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# A PROTON MAGNETIC RESONANCE STUDY OF CARBOHYDRATE 2,3-EPOXIDES AND RELATED COMPOUNDS

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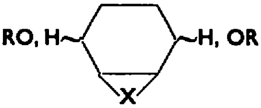
**Abstract**—The stereospecificity of certain vicinal coupling constants has been deduced from partial analyses of the PMR spectra of some 2,3-epoxide, -episulphide and -epimine derivatives of pyranosides. The spectra of these compounds also showed interesting solvent dependences associated with virtual spin-spin coupling.

THE stereospecificity of proton-proton coupling between vicinal hydrogens attached to $sp^3$-hybridized and to $sp^2$-hybridized systems is now well established.[1,2] However, apart from some values for steroidal epoxides[3–5] little data appeared to be available concerning the stereospecificity of the couplings of vicinal protons associated with "*epi*"-rings[6] where the precise hybridization is uncertain. Knowledge of such stereospecificity, if any, would clearly aid PMR configurational investigations of derivatives containing an *epi*-ring. A series of methyl 4,6-O-benzylidene-2,3-*epi*-α-D-mannopyranosides and the corresponding α-D-allopyranosides were available and seemed admirably suited to a study of proton coupling within the general system shown below. Accordingly their PMR spectra were



X = O, S, NH, NAc

measured and analysed.

## EXPERIMENTAL

The PMR spectra were measured on a Varian A60 spectrometer using tetramethylsilane as internal reference. Unless otherwise stated ethanol-free chloroform was used as solvent. Spectra were run at ca. 25° except for a few cases where low solubility necessitated a temp of ca. 55°.

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[1] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry.* Pergamon, London (1959), and Refs therein.

[2a] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959);

[b] *J. Amer. Chem. Soc.* **85**, 2870 (1963).

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

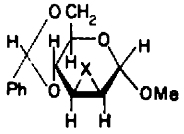
[4] D. J. Collins, J. J. Hobbs and S. Sternhell, *Tetrahedron Letters* 623 (1963).

[5] J. E. Page, G. F. H. Green and S. E. Staniforth, Private communication.

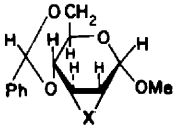
[6] The term "*epi*" is used herein whenever it is required to refer in a general sense to a 3-membered ring fused to another ring, two carbon atoms being common to each ring and the third atom of the *epi*-ring being either oxygen, sulphur or nitrogen.

The compounds included in this study had been prepared during the course of other investigations and their syntheses have been described elsewhere.

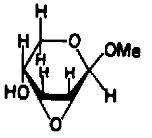
Methyl 2,3-acetylepimino-4,6-O-benzylidene-2,3-dideoxy-α-D-mannopyranoside (I)[7]
Methyl 2,3-acetylepimino-4,6-O-benzylidene-2,3-dideoxy-α-D-allopyranoside (II)[7]
Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-mannopyranoside (III)[7]
Methyl 4,6,O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside (IV)[7]
Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (V)[8]
Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (VI)[8]
Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epithio-α-D-allopyranoside (VII)[9]
Methyl 2,3-anhydro-β-D-ribopyranoside (VIII)[10]
Methyl 2,3-anhydro-4-O-methyl-β-L-ribopyranoside (IX)[10]
Cyclohexene Oxide (X)[11]
Cyclohexene sulphide (XI)[12]



