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THE DETERMINATION OF OPTICAL PURITY BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY. II. COMPOUNDS WHICH OWE THEIR DISSYMMETRY TO DEUTERIUM SUBSTITUTION (1)

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In the first paper of this series (1) we pointed out that optical purities can often be conveniently determined through the use of nuclear magnetic resonance spectroscopy (2). In the n.m.r. method a mixture of enantiomers A and $\bar{A}$ is completely converted into a mixture of diastereomers AB and $\bar{A}$B by reaction with a chiral reagent B which is optically pure, and under conditions which exclude the possibility of racemization or epimerization. The ratio of diastereomers $\bar{A}$B/AB, which must equal the ratio $\bar{A}$/A, is determined by n.m.r. spectroscopy. Because the diastereomers need not be separated, this method is applicable to compounds which owe their chirality to dissymmetric deuterium substitution, and we now report the application of the n.m.r. method to the determination of the optical purities of (S)-propan-2-ol-1-d_3 (I) (3) and (S)-2,2-dimethylpropan-1-ol-1-d (II) (4).

The two methyl groups in isopropyl alcohol reside in enantiomeric environments and in achiral solvents will have the same n.m.r. chemical shift, i.e. the methyl groups are magnetically equivalent in the chemical shift sense. Such groups have been described as enantiomeric (5) by internal comparison. An analogous situation is encountered in racemic I in which the methyl groups in the two enantiomers also reside in enantiomeric environments. They are enantiomeric by external comparison, and must also show chemical shift equivalence.

When isopropyl alcohol is esterified with a chiral reagent, such as the acid chloride derived from (R)-O-methylmandelic acid (6) (III), the two methyl groups reside in diastereomeric environments, i.e. they are diastereomeric (5) by internal comparison. Such methyl hydrogens must, in principle, be magnetically nonequivalent in the chemical shift sense, and in many cases the nonequivalence is large enough to be observed. The two diastereomeric methyl groups in isopropyl O-methylmandelate give rise to two doublets (J_a = 6.2 c.p.s., J_b = 6.3 c.p.s.) which are chemically shifted by 0.085 p.p.m. (7) (Figure 1). The two diastereomeric methyl groups in the two epimeric esters formed by reaction of racemic I with optically pure III must show an analogous chemical shift. The optical purity of I (α_D^{25} + 0.27° (ℓ 1, neat)) was determined by complete conversion into the O-methylmandelate by reaction with an excess of III, prepared from optically pure O-methylmandelic acid (8). The n.m.r. of the resulting ester was identical with that of the undeuterated material except that the isopropyl methine signal occurred as a broadened quartet rather than as a multiplet, and that the doublet corresponding to the low-field methyl group was absent (Figure 2). Increased spectrum amplitude scans indicated that less than 1% of the other diastereomer could be present. The optical purity of the sample was therefore 99 ± 1%.

A similar situation obtains for neopentyl O-methylmandelate, although it is somewhat complicated by spin-spin splitting. In neopentyl alcohol the two enantiomeric α-hydrogens give rise to a singlet while in the O-methylmandelate they are diastereomeric and an AB quartet is observed (Figure 3, $\Delta\nu$ = 0.10 p.p.m., J_{AB} = 11 c.p.s.). Similarly, although the enantiomeric hydrogens in racemic II exhibit chemical shift equivalence, the diastereomeric hydrogens in the epimeric esters formed by reaction

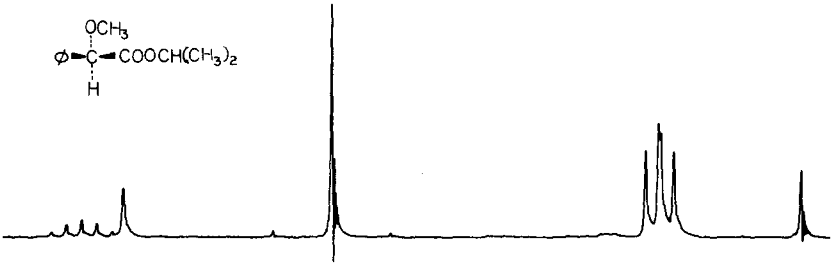

Figure 1. Isopropyl O-methylmandelate (500 cycle sweep width)(7)

