller.

RESULTS AND DISCUSSION

The basic assumption made in the following discussion is that the compounds examined exist in one conformation in which the dihedral angle between the *gem*-protons of the 1-methylene group is 120°. The self-consistency of the results obtained supports the assumption. On this basis equations (1) reduce to

$$\left. \begin{array}{l} J_1 = k_1 \cos^2 \phi \\ J_2 = k_2 \cos^2 (120° \pm \phi) \end{array} \right\} \qquad (2)$$

where J_1 and J_2 are the coupling constants between the 2-proton and the two 1-protons, respectively. Further, if the bromine atom at position 2 lies between the 1-protons, the second of these equations will have a positive sign, *i.e.*, the angle will be greater than 120°, whereas if the 2-proton lies between the 1-protons the equation will have the negative sign, *i.e.*, the angle will be smaller than 120°. The known range of values of the coefficients k_1 and k_2 and the shape of the cos$^2 \phi$ curve show that when J_1 and J_2 are large, *i.e.*, greater than 5·5 c./sec., then the angles must be ϕ and $(120° + \phi)$. Table 1 shows that this applies for all the compounds examined.

Even this type of semi-quantitative approach can give valuable information. Thus, the spectrum of the bromination product derived from 4,4,6-trimethylcholest-5-en-3-one (V) has the typical X-spectrum at 5·70 τ, indicating that the compound is a 2-bromo-derivative. The positions of the carbonyl band at 1706 cm.$^{-1}$ in the infrared spectrum and the R-band at 314 mμ in the ultraviolet spectrum show that the compound contains axial bromine and is thus either the 2α-bromo-derivative (VI) with a boat ring A or the 2β-bromo-derivative with a chair ring A. Since on the above basis the dihedral angles between the 1-methylene and the 2-hydrogen are ϕ and $(120° + \phi)$ the only possible structure is the 2α-bromo-derivative (VI) in which ring A has a boat conformation. Confirmation is provided by the similarity between the coupling constants and chemical shifts of the 1- and the 2-protons in this compound and those of 2α-bromo-4,4-dimethylcholest-5-en-3-one (IV) in which the boat conformation of ring A is known to be present.[17]

Before equations (2) can be applied quantitatively to the observed coupling constants, it is necessary to assign peaks A and B in the spectra to the α- and the β-proton at position 1, since the two possible assignments will give, in general, different values of the coefficients (k_1, k_2) and the dihedral angles. For 2α-bromolanost-8-en-3-one (I) and 2α-bromo-cholestan-3-one (VII) this assignment may be obtained directly, since it is known that in both these compounds ring A has a chair conformation in which the bromine is equatorial. Thus the dihedral angles between the 2-proton and the 1α- and 1β-proton approximate to 180° and 60°, respectively. Consequently the 1α-proton has the larger coupling constant

with the 2-proton and is therefore assigned to peak B. It should be noted that the dihedral angles would have to decrease to less than 150° and 30° before the alternative assignment would be possible. As this is very unlikely, equations (2) for the above two compounds can be written

$$\left.\begin{array}{l} J_{AX} = k_1 \cos^2 \phi \\ J_{BX} = k_2 \cos^2 (120° + \phi) \end{array}\right\} \tag{3}$$

The remaining three compounds in the series are known to have flexible boat conformations of ring A in which no unique assignments of peaks A and B can be made. Combination of the two possible assignments for compounds (II), (IV), and (VI) with equations (3) give a total of eight theoretically possible sets of values for k_1, k_2, and the dihedral angles. These can immediately be reduced to four since the very close similarity between the spectra of compounds (IV) and (VI) is obviously due to almost identical conformations of ring A with the same assignments of peaks A and B. In evaluating the four sets of values it is found that only one is compatible with all the observed coupling constants and so a unique solution results. The values of the dihedral angles so obtained are summarised in Table 2.

An examination of the values for the dihedral angles in 2α-bromocholestan-3-one (VII) gives some measure of the validity of the calculations. Thus, it would be expected that the chair conformation of ring A in this compound would be relatively undistorted since 1,3-diaxial interactions are at a minimum. Hence the dihedral angles measured in Dreiding models should give a close approximation to the true values for the compound. In fact, the angles observed from models are closely similar to those obtained in the above calculations, the departure from the cyclohexane values of 180° and 60° being of the right order for a fused cyclohexanone ring. It is interesting that the coupling constants, and hence dihedral angles, for 2α-bromolanost-8-en-3-one (I) are closely similar to those for

TABLE 2.