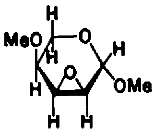
I, X = NAc
III, X = NH
V, X = O



II, X = NAc
IV, X = NH
VI, X = O
VII, X = S



VIII



IX

## DISCUSSION

Spectral assignments in this series of compounds gave the first order values shown in the Table. The N-acetyl-epimine compounds (I) and (III) can be discussed as typical of the D-*manno* and of the D-*allo* series respectively and their spectra are shown in Fig. 1. Common to both series of compounds and immediately assignable, were the singlets due to the phenyl, benzylidene-methine, methoxyl and N-acetyl protons. For the D-*manno*-isomer (I) the resonances of the ring hydrogens could only be assigned on the basis of a zero coupling between $H_1$, $H_2$ and between $H_3$, $H_4$. On this basis $H_1$ gave a singlet ($\tau$ 5·13) whilst $H_2$ and $H_3$ gave the "AB"-quartet[13] ($\tau$ 6·93; 7·25). In contrast to this simple behaviour, the D-*allo*-isomer (II) showed $H_1$ as a doublet ($\tau$ 5·10) whilst the $H_2$, $H_3$ region was more complex than for I. Assuming that $J_{1,2} = J_{3,4}$ and that the value of $J_{2,3}$ was identical to that of I gave the "line-spectrum" shown as the inset in Fig. 1 (b), where the intensities are assumed.

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[7] R. D. Guthrie, D. Murphy, D. H. Buss, L. Hough and A. C. Richardson, *Proc. Chem. Soc.* 84 (1963): *J. Chem. Soc.* 3658, 5295 (1963).

[8] G. J. Robertson and C. F. Griffith, *J. Chem. Soc.* 1193 (1935).

[9] J. E. Christensen and L. Goodman, *J. Amer. Chem. Soc.* **83**, 3827 (1961).

[10] L. Hough and J. K. N. Jones, *J. Chem. Soc.* 4349 (1952).

[11] Commercial sample from K. and K. Laboratories Inc., Plainview, L.I., N.Y.

[12] E. E. van Tamelen, *J. Amer. Chem. Soc.* **73**, 3444 (1951).

[13] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* McGraw-Hill, New York, N.Y. (1959).

TABLE 1. CHEMICAL SHIFTS ($\tau$-VALUES) AND FIRST-ORDER COUPLING CONSTANTS (C.P.S.)

| COMPOUND | | $H_1$ | $H_2$ | $H_3$ | $H_4$ | $H_5$ | $H_6$ | Methine | -OMe | *N*-Ac | *N*-H | Phenyl |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Manno*-acetylepimine | I | 5·13<br>$J_{1,2} = 0$ | 6·93<br>$J_{2,3} = 6·5$ | 7·25<br>$J_{3,4} = 0$ | 5·74<br>$J_{4,5} = 7·5$ | 6·30[a] | 6·33 | 4·46 | 6·57 | 7·84 | — | 2·63 |
| *Allo*-acetylepimine | II | 5·10<br>$J_{1,2} = 4·5$ | 6·9<br>$J_{2,3} = 6·0$ | 7·0<br>$J_{3,4} = 4·5$ | 5·8<br>$J_{4,5} = 10·5$ | 5·95–6·45 | | 4·43 | 6·58 | 7·85 | — | 2·61 |
| *Manno*-epimine | III | 5·21<br>$J_{1,2} = 0$ | 7·4<br>$J_{2,3} = 6·5$ | 7·7<br>$J_{3,4} = 0$ | 5·8 | 6·38 | 6·42 | 4·46 | 6·60 | — | 8·7[a] | 2·63 |
| *Allo*-epimine | IV | 5·14[c]<br>$J_{1,2} = 3·5$ | 7·34 | <br>$J_{3,4} = 5$ | 5·8<br>$J_{4,5} = 8$ | 6·0–6·45 | | 4·44 | 6·58 | — | 8·0[a] | 2·63 |
| *Manno*-Epoxide | V | 5·14<br>$J_{1,2} = 0$ | 6·56[b]<br>$J_{2,3} = 4·0$ | 6·88<br>$J_{3,4} = 0$ | 5·77<br>$J_{4,5} = 5$ | 6·25[a] | 6·36 | 4·51 | 6·60 | — | — | 2·63 |
| *Allo*-Epoxide | VI | 5·12[c]<br>$J_{1,2} = 2·5$ | 6·40–6·65[c]<br>$J_{2,3} = 4·5$ | <br>$J_{3,4} = 4·5$ | 5·7<br>$J_{4,5} = 10$ | 5·93–6·40 | | 4·43 | 6·52 | — | — | 2·61 |
| *Allo*-Episulfide | VII | 4·88[c]<br>$J_{1,2} = 4·2$ | 6·43–6·63<br>$J_{2,3} = 7·2$ | | 5·6–6·4 | | 5·76 | 4·38 | 6·56 | — | — | 2·61 |
| $\beta$-D-Ribo-pyranoside | VIII | 5·16<br>$J_{1,2} = 0$ | 6·44[b]<br>$J_{2,3} = 4$ | 6·80<br>$J_{3,4} = 0$ | 6·0–6·4 | | — | — | 6·55 | — | — | — |
| $\beta$-L-Ribo-pyranoside | IX | 5·15<br>$J_{1,2} = 0$ | 6·48<br>$J_{2,3} = 3·8$ | 6·83<br>$J_{3,4} = 0$ | 6·05–6·45 | | — | — | 6·47<br>&<br>6·52 | — | — | — |
| Cyclohexane oxide | X | — | 6·96 | | — | — | — | — | — | — | — | — |
| Cyclohexane sulfide | XI | — | 6·79 | | — | — | — | — | — | — | — | — |

