Tetrahedron Letters No. 10, pp. 623-628, 1963. Pergamon Press Ltd.
Printed in Great Britain.

AN NMR STUDY OF THE STEREOCHEMISTRY OF SOME STEROIDAL 4,5-EPOXY DERIVATIVES

D.J. Collins and J.J. Hobbs,
Research Laboratory, Royal Hospital for Women, Paddington, New South Wales
and S. Sternhell,
Division of Coal Research, C.S.I.R.O., P.O. Box 175, Chatswood, New South Wales

(Received 17 January 1963)

IN connection with another project[1] a simple means of defining the epoxide stereochemistry in some 3-substituted 4,5-epoxysteroids was required. The configuration of a 4,5-epoxide group can be determined chemically by its reduction with lithium aluminium hydride to a 5α- or 5β-hydroxysteroid, the stereochemistry of the 5-hydroxyl group being the same as that of the original 4,5-epoxide[2]. Since the work involved the preparation of 6-halogenated 4,5-epoxysteroids, complications[3] could be expected in their reduction with lithium aluminium hydride. It also seemed likely that the vicinal effect of a bulky 6α- or 6β-halogen atom might render the method of molecular rotation differences inconclusive; therefore consideration

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[1] D.J. Collins and J.J. Hobbs, unpublished work.

[2] Pl.A. Plattner, H. Heusser and A.B. Kulkarni, Helv.Chim.Acta 31, 1885 (1948).

[3] For example, the possible participation of the 6α-halogen in the reduction of a 6α-halo-4β,5β-epoxide to give a 5β,6β-epoxide intermediate, which would be further reduced to a 6β-hydroxysteroid.

was given to the application of NMR spectroscopy to the solution of this problem. The presence of a substituent on C_3 and the quaternary nature of C_5 enable the spin-spin coupling between H_4 and H_3 to be easily observed, and as the magnitude of the coupling constant between hydrogen atoms bound to vicinal carbon atoms is simply related to the dihedral angle[4,5] the relative stereochemistry of the 4,5-epoxide and the 3-substituent can be determined.

A recent report by Cross[6] on the determination of the stereochemistry of steroidal 5,6-epoxides by NMR spectroscopy prompts us to record our NMR data (Table 1) for a series of stereoisomeric 4,5-epoxycholestan-3-ols and a useful correlation which emerges from them. Examination of Table 1 shows that *the 4-proton in cis[7]4,5-epoxy-3-alcohols appears as a doublet while in the trans[7]4,5-epoxy-3-alcohols the 4-proton appears as a singlet*.

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[4] M. Karplus, *J.Chem.Phys.* **30**, 11 (1959).

[5] L.M. Jackman, "*Applications of N.M.R. Spectroscopy in Organic Chemistry*", p.87. Pergamon Press (1959).

[6] A.D. Cross, *J.Amer.Chem.Soc.* **84**, 3206 (1962).

[7] Relative configuration of the 3-hydroxyl (or derivative) to the 4,5-epoxide; i.e. 3-α-substituted-4α,5α-epoxides and 3-β-substituted-4β,5β-epoxides are *cis*, the remainder are *trans*.

Table 1. NMR data[8,9] on 4,5-epoxycholestane derivatives

Compound	Substituents			τ[10] (Multiplicity[11], J or W[12], c/s)			τ CH$_3$	
	C$_3$	4,5-epoxide	C$_6$	H$_3$	H$_4$	H$_6$	C$_{19}$	C$_{18}$
1	βOH	β	H	6.18(M)	7.03 (D,J=4.0	Obscured	9.09	9.33
2	βOAc	β	H	5.10(M)	7.01 (D,J=3.3)	Obscured	9.01	9.33
3	β OH	β	αBr	6.05(M)	6.32 (D,J=4.5)	5.50 (BM)	8.95	9.32
4	β OH	β	β Br	6.10(M)	6.71 (D,J=3.4)	6.10(M)	8.72	9.26
5	αOH	α	H	6.14(M)	6.95 (D,J=4.5)	Obscured	9.01	9.33
6	αOAc	α	H	5.0 (M)	6.96 (D,J=4.0)	Obscured	9.01	9.33
7	β OH	α	H	6.19(BM)	7.25 (S,W=2.2)	Obscured	8.90	9.32
8	β OAc	α	H	5.20(BM)	7.30 (S,W=2.2)	Obscured	8.92	9.31
9	β OH	α	αBr	6.08(BM)	6.63 (S,W=2.3)	5.50 (BM)	8.88	9.35
10	β OH	α	β Br	6.05(BM)	7.10 (S,W=2.1)	6.45 (M)	8.57	9.27
11	α OH	β	H	6.21(BM)	7.30 (S,W=2.5)	Obscured	9.05	9.33
12	α OH	β	α Br	6.05(BM)	6.63 (S,W=2.0)	5.50 (BM)	9.00	9.33
13	=O	β	H	-	7.22 (S,W=1.5)	Obscured	8.90	9.33
14	=O	α	H	-	7.15 (S,W=1.1)	Obscured	8.97	9.32
15	=O	β	α Br	-	6.57 (S,W=1.5)	5.45 (BM)	8.85	9.32
16	=O	α	α Br	-	6.50 (S,W=1.5)	5.45 (BM)	8.90	9.31
17	=O	α	β Br	-	6.94 (S,W=1.1)	6.39 (M)	8.62	9.25

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[8] Taken in dilute (less than 7%) solution in CCl_4 with tetramethylsilane as internal reference on a Varian A60 spectrometer. The τ values are believed to be accurate to within 0.03 p.p.m. and the J values to within 0.2 c/s. The latter are derived from first-order considerations only.