Values of dihedral angles between the 2-proton and the 1-protons in some
2-bromo-3-oxo-steroids.

$(k_1 = 12{\cdot}4 \pm 0{\cdot}5; \ k_2 = 14{\cdot}3 \pm 0{\cdot}5)$.

	Assignment		Dihedral angles * between 2-proton and	
Compound	A	B	1 α-proton	1 β-proton
2α-Bromolanost-8-en-3-one (I)	β	α	167°	47°
2β-Bromolanost-8-en-3-one (II)	α	β	19	139
2α-Bromo-4,4-dimethylcholest-5-en-3-one (IV) ....} 2α-Bromo-4,4,6-trimethylcholest-5-en-3-one (VI) ...... }	β	α	157·5	37·5
2α-Bromocholestan-3-one (VII)	β	α	166	46

* The dihedral angles are estimated to be correct within $\pm 2{\cdot}0°$.

the unmethylated 2α-bromocholestan-3-one (VII). It thus appears that steric repulsion between the axial methyl substituents in compound (I) has little effect on the dihedral angles between the protons at positions 1 and 2. A study of models suggests that some separation of axial 4- and 10-substituents can be accommodated without significant change in these angles. This seems particularly significant in view of the various conformations of ring A which have been suggested by different groups of workers for the unbrominated 4,4-dimethyl-3-oxo-steroids and 3-oxo-triterpenoids.[23]

For 2β-bromolanost-8-en-3-one (II) the dihedral angles show that ring A has a conformation intermediate between the classical boat forms with $C_{(2)}$–$C_{(5)}$ and $C_{(3)}$–$C_{(10)}$ at the stem–stern positions, but nearer to the latter. This is in keeping with the greater destabilising interactions in the former classical boat conformation. For 2α-bromo-4,4-dimethyl-cholest-5-en-3-one (IV) and its 6-methyl homologue (VI) the dihedral angles are identical,

[23] Allinger and Da Rooge, *Tetrahedron Letters*, 1961, 676; Lehn, Levisalles, and Ourisson, *ibid.*, 1961, 682; Holker and Whalley, *Proc. Chem. Soc.*, 1961, 464.

indicating that rings A have the same conformations, quite close to classical boats with $C_{(3)}$–$C_{(10)}$ at the stem–stern positions. For compound (VI) this is the expected conformation since maximum separation of about 2·9 Å then occurs between the 4- and 6-methyl groups. In any other conformation the 6-methyl group would be closer to one or other of the two 4-methyl groups and it seems unlikely that this type of high-energy interaction could occur. For compound (IV), where there is no equivalent interaction, it is perhaps surprising that the conformation of ring A is nearer to the classical boat than to an extended boat intermediate between the classical conformations with $C_{(2)}$–$C_{(5)}$ and $C_{(3)}$–$C_{(10)}$ at the stem–stern positions.

The values of k_1 and k_2 obtained above (Table 2) for the –CO·CHBr·CH$_2$·C$\lessgtr$ fragment are closely similar to those found for other fragments, *e.g.*, k_1 10·5 and k_2 13·7 c./sec. for the –NH$_2^+$·CH(CO$_2^-$)·CH$_2$·C$\lessgtr$ fragment in the proline ring,[3] and k_1 10 and k_2 16 c./sec. as less precise values based on first-order splittings for the –CO·CH(OAc)·CH$_2$·C$\lessgtr$ fragment in 2-acetoxy-3-oxo-steroids.[8] As yet there are insufficient examples known to determine the effect of molecular environment on these coefficients.

Finally, it is of interest to consider the values of the chemical shifts for the compounds listed in Table 1. The τ-values of the 1-protons are remarkably consistent, particularly in view of the wide divergence of conformations in the various compounds. In 2α-bromo-lanost-8-en-3-one (I), 2α-bromo-4,4-dimethylcholest-5-en-3-one (IV), its 6-methyl homo-logue (VI), and 2α-bromocholestan-3-one (VII) the equatorial 1-proton occurs at lower field than the axial proton, in keeping with the usual rule.[24a] In compound (II), where an extended boat conformation occurs, the terms equatorial and axial have no real meaning and so the rule cannot be applied. Under these conditions it is surprising that the τ values for the 1-protons in this compound should be identical with those for the other compounds.