[a] centre of a broad band.

[b] calculated value, (AB) analysis.

[c] benzene solvent used to measure coupling constant(s).

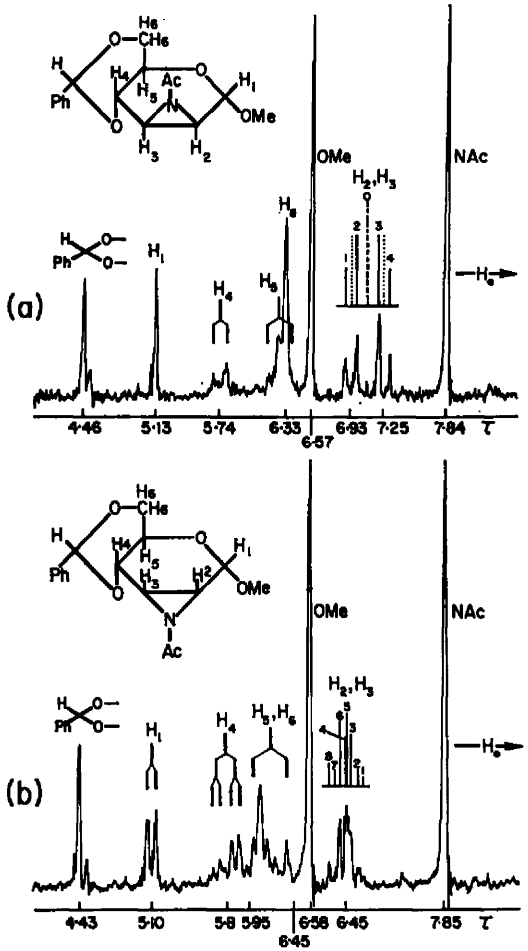

FIG. 1. Partial PMR Spectra of the methyl 2,3-acetylepimino-4,6-O-benzylidene-2,3-dideoxy-α-D-pyranosides: (a) the *manno*-isomer (I) and (b) the *allo*-isomer (II).

The spectra of the remaining compounds could be assigned by analogy with compounds I and II, although in no case was it possible to distinguish between $H_2$ and $H_3$. In several cases the methoxyl peak obscured part of the $H_2$, $H_3$ region, as for example in the *manno*-epoxide (V), however, the chemical shift of the obscured resonance could be readily calculated from an AB-analysis using the relative intensities of the observable peaks. This simple procedure eliminated the need for proton-proton decoupling experiments.

