NOTES

The Differentiation of Diastereoisomers of 1-Phenyl-2-acetamidopropane-1-ol Derivatives by Means of the NMR Spectrum

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During the course of studies[1] of the synthesis of 1-phenyl-2-aminopropane-1-ol derivatives, it became disirable to find a simple method for determining whether the 1-phenyl-2-acetamidopropane-1-ol derivatives belonged to the *threo* or the *erythro* series. The differentiation of these isomers by means of the infrared spectrum has been studied by Suzuki and Shindo.[2] In the present paper, we should like to show that these compounds may also be distinguished by their NMR spectra.

The hydroxyl groups of *threo* and *erythro* α-glycols have been shown to exhibit in the NMR spectra distinctly different chemical shifts when measured in pyridine - trifluoroacetic acid.[3] Namely, the resonance line arising from the exchanging-hydroxyl group of the threo isomers appears at a higher field than that of the erythro isomer.

A similar comparison of the NMR peaks of *threo* and *erythro* 1-phenyl-2-acetamidopropane-1-ol and 1-phenyl-2-acetamido-3-ethoxypropane-1-ol[1] (Table I) also shows that the peak due to the exchanging-hydroxyl and amide protons in the threo isomer appears at the higher field. Although only two pairs have been measured, this tendency of the threo isomer to

TABLE I

Sample	Concn. mol. %	Shift[a] c. p. s.
Solvent (3.80 mol. solution of trifluoroacetic acid in pyridine)		375.8
N-Acetylnorephedrine (*erythro*)	1.973	230.5
N-Acetylnor-ψ-ephedrine (*threo*)	1.973	158.7
erythro-1-Phenyl-2-acetamido-3-ethoxypropane-1-ol	0.7305	283.1
threo-1-Phenyl-2-acetamido-3-ethoxypropane-1-ol	0.7305	204.5

a) The NMR spectra were measured on a Varian V 4300 high resolution spectrometer at a fixed frequency of 40 Mc./sec. Shift is relative to the signal of the γ proton of pyridine.

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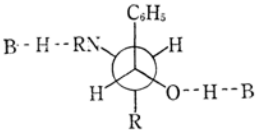
[1] T. Matsumoto, T. Nishida and H. Shirahama, *J. Org. Chem.*, **27**, 79 (1962); H. Shirahama and T. Matsumoto, This Bulletin, **38**, 1289, 1293 (1965).,

[2] M. Suzuki and H. Shindo, *J. Pharm. Soc. Japan*, **76**, 927 (1956).

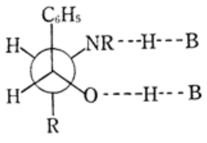
[3] S. Fujise, G. Hazato, T. Ikenoue, S. Sasaki and Y. Senda, unpublished results; Y. Senda, M. Sc. Thesis, Tohoku University (1958). Our thanks are due to Dr. Tsuneo Ikenoue, Tohoku University, for informing us of these results prior to publication and for his valuable discussions. For the concentration shift of *threo* and *erythro* α-glycols in pyridine and in acetic acid, see S. Fujise, G. Hazato, T. Ikenoue, S. Sasaki and Y. Senda, This Bulletin, **25**, 1742 (1962).

exhibit its resonance peak at higher fields is presumably quite general, since similar results have been obtained, without exception, with the eight α-glycols so far examined.[3]

An explanation for the above findings may be added here, although it is only tentative. The chemical shift of an exchanging proton depends on the time-averaged environment of the active hydrogen. Assuming that all proton exchanges take place by way of hydrogen-bonded structures,[4] the interaction between the most stable form of each acetamido alcohol and surrounding species can be illustrated as follows:[5]



erythro



threo

The interaction is clearly more effective in the *erythro* isomer, and, therefore, the exchangeable proton in the erythro form is more deshielded.

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[4] J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, New York (1959), See. 15-6 and p. 441.

[5] B represents one of pyridine, trifluoroacetate ion and trifluoroacetic acid. The species with an intramolecular hydrogen bond, as illustrated below, may be neglected in a pyridine-trifluoroacetic acid solution.