The chemical shifts of the 2-proton in the compounds studied show large and perplexing variations. At first sight this might be expected to be due to the proximity of this proton to the ketonic 3-carbonyl group as this is diamagnetically anisotropic [24b] and has a large dipole moment.[25] However, neither of these properties explains the observed effects. This can be seen by comparing 2α-bromolanost-8-en-3-one (I) and 2α-bromocholestan-3-one (VII) which show a difference of 0·4 p.p.m. in the 2-proton chemical shift despite having closely similar conformations and correspondingly similar spatial relations of the carbonyl groups and ring protons. The only differences between these compounds are the presence of an 8,9-double bond and 4,4-dimethyl groups in compound (I). Since the double bond is approximately 6 Å away from the 2-proton it is unlikely that the diamagnetic anisotropy of this bond will affect the 2-proton. Thus, it appears that the presence of two methyl groups at position 4 in compound (I) deshields the 2-proton by 0·4 p.p.m. The only long-range mechanism so far used to explain such effects is that arising from the magnetic anisotropy of carbon–carbon single bonds. This has been proposed to explain the difference in the chemical shifts of the axial and equatorial protons in cyclohexane.[24a] The mechanism does not explain the above result as it predicts a low field shift of the 2-proton in compound (I) compared with (VII) of only 0·08 p.p.m. (if we use the values $-5·5 \times 10^{-30}$ cm.^{3}/molecule for the anisotropy of the carbon–carbon single bond [26] and 2·8 Å for the separation of the axial proton from the centre of the nearer C–CH$_3$ bond, as deduced from Dreiding models).

Recently, a further type of interaction, affecting proton chemical shifts in gases, has been proposed.[27] This is due to van der Waals forces in any molecule. Such forces, which can be regarded as fluctuating dipoles, affect a neighbouring molecule by expanding its electron cloud which, in turn, produces a decrease in the shielding of any attached

[24] Jackman, " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959, (*a*) p. 116, (*b*) p. 124.
[25] Buckingham, *Canad. J. Chem.*, 1960, **38**, 300.
[26] Bothner-By and Naar-Colin, *Ann. New York Acad. Sci.*, 1958, **70**, 833.
[27] Raynes, Buckingham, and Bernstein, *J. Chem. Phys.*, 1962, **36**, 3481.

protons. The effect of these fluctuating dipoles on the chemical shift of a proton in a molecule r Å away is given by

$$\sigma_{\mathrm{w}} = -3B\alpha I/r^6, \tag{4}$$

where α and I are the polarisibility and ionisation energy of the perturbing molecule, and B is an experimentally determined constant.

An extension of this equation to effects within a single molecule may be possible. Thus, in the case of compound (I) the effect of the 4β-methyl group on the 2β-proton can be calculated by considering this methyl group as similar to methane for which $\alpha = 2\cdot60 \times 10^{-24}$ cm.$^{-1}$ and $I = 20\cdot8 \times 10^{-12}$ erg. With $B = 1\cdot0 \times 10^{-18}$ e.s.u. and r in Å, equation (4) reduces to

$$\sigma_{\mathrm{w}} = -163/r^6 \text{ (p.p.m.).} \tag{5}$$

Dreiding models indicate that the separation of the 4β-methyl group and the 2-proton is 2·9 Å. Substituting this value in equation (5) we find $\sigma_{\mathrm{w}} = -0\cdot27$ p.p.m. In view of the assumptions involved in extending equation (4) to groups within a molecule and the experimental uncertainty in the values of the parameters this is reasonably good agreement with the experimental value of 0·4 p.p.m. Although the extent of the agreement may be fortuitous, this calculation does show that the mechanism can account satisfactorily for the observed effect and, in the general case, could give rise to appreciable chemical-shift differences. It is obvious, however, that in these compounds there must be other complex effects operating. Thus, for example, in compound (VI) the presence of a methyl group five bonds away from the 2-proton gives a chemical shift difference of 0·17 p.p.m. when compared with compound (IV) which has an identical conformation of ring A.