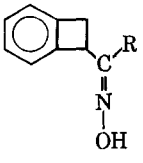
Stereochemical Assignments of 1-Benzocyclobutenyl Ketoximes

Sir:

The 1-benzocyclobutenyl ketoximes, listed in Table I, exhibit muscle relaxant characteristics (1). No assignments of the oxime configurations were made for the compounds used in the pharmacological tests. This study was undertaken to establish the configurations of the oximes.

TABLE I—1-BENZOCYCLOBUTENYL KETOXIMES



Compd.	R	Oxime Configuration Relative to R
I	Methyl	*syn*
II	Phenyl	*anti*
III	*n*-Butyl	*syn*
IV	Benzyl	*syn*
V	Cyclohexyl	*syn*

Initially, NMR appeared to be useful for assigning the stereochemistry of I. Oximes of structurally related ketones (benzyl methyl ketone and α-phenethyl methyl ketone) were prepared. Only a single isomer (*syn* to the methyl group) could be detected for each compound on thin-layer chromatography using benzene–ethyl acetate (10:1) as the solvent system. Only a single isomer is reported in the literature for each compound (2). Silica gel was the adsorbent for this experiment and all other chromatography in the study. Since both isomers of the model compounds were not available, no definite assignment could be made for I based upon comparisons with the NMR spectra of the model oximes.

A Beckmann rearrangement was run on I with phosphorus pentachloride in anhydrous ether (3). The resulting amide had a peak in the infrared spectrum at 7.35 μ which is characteristic of CH_3CO—groups (4). This amide is consistent with a *syn* assignment for I, since the group *anti* to the oxime hydroxyl migrates in the Beckmann rearrangement (3). Basic hydrolysis and ether extraction gave a solid amine which had aromatic and aliphatic C-H absorption in its infrared spectrum, confirming the stereochemistry of I.

Compound II, after Beckmann rearrangement, basic hydrolysis, and ether extraction, afforded an amine which had a R_f value identical to aniline on thin-layer chromatography with benzene–methanol (95:5). In this solvent system, the amine from I failed to migrate from its origin. Thus, II was assigned an *anti* configuration.

When III, IV, and V were treated with the same series of reactions, the amines produced had the same R_f value as the amine from I on thin-layer chromatography with *n*-butanol–acetic acid–water (4:1:1). The amines failed to migrate in the benzene–methanol system. A tentative *syn* assignment for III, IV, and V was made. The hydrolysis residues from II, III, IV, and V were acidified and extracted with ether. These acids exhibited individual R_f values on thin-layer chromatography with benzene–dioxane–acetic acid (90:25:4). The acids from III, IV, and V had R_f values identical to valeric, phenylacetic, and cyclohexane carboxylic acids, respectively. This observation confirmed the assignments of the stereochemical configuration of III, IV, and V.

(1) Skorcz, J. A., Suh, J. T., Judd, C. I., Finkelstein, M., and Conway, A. C., *J. Med. Chem.*, **9**, 656(1966).
(2) "Dictionary of Organic Compounds," Heilbron, I., ed., Oxford University Press, New York, N. Y., 1946.
(3) Donaruma, L. G., and Heldt, W. Z., "Organic Reactions," vol. 11, Cope, A. C., ed., John Wiley & Sons, Inc., New York, N. Y., 1960, p. 1.
(4) Nakanishi, K., "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p. 21.

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