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SUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES. MEASUREMENT OF OPTICAL PURITY BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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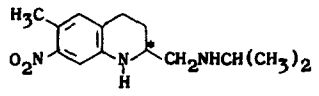
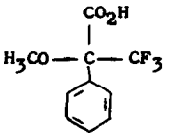
We wish to report a novel nmr method for determining the optical purity of enantiomeric bases. This method depends on differences in chemical shift between diastereomeric salts (produced from the enantiomers and an optically active acid) which exist as ion pairs in $CDCl_3$.

In the course of our studies[1] on antischistosomal 1,2,3,4-tetrahydroquinolines we wished to determine the optical purity of a sample of the more biologically active (+)isomer of 2-N-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (I).



(I)



(II)

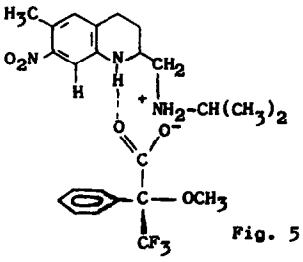


Fig. 5

Use of the acid chloride of (+)(II) for the conversion of enantiomeric amines to diastereomeric amides for the determination of optical purity has been described[2], but studies relating to salts of (II) with enantiomeric amines do not appear to have been reported.

Reaction of equimolar quantities of (±)(I) and (+)(II) in ethyl acetate yielded the salt (III) quantitatively as a yellow solid m.p. 148-149°. The ^1H nmr spectrum of (III) in $CDCl_3$,‡ a solvent which is particularly good for ion pair formation[3], showed an interesting feature in the aromatic region (Fig. 2) compared with that of the methanesulphonate salt, (Fig. 1).

In the case of the methanesulphonate salt (Fig. 1) the aromatic proton H-5 appeared as a singlet at δ6.7 whereas H-8 appeared downfield as a singlet at δ7.2 due to the deshielding effect of the 7-nitro group[1]. However, in the case of the α-methoxy-α-trifluoromethylphenyl-acetate salt (Fig. 2) three singlets were observed; that at δ6.6 was attributed to H-5 whereas

‡Throughout this study spectra were run as 10% w.v. solutions using a Varian T60 spectrometer with TMS as internal standard.

(±)(I) Methanesulphonate (±)(I).(+)(II) Salt (III) (+)(I).(+)(II) Salt (-)(I).(+)(II) Salt

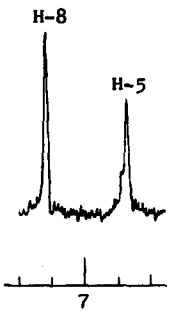


Fig. 1

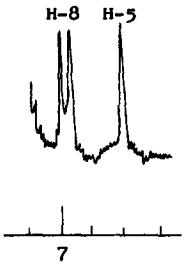


Fig. 2

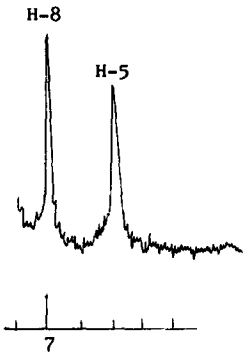


Fig. 3

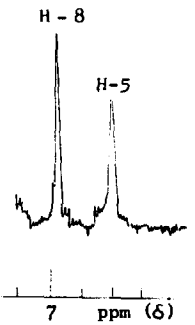


Fig. 4

the singlets at δ6.95 and δ7.0, each of which integrated for "half a proton", were attributed to the respective H-8 signals in the diastereomeric salt pairs. This was confirmed by preparing and examining the respective salt pairs of the resolved enantiomers of (I) with (+)(II). In the spectra obtained for (+)(I).(+)(II) and (-)(I).(+)(II) the H-8 signals appeared as singlets at δ7.0 and δ6.95 respectively, whereas in both cases the H-5 signal appeared at δ6.6 (Fig. 3 and 4). From the integrated intensities of the H-8 signal(s) of authentic mixtures of the enantiomers it was possible to assay for 95% enantiomeric purity.

To explain this effect it is assumed that a salt pair conformation exists in $CDCl_3$ in which the aromatic ring of the acid (II) exerts an influence (shielding or deshielding) upon H-8, e.g. as depicted in Fig. 5. Chemical shift differences arise from the diastereomeric salts existing as distinct species. As expected therefore H-8 nonequivalence was not observed in the spectrum of the salt formed between (±)(I) and phenylacetic acid. Again, this effect was lost when the solvent was changed to one capable of strong hydrogen bonding such as deuteriomethanol.

Work is currently in progress to examine the scope and limitations of this method.

Acknowledgements

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References

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2. J. A. Dale, D. L. Dull and H. S. Mosher, J. Org. Chem., 1969, 34(9), 2543.

3. cf. B. A. Persson and S. Eksborg, Acta. Pharm. Suecica, 1970, 7, 353.