Studies on Steroids. Part 41.[1] Conformational Analysis of Steroidal Side Chains by Proton Magnetic Resonance Spectroscopy

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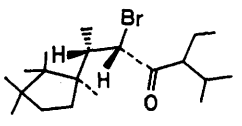
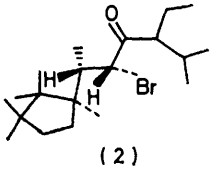
^{1}H N.m.r. spectra of the substituted side chains of a series of steroids (1)—(8) over the temperature range −50 to +60 °C support the presence of the predicted conformers, showing that parallel 1,3-interactions are important factors in determining conformation. The conformations of the side chains of some naturally occurring 22-substituted steroids are discussed.

A RECENT assumption that the rotation of the steroidal side chain is restricted is supported by several types of data, *e.g.* spin–lattice relaxation times (T_1) of side-chain carbon atoms of cholesteryl chloride [2] and cholesterol,[3] large Cotton effects in c.d. spectra due to side-chain



(1)



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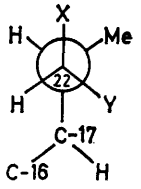

(I) X = Br, Y = C-23
(II) X = C-23 Y = Br

chromophores,[4-6] and the stereoselectivity of reactions at the 22,23-double bond.[5,7,8] The nature of the predominant conformer of a substituted side chain might therefore be predicted from an assumption that this was controlled by parallel 1,3-interaction of bulky groups.[9]

^{1}H N.m.r. and c.d. spectra of 22-bromo-23-oxo- [(1) and (2)], 23-bromo-22-oxo- [(3) and (4)], and 22(23)-bromo-23(22)-acetoxy-stigmastan-3-ones [(5)—(8)] [5] have indicated the possibility of one conformer being predominant in each compound. An attempt has now been made to analyse qualitatively the side-chain conformations by observing the temperature dependence of vicinal coupling constants.[10]

The vicinal 20,22-coupling constants of compounds (1) and (2) (Table) are indicative of a *gauche* conformation and are independent of sample temperature. On the other hand, the observed 17,20-coupling constants (9.8 and 9.9 Hz) of compounds (3) and (4), respectively, are consistent with an antiparallel relationship of these protons, as shown by *X*-ray crystallographic analysis.[11]

Vicinal coupling constants for the side chains of stigmastan-3-one derivatives (J/Hz) *

Temp (°C):	−50	−30	0	30	60
$J_{20.22}$					
(22*S*)-22-Bromo-23-oxo (1)	2.9	2.9	3.0	3.0	3.0
(22*R*)-22-Bromo-23-oxo (2)			1.4	1.4	1.4
$J_{23.24}$					
(23*S*)-23-Bromo-22-oxo- (3)	10.1	9.7	9.2	8.9	8.3
(23*R*)-23-Bromo-22-oxo- (4)	2.0	2.2	2.5	2.8	3.1
$J_{22.23}$					
(22*S*,23*R*)-23-Acetoxy-22-bromo- (5) [a]	9.9	9.9	9.8	9.8	9.8
(22*S*,23*R*)-22-Acetoxy-23-bromo- (6) [b]	8.9	8.7	8.7	8.7	8.7
$J_{22.23}$					
(22*R*,23*S*)-23-Acetoxy-22-bromo- (7) [c]	9.8	10.1	10.1	10.1	10.1
(22*R*,23*S*)-22-Acetoxy-23-bromo- (8) [d]	10.1	10.3	10.4	10.5	10.5

* A JEOL FX-60 (15.3 MHz) FT instrument with a temperature variation system attached was used. Temperatures above 0 °C were determined by using an ethylene glycol standard and temperatures below 0 °C with a methanol standard. Steroid concentrations were *ca.* 0.1—0.2M in $CDCl_3$. Me_4Si was used as internal standard.

[a] $J_{20,22}$ 1.9, $J_{23.24}$ 1.5 (at 25 °C). [b] $J_{20,22}$ 1.5, $J_{23.24}$ 1.4 (at 25 °C). [c] $J_{20.22}$ <1.0, $J_{23.24}$ 1.7 (at 25 °C). [d] $J_{20.22}$ <1.0, $J_{23.24}$ 1.5 (at 25 °C).

The establishment of the antiparallel relationship between H-17 and H-20 enables us to predict the most stable conformer [(I) or (II)] for compounds (1) and (2), which avoids parallel 1,3-interaction between C-22 substituents and the C-16 methylene group.

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[5] M. Nakane, M. Morisaki, and N. Ikekawa, *Tetrahedron*, 1975, **31**, 2755.
[6] T. C. McMorris, R. Seshadri, and T. Arunachalam, *J. Org. Chem.*, 1974, **39**, 669.
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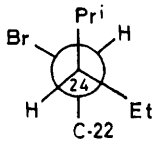
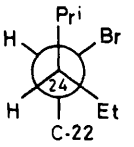
[8] D. H. R. Barton, J. P. Poyser, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 53.
[9] N. L. Allinger and E. L. Eliel, 'Conformational Analysis,' Wiley, New York, 1965.
[10] L. M. Jackman, 'Nuclear Magnetic Resonance Spectroscopy,' Pergamon, London, 1969.
[11] J. Fridrichsons and A. M. Mathieson, *J. Chem. Soc.*, 1953, 2159; D. C. Hodgkin, M. S. Webster, and J. D. Dunitz, *Chem. and Ind.*, 1957, 1148; J. K. Fawecett and J. Trotter, *J. Chem. Soc. (B)*, 1966, 174; J. F. Griffin, M. G. Erman, W. L. Daux, D. S. Watt, and F. A. Carey, *J. Org. Chem.*, 1975, **40**, 2956; T. Akiyama, D. Pedder, and J. V. Silverton, *ibid.*, p. 3765.