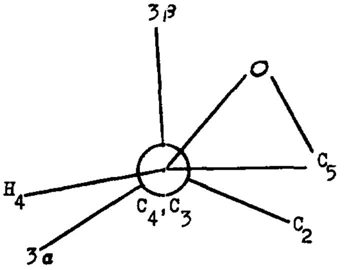
[9] All new compounds gave correct analyses and showed the expected spectral characteristics. They will be fully described elsewhere.

[10] With multiplets the centre of gravity was taken as the origin.

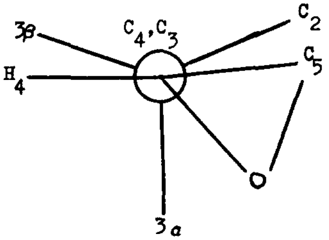
[11] S: singlet;D:doublet,M:Multiplet with W approximately 12 c/s; BM:multiplet with W approximately 20 c/s.

[12] W: half height width of singlets at maximum resolution. As oxygen was not excluded, the widths quoted are maximum values.

Assuming that the conformation of ring A in the α 4,5-epoxides is "cholestane-like" (1β-equatorial, 2β- axial) and that in the β 4,5-epoxides ring A is in a "caprostane-like" conformation (1β-axial, 2β-equatorial), and examination of Dreiding models shows the following approximate angular relationships:



β-epoxides



α-epoxides

Thus the empirical rule deduced from the results shown in table 1 is in agreement with the Karplus relation[4]. Conversely, assuming that the Karplus relation holds, the empirical rule deduced from the above results can be used to define the conformation of ring A in this series of compounds. An important corallary is that this rule will not hold if a stereochemical influence (such as perhaps, the presence of a bulky substituent in position 2) prevails, to alter the conformation of ring A.

Table 1 further shows that the presence of bromine in the 6-position does not alter the multiplicity of the signal attributed to H4 and hence it may be deduced that the conformation of ring A remains unaffected. No evidence could be detected of direct coupling between H4 and H6; this is to be expected from the known[13] coupling constants of simple epoxide systems.

The chemical shifts of H4 in the α-epoxides appear to be generally upfield from those of the β-epoxides by about 0.2 - 0.4 p.p.m. provided that

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[13] C.A. Reilly and J.D. Swalen, *J. Chem.Phys.* **35**, 1522 (1961)

the substitution pattern elsewhere remains unaltered. Even this limited correlation does not hold for 3-α hydroxy compounds 5 and 11 (Table 1) or for 3-ketones, some of which have also been examined (see Table 1). The chemical shift attributed to the C_{19} methyl in the α-epoxides is downfield compared with the corresponding signal in the β-epoxides - this correlation is reversed for the 3-ketones. However, owing to great variations with other substituents, stereochemical assignments based on chemical-shift differences appear to be less reliable than those based on coupling constants only, and the number of examples available did not warrant the calculation of additivity values[14,15] for the C_{19} methyl shifts.

The conformation assigned to ring A is supported in all cases (see Table 1) by the appearance of the signal assigned to H3, which is always much broader for axial than for equatorial hydrogens owing to large diaxial spin-spin coupling[16] with one of the hydrogens of the adjacent methylene at C2.

With 6-bromo-derivatives, the configuration of H6 can also be confirmed by the appearance of the NMR signals for compounds 15,16 and 17. With compounds 3 and 10, which have electronegative substituents at C_3 and C_6, the assignments in Table 1 are based on both appearance of the signals and their chemical shifts. With compounds 9 and 12, where both H3 and H6 are axial, and give rise to broad multiplets, only the relative values of the chemical shifts could be used for the assignment.

The signals attributed to C_{18} methyl in the spectra of 6-β-bromo-

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[14] J.N. Shoolery and M.T. Rogers, J.Amer.Chem.Soc. 80, 5121 (1958)

[15] R.F. Zurcher, Helv.Chim.Acta 44, 1380 (1961)

[16] L.M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry", p.117. Pergamon Press (1959)

derivatives are displaced by 0.05 - 0.07 p.p.m. and those attributed to the C_{19} methyl are displaced by 0.31 - 0.35 p.p.m. downfield in comparison with the analogous compounds not substituted at C_6. This displacement appears to be independent of the configuration of ring A; i.e. it is the same for both α- and β-4,5-epoxides.

Acknowledgements- That part of the investigation which was carried out at the Research Laboratory, Royal Hospital for Women, Paddington, New South Wales, was supported by a generous grant from an anonymous benefactor, and by the Benevolent Society of New South Wales. The authors are indebted to Mr. H.R. Brown, Chief, Division of Coal Research, C.S.I.R.O., for support and encouragement.