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Nuclear Magnetic Resonance Spectral Analyses of Isothiazoles

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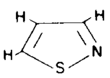
N.m.r. spectral analyses of isothiazole and its methyl homologs permits assignment of chemical shifts and coupling constants for each of the protons in these molecules. The chemical shift values for hydrogens attached to the isothiazole nucleus substantiate electron density values calculated from molecular orbital theory. In 5-methylisothiazole, the coupling constant for the hydrogen atom at position 3 and those on the methyl group is larger than for hydrogens attached directly to the isothiazole nucleus at positions 3 and 5.

Simple mononuclear isothiazoles have only recently been synthesized (1). Consequently, the fundamental chemical properties of the isothiazole ring system are poorly understood compared with what we know about other heterocyclic systems of similar complexity. Nuclear magnetic resonance spectral analyses of isothiazole and its methyl homologs which permit assignment of chemical shifts and coupling constants for all of the protons in these molecules are reported here.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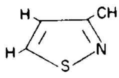
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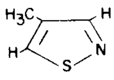
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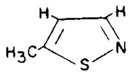
IV

EXPERIMENTAL

Samples of isothiazole (I), 3-methylisothiazole (II), 4-methylisothiazole (III), and 5-methylisothiazole (IV) (2) were purified by fractional distillation. Center-cuts from each distillation having the following boiling points at 645 mm were used for n.m.r. analyses: I, 109°; II, 128°; III, 139.5°; and IV, 136°. Spectra were obtained for 20% solutions in $CDCl_3$ using a Varian A-60 Nuclear Magnetic Resonance Spectrometer. Tetramethylsilane was used as an internal standard.

DISCUSSION

The signals arising from hydrogen at position 2 are easily identified because they are broadened by nuclear quadripole relaxation, whereas the signals from hydrogen at positions 4 and 5 are sharp and well-resolved.

The chemical shifts of the hydrogens in isothiazole are in substantial agreement with the π-electron densities calculated by Adams and Slack using the Hückel M.O. approach (3). In the ground state, it appears that the electron density is slightly lower at position 5 than at position 3. Introduction of a methyl group at position 4 leads to a reversal in apparent order of electron density, indicating that such a methyl group can supply electrons more efficiently to position 5 than to position 3. This is consistent with the notion that the magnitude of the coupling constant for hydrogens on adjacent ring positions ($J_{34} < J_{35}$) reflects the degree of double bond character between such positions. Hence, donation of electrons by a substituent at position 4 to position 5, via either hyperconjugation or field effect, should be favored over similar donation to position 3. The signals for the 4-hydrogen occur at higher field, which is in agreement with the higher electron density predicted by both resonance theory and Hückel M.O. approaches.

Nuclear Magnetic Resonance Parameters for Isothiazoles

	Chemical Shift (δ)				Coupling Constant (c.p.s.)					
Cmpd.	3H	4H	5H	$CH_3(\alpha)$	J_{34}	J_{35}	J_{45}	$J_{3\alpha}$	$J_{4\alpha}$	$J_{5\alpha}$
I	8.57 (a)	7.18 (c)	8.69 (c)	----	1.8	0	4.7	---	---	---
II	----	6.95 (c)	8.54 (c)	2.41 (b)	---	---	4.6	---	0	0
III	8.26 (a)	----	8.21 (f)	2.17 (e)	---	0.35	---	0.45	---	0
IV	8.28 (a)	6.81 (f)	----	2.41 (e)	1.8	---	---	0.55	1.1	---

(a) Broad singlet. (b) Singlet. (c) Doublet. (d) Quartet. (e) Two overlapping doublets. (f) Two overlapping quartets.

The long-range spin-spin splitting that involves the 3-hydrogen and the methyl hydrogens in 5-methylisothiazole is of greater magnitude (0.55 c.p.s.) than that involving hydrogens at positions 3 and 5 on the ring (J_{35} = 0 for isothiozole and 0.35 c.p.s. for 4-methylisothiazole), even though an additional σ-bond is interposed between the interacting nuclei in the former case. The other coupling constants that correspond to side-chain couplings follow the same order as those for coupling between hydrogens on the ring, the attenuating effect of the additional σ-bond being reflected in somewhat lower values of coupling constants for side-chain coupling.

REFERENCES

(1) A. Adams and R. Slack, *Chem. and Ind.*, 1232 (1956).

(2) The isothiazoles were kindly furnished by Dr. F. Hübenett, Hans J. Zimmer, Verfahrenstechnik, Frankfurt, West Germany.

(3) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

(4) R. A. Hoffman and S. Gronowitz, *Arkiv. Kemi*, 15, 45 (1959).

Received November 6, 1964 Logan, Utah 84321