The stable conformers of compounds (3) and (4) can be drawn as (III) and (IV) [or (V)], respectively, on the basis of the temperature dependent 23,24-coupling constants.



(III)



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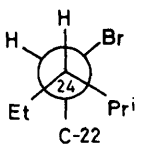

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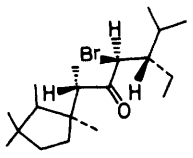

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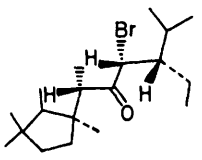
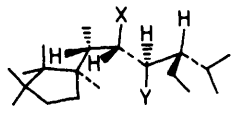


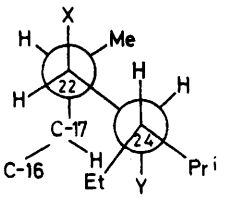
(4)

The stabilities may not be markedly different from those of other possible conformers, since the vicinal coupling constants are temperature dependent.

The conformations of the side chains of the four bromo-



(5) X = Br, Y = OAc
(6) X = OAc, Y = Br
(5′) X = Br, Y = OH
(6′) X = OH, Y = Br



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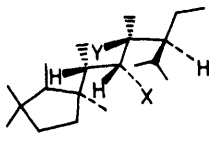
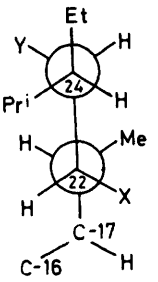


(7) X = Br, Y = OAc
(8) X = OAc, Y = Br
(7′) X = Br, Y = OH
(8′) X = OH, Y = Br



(VII)

acetoxy-compounds (5)—(8) can be represented in two sets, (VI) and (VII), from the vicinal 20,22-, 22,23-, and 23,24-coupling constants and also from the results for compounds (1)—(4).

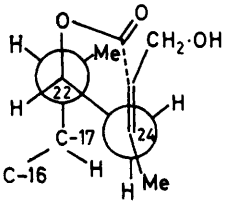
* With acetic anhydride–pyridine at room temperature for 10 days, compound (5′) gave the 22*R*,23*R*-epoxide and starting material. However, treatment with isopropenyl acetate and toluene-*p*-sulphonic acid at room temperature for a week gave the acetate (5).

[12] K. Nakanishi, 'Chemistry of Natural Products,' vol. 7, Butterworths, London, 1970, p. 167.

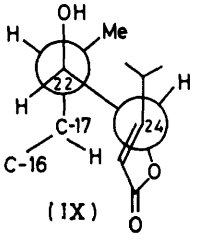
[13] D. Lavie, E. Glotter, and Y. Shvo, *J. Chem. Soc.*, 1965, 7517; I. Kirson, D. Lavie, S. S. Subramanian, P. D. Sethi, and E. Glotter, *J.C.S. Perkin I*, 1972, 2109; I. Kirson, E. Glotter, D. Lavie, and A. Abraham, *ibid.*, 1971, 2032.

The strong resistance of the bromohydrin (5′) towards acetylation under conditions that readily afforded compounds (6)—(7) from (6′)—(8′), respectively, can be attributed to a parallel 1,3-interaction of C-17 with the 23-hydroxy-group.*

The most important conclusion from our results is that the stable conformation about the 20,22-bond in 22-substituted steroids is that which avoids a parallel 1,3-interaction between C-22 substituents and the C-16 methylene group. The application of this result to naturally occurring 22-substituted steroids, such as ecdysones,[12] withanolides,[13] and antheridiol,[14] leads to the assignment of conformations (X; X = OH), (VIII), and (IX), respectively, to these compounds. These steroids all have the β_F-configuration at C-22. The



(VIII)



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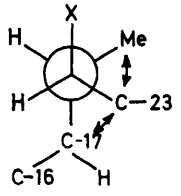
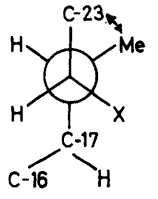


(X)



(XI)

structures of α-ecdysone [15] and withaferin A,[16] determined by *X*-ray crystallography, are consistent with these conformations. In the case of antheridiol, McMorris *et al.*[17] have reported a small vicinal 20,22-coupling constant and a torsion angle of 180° between C(22)–H and C(23)–H. These data are in good agreement with those expected of the conformer (IX) for this substance.

Recently, Letourneux *et al.*[18] have observed a marked difference in the C-23 chemical shifts between 22-epimers in the ^{13}C n.m.r. spectra of cholesterol derivatives. In every case the C-23 chemical shift of the 22*R*-series was 5—7 p.p.m. to higher field than that of the 22*S*-series. This observation may be explained in terms of our results. The predominant conformers about the C(20)–C(22) bond in 22*R*- and 22*S*-substituted cholesterols can be drawn as (X) and (XI), respectively. In the *R*-series there is one additional *gauche* interaction between C-23

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[18] Y. Letourneux, Q. Khuong-Huu, M. Gut, and G. Lukacs, *J. Org. Chem.*, 1975, **40**, 1674.

and the C-17 methylene group, which may cause the *ca.* 6 p.p.m. upfield [19] shift in comparison with the *S*-series.

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