Figure 2. O-Methylmandelate of I (500 cycle sweep width)

of racemic II with optically pure III will be chemically shifted by about the same amount. However, they will occur as two triplets which are A portions of the AX spin systems (deuterium splitting), rather than as an AB quartet. A sample of II (4), formed by fermentation of trimethylacetaldehyde-1-d by actively growing yeast, and reportedly (4) containing 82 ± 3% gram equivalents deuterium, was reacted with an excess of optically pure III (8). The n.m.r. spectrum (Figure 4) showed the presence of the methylene AB quartet corresponding to 20 ± 1% of undeuterated neopentyl O-methylmandelate, and a single triplet (J_{HD} = 1.5 c.p.s.) near the position where the high-field proton of the AB quartet would absorb in the absence of spin-spin coupling. Analysis of the n.m.r. spectra of the esters prepared from II and (R)-, (S)- and rac-O-methylmandelyl chlorides indicated that not more than 1% of the (R)-enantiomer could have been present in II (9). The optical purity of the II in this sample was thus 99 ± 1%.

Our results bear out the reasonable assumption (4) that II obtained by fermentation is essentially optically pure, and provide a foundation for the method for determining optical purities of α-deuterated primary alcohols based on partial resolution which is discussed by A. Horeau and A. Nouaille in the accompanying communication. We have learned that the n.m.r. method has been independently applied to compounds which owe their chirality to deuterium substitution by Dr. Hans Gerlach (E.T.H., Zürich), who has determined the optical purity of benzylamine-1-d by conversion to N-benzyl-4-phenyloxazolidine-2-thione.

Previously the determination of optical purity of compounds which owe their chirality to dissymmetric deuterium substitution could be accomplished only enzymatically and by methods of correlation. The isotope dilution and the gas chromatographic methods are inapplicable in such cases. We feel that the n.m.r. method is superior in point of convenience, accuracy and

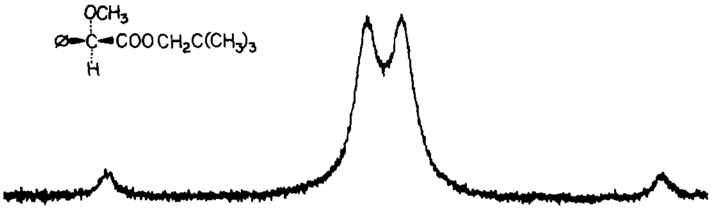

Figure 3. Neopentyl O-methylmandelate (methylene hydrogens, 50 cycle sweep width).

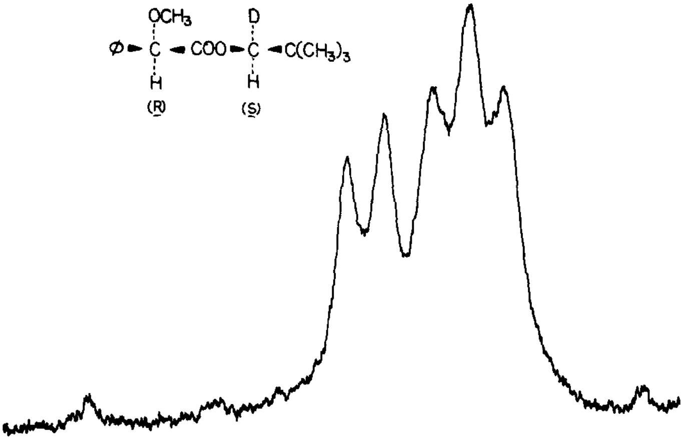

Figure 4. O-Methylmandelate of II (methylene hydrogens, 50 cycle sweep width).

generality to previously existing methods, and we feel that it will be the method of choice in those cases where it can be applied.

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5. For definitions of these terms, see K. Mislow, Introduction to Stereochemistry, W. A. Benjamin, Inc., New York, N. Y., 1965, p. 72ff. It must be emphasized that, in this context, the terms enantiomeric and diastereomeric refer to the environments of the atoms or groups in question.
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7. This and all other spectra were measured on a Varian A-60A spectrometer, on solutions in benzene, using TMS as an internal standard. All measurements of chemical shift nonequivalence of diastereomeric hydrogens, coupling constants and ratios of diastereomers were made on 50 cycle sweep width scans.
8. The optical purity of the III used was determined by reaction with an excess of (-)-menthol. Only one diastereomer could be observed in the n.m.r. spectrum under conditions where a measurable chemical shift was observed to occur for the ester mixture prepared from racemic III and (-)-menthol.
9. A full discussion of the analysis and of the n.m.r. spectra will be presented in a detailed paper.