All derivatives having the D-*manno* configuration showed $J_{1,2} = J_{3,4} = 0$ whilst those with the D-*allo* configuration had $J_{1,2} \simeq J_{3,4} = 2{\cdot}5 - 4{\cdot}5$ c.p.s. The *ribo*-epoxides (VIII and IX) also showed $J_{1,2} = 0$. Thus the coupling from the epi-ring hydrogens at $C_2$ (and $C_3$) to adjacent hydrogens at $C_1$ (and $C_4$) is smaller when these hydrogens have a *trans* relationship than when they are *cis*, and this effect is independent of the hetero atom in the *epi*-ring. The relative magnitudes of the *epi*-coupling constants observed in this study may be rationalised by reference to the Karplus equation.[2] Owing to the "$\cos^2 \phi$" term in this relationship two dihedral angles are theoretically possible for any particular coupling constant between two

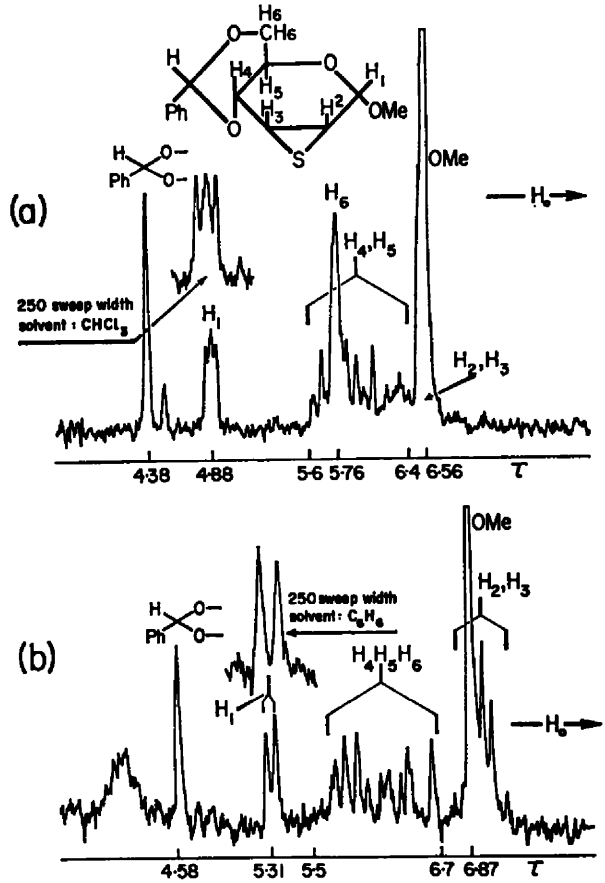

FIG. 2. Partial PMR spectra of methyl 4,6-O-benzylidene 2,3-dideoxy-2,3-epithio-α-D-allopyranoside (VII): (a) in chloroform solution and (b) in benzene solution. The peaks at ca. τ 4·4 in (a) and τ 4·1 in (b) are solvent $C^{13}$-satellites.

protons attached to adjacent carbon atoms. Evidently for these *epi*-derivatives a small coupling constant corresponds to a comparatively large dihedral angle so that $J_{trans} < J_{cis}$, which is in contrast to the more general observation[1] that $J_{trans} > J_{cis}$ for protons attached to $sp^3$-hybridized carbon atoms. Previous investigations[3–5] of steroidal epoxides had lead to similar conclusions and in addition Cross[3] attempted to calculate the theoretical magnitudes of the coupling constants by Karplus calculations; however, this quantitative approach is open to some criticism. It is now well known[2b] that $J_0$-parameters used in the Karplus calculation are dependent on substituent electronegativities and failure to use appropriately corrected parameters can thus lead to considerable systematic errors. In addition the mechanism of proton coupling within *epi*-substituents may well be unusual since, for example, the relative signs of long range coupling constants of indene oxide are unusual.[14]

The general stereospecificity of *epi*-coupling constants, $J_{trans} < J_{cis}$, will probably prevail regardless of the size of the attached ring and this should aid configurational assignments for such compounds. Indene oxide provides a simple example where the assignment of the $C_3$-methylene resonance could be most easily made on the

[14] S. L. Maunatt, D. D. Elleman and C. D. Pearce, Private communication.

