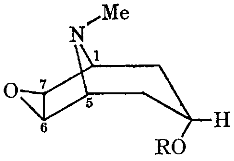
Magnetic Non-equivalence of the Epoxide Ring (C-6 and C-7) Protons of Scopolamine

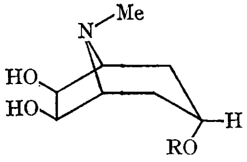
By S. R. JOHNS and J. A. LAMBERTON
(*C.S.I.R.O. Division of Organic Chemistry, P.O. Box 4331, Melbourne, Australia*)

IN molecules having a substituted methyl group (CH_2X) adjacent to an asymmetric centre, the geminal protons of the group CH_2X may be magnetically non-equivalent and give rise to a pair of AB doublets in the n.m.r. spectrum of the molecule.[1,2] It has been shown that this effect is not restricted to the methylene protons adjacent to the asymmetric centre, but can also be observed in methylene groups further removed.[1]



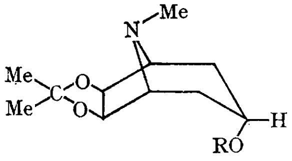
(I)

(a) R=CO·CH(CH$_2$OH)Ph
(b) R=CO·CH(CH$_2$OAc)Ph
(c) R=CO·CH·Me·Ph
(d) R=CO·CPh:CH$_2$
(e) R=H



(II)

(a) R=H
(b) R=CO·CMe:CHMe
(c) R=CO·CHMe·Ph
(d) R=CO·CHMe·Et



(III)

(a) R=H
(b) R=CO·CH·Ph$_2$
(c) R=CO·CHMe·Ph
(d) R=CO·CHMe·Et

The alkaloid (−)-scopolamine (Ia) (hyoscine) provides an unusual example of magnetic non-equivalence resulting from molecular asymmetry, in that the signals from the epoxide ring protons (C-6 and C-7) appear in the 60 Mc./sec. spectrum* as a pair of AB doublets (δ 2·80, 3·38; J_{AB} 3 c./sec.). This is the first observation of magnetic non-equivalence induced in vicinal rather than geminal protons, and where the protons are separated from the asymmetric centre by as many as six chemical bonds. Magnetic non-equivalence of the C-6 and C-7 protons was also observed in the spectra of (−)-scopolamine acetate (Ib) (δ 2·87, 3·38; J_{AB} 3 c./sec.) and (±)-dihydroaposcopolamine (Ic) (δ 2·78, 3·27; J_{AB} 3 c./sec.), but the signals from the C-6 and C-7 protons appear as a sharp singlet at δ 3·33 in the spectrum of aposcopolamine (Id). There is no visible coupling between the C-6 and C-5 protons, or between the C-7 and C-1 in the compounds (Ia, Ib, Ic, and Id), which is in agreement with the lack of observable coupling between similarly situated vicinal protons in the spectra of bicycloalkane epoxides.[3] Because of the difficulty of preparing oscine (Ie), no chemical shift values are quoted for the protons on an epoxide ring in a tropane uninfluenced by an ester group. Comparison with the chemical shift of the epoxide ring protons of bicycloalkanes[3] suggests, however, that the different chemical shifts of the C-6 and C-7 protons in (Ia, Ib, and Ic) are due to differential shielding by the phenyl ring, and this suggestion has been confirmed by a study of analogous esters of teloidine (IIa) and teloidine acetonide (IIIa).

The signals of the C-6 and C-7 protons appear as an AB quartet in the spectra of teloidine 2-phenylpropionate (IIc) (δ 3·73, 4·13; J_{AB} 6 c./sec.) and teloidine acetonide 2-phenylpropionate (IIIc) (δ 4·18, 4·71; J_{AB} 6 c./sec.)

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* Spectra were measued in $CDCl_3$ solution on a Varian A60 spectrometer, and spin–spin couplings were confirmed on a Varian V6058 Spin Decoupler.

[1] G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1964, **86**, 2628.

[2] P. L. Southwick, J. A. Fitzgerald, and G. E. Milliman, *Tetrahedron Letters*, 1965, 1247, and references 1—7 cited therein.

[3] K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, 1964, 559.

but as a singlet in the spectra of meteloidine (IIb) (δ 4·38), IIIa (δ 4·96), and teloidine acetonide diphenylacetate (IIIb) (δ 4·33). A sharp singlet is also observed for the C-6 and C-7 protons in the spectra of dihydrometeloidine (IIc) (δ 4·41) and dihydrometeloidine acetonide (IIId) (δ 4·83) because the anisotropy contributions of the groups attached to the asymmetric centre are not sufficiently different or large enough to produce significant differences in the chemical shifts of the two protons.

These results indicate that the magnetic non-equivalence of the C-6 and C-7 protons of the tropane esters studied depends upon the presence of both an asymmetric centre and an attached group of sufficient magnetic anisotropy to produce observable shielding. The magnitude of the observed diamagnetic shift suggests inequalities in conformer populations favouring orientations with the phenyl ring close to the C-6 and C-7 protons.

The spectra of scopolamine (Ia) in a range of solvents (CCl_4, C_6H_6, C_5H_5N, dimethyl sulphoxide) and of scopolamine hydrobromide (D_2O) show similar AB quartets for the C-6 and C-7 protons with only small variations in δ_A, δ_B, and $/\delta_A - \delta_B/$ and with no change in J_{AB}. Change of temperature produces only a small decrease in $/\delta_A - \delta_B/$ with increasing temperature (2—3 c./sec. per 100°).

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