basis of the stereospecifity previously found for the above carbohydrates. Similarly the spectra of a variety of cyclopentene epoxides could only be analysed[15] on the basis of a zero *trans* couplings, as also could the methyl 2,3-anhydro-ribofuranosides.[16]

The pyranose ring of the 4,6-O-benzylidene-2,3-*epi*-derivatives should adopt a half-chair conformation with $C_6$ below and $O_5$ above the general plane defined by $C_1$, $C_2$, $C_3$ and $C_4$ and the comparatively large splitting[2] between $H_4$ and $H_5$ in all of these derivatives confirms this. However, the value for compounds having the D-manno configuration is always smaller than that of the corresponding *allo* derivatives which may reflect some conformational flattening for the former compounds. Unfortunately the spectra of the *ribo*-epoxides (VIII and IX) were insufficiently resolved to enable their conformations to be determined in this way.

Most of the compounds showed overlapping resonances in chloroform solution and their spectra were remeasured in benzene solution in an attempt to effect some solvent shifts. Generally these shifts were quite small and the spectra of the *allo*-episulphide shown in Fig. 2 are typical. These spectra also illustrate an interesting example of virtual coupling.[17] In benzene solution, $H_1$ appears as the expected doublet whilst in chloroform it is shown as a partially resolved "triplet". This latter behaviour is due to virtual coupling of $H_1$ with the strongly coupled $H_2$, $H_3$ system as evidence by inspection of these latter resonances. In chloroform these two protons are almost equivalent since they lie entirely beneath the methoxyl resonances, whereas in benzene they are inequivalent and hence do not induce virtual couplings into the $H_1$ resonance.

Attempts were also made to correlate the chemical shifts of these epi-protons with those of other related compounds. Values are available in the literature for ethylene oxide[18] ($\tau$ 7·28), ethylene sulphide[18] ($\tau$ 6·98) and ethylene imine[19] ($\tau$ 8·38), for *cis*-2,3-butene epoxide[20] ($\tau$ 6·89) and episulphide[20] ($\tau$ 6·79) and were measured for cyclohexene epoxide ($\tau$ 6·96) and episulphide ($\tau$ 6·79) in dilute chloroform solution. Clearly it is not possible to make any general comparison of these values although the relative chemical shifts in each series always increases in the order episulphide < epoxide < *N*-acetylepimine < epimene.[21]

*Acknowledgements*—Financial assistance from the National Research Council of Canada to one of us (L. D. H.) is gratefully acknowledged. Thanks are also due to the Department of Scientific and Industrial Research (U.K.) for a Studentship (to D. H. B.).

[15] H. Z. Sable, W. M. Ritchey and J. E. Nordlander, Private communication.

[16] L. D. Hall, *Chem. & Ind.* 950 (1963).

[17] J. I. Musher and E. J. Corey, *Tetrahedron* **18**, 791 (1962).

[18] H. S. Gutowski, R. L. Rutledge, M. Tamres and S. Searles, *J. Amer. Chem. Soc.* **76**, 4242 (1954).

[19] N. F. Bhacca, D. P. Hollis, L. F. Johnson and E. A. Pier, *Varian Spectra Catalogue* Vol. II Spectrum #372.

[20] N. F. Chamberlain and N. F. Neathcock, *A catalogue of N.M.R. Spectra* Spectra #644 and #658.

[21] Since the completion of this work two papers of relevance have been published: B. R. Baker and T. Neilson, [*J. Org. Chem.* **29**, 1051 (1964)] have reported the chemical shifts for the epi-protons of the mannoepoxide (V), the *allo*epimine (IV), the *allo*-acetyl epimine (II) and of methyl 4,6-di-O-acetyl-2,3-acetylepimino-2,3-dideoxy-α-D-allo-pyranoside. Their chemical shifts were in essential agreement with those reported herein.

K. Tori, T. Komeno and T. Nakagawa, [*J. Org. Chem.* **29**, 1136 (1964)] have reported further chemical shifts and coupling constants for various steroidal epoxides and episulphides, and have suggested empirically modified Karplus parameters to rationalise their observed coupling constants.