was determined using samples of VI and III_A. The two compounds gave identical infrared spectra.

Anal. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.02. Found: C, 57.92; H, 3.52.

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Structure Proof of 2,6-Di-*t*-butylpyridine-3-sulfonic Acid by Proton Magnetic Resonance

NORBERT MULLER AND WILLIAM J. WALLACE

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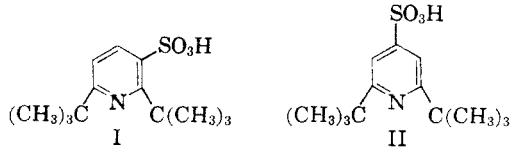
In contrast to ordinary pyridine bases, 2,6-di-*t*-butylpyridine undergoes ready sulfonation[1] by sulfur trioxide in liquid sulfur dioxide at $-10°$. Because of the large steric effect anticipated for a sulfonic acid substituent ortho to a *t*-butyl group, the original authors suggest that perhaps the substituent enters the pyridine ring in the 4- position rather than in the 3- position, as is customary for simple pyridine bases under vigorous conditions. Recently den Hertog[2] found that this sulfonic acid is rather inert to hydrolysis, and from this and from the properties of the hydrolysis product he concluded that it must be the 3- and not the 4- derivative. Although the likelihood of a molecular rearrangement during the hydrolysis is considered small, it seemed worthwhile to test this conclusion by examining the nuclear magnetic resonance (NMR) spectrum of the sulfonic acid itself. The results show unequivocally that the material is indeed the 3-sulfonic acid.

The NMR technique is particularly helpful when chemical evidence is available that rules out all but a small number of structures for the unknown material. In the present instance, it was anticipated that a decision between formulas I and II could readily be made because the difference in symmetry of these two structures should lead to several clearcut differences in their NMR spectra.



Structure I contains a pair of structurally nonequivalent protons attached to the ring. These should give rise to two resonance signals, each perhaps split into a doublet by their mutual electron-coupled spin-spin interaction. In structure II, the ring protons are equivalent and should produce a single, sharp peak. Similarly, I has two nonequivalent *t*-butyl groups, while both are equivalent in II. Thus structure I should show a second pair of peaks, each about nine times as strong as one of the ring-proton signals, while structure II should have only one strong peak at the field-value corresponding to methyl protons. The acid hydrogen in either molecule should contribute an additional peak comparable in strength with that of the ring-protons.

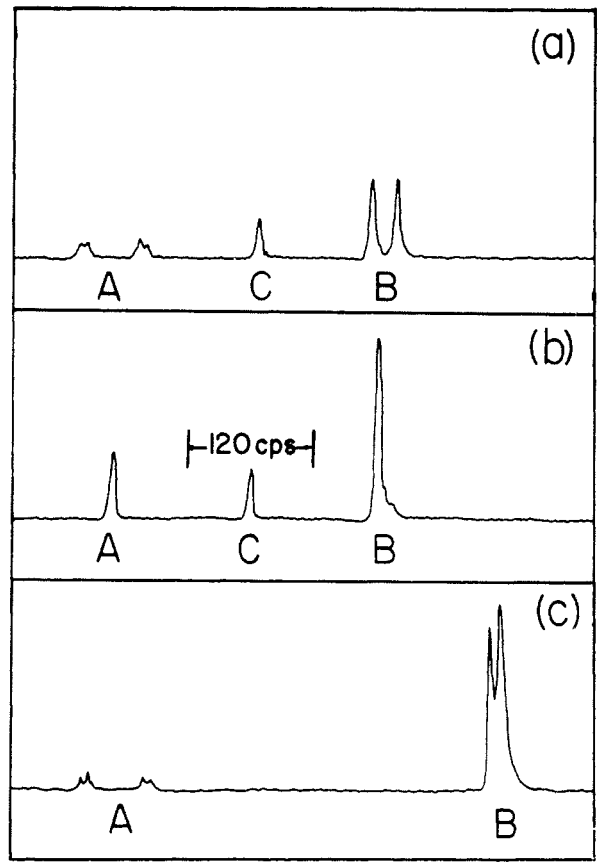


Fig. 1. NMR spectra of the sodium salts of 2,6-lutidine-3-sulfonic acid (a) and of 2,6-lutidine-4-sulfonic acid (b) in D_2O, and spectrum of 2,6-di-*t*-butylpyridine-3-sulfonic acid in liquid SO_2 (c). Peaks at A are due to ring protons, at B to methyl or *t*-butyl group protons, and at C to H_2O. The magnetic field increases towards the right for each trace.

To confirm this reasoning, we first obtained the spectra of authentic samples[3] of the two 2,6-lutidinesulfonic acids analogous to I and II. The spectra, shown in Figs. 1(a) and 1(b), have precisely the anticipated features. The samples consisted of solutions containing 2 moles of the acid

(1) H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, **75**, 3865 (1953).

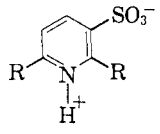
(2) H. J. den Hertog, *Chem. Weekblad*, **53**, 560 (1957).

(3) R. F. Evans and H. C. Brown, to be published.

and 1 mole of sodium carbonate per liter of D_2O, so that the observed spectra are those of the sulfonate ions and of a small amount of H_2O formed when the acid is neutralized.

A usable sample of the 2,6-di-*t*-butylpyridinesulfonic acid could not be obtained in the analogous way because of the unexpectedly low water-solubility of the sodium salt. The solvent finally found most suitable was that used originally[1] in the sulfonation reaction, liquid sulfur dioxide. Sealed sample tubes containing liquid sulfur dioxide may safely be stored, and examined, at room temperature, and the solvent is ideal in that it produces no proton spectrum which would obscure that of the solute. Since the lutidinesulfonic acids are insoluble in liquid sulfur dioxide, the three spectra could not be compared in identical solvent, and therefore no attempt was made to measure the chemical shifts of the various peaks relative to a fixed standard. However, the spectrum of the 2,6-di-*t*-butylpyridinesulfonic acid, shown in Fig. 1(c), leaves no doubt that the material has structure I and not structure II.

An interesting feature of the latter spectrum is the apparent absence of a signal for the acid proton. The most likely explanation appears to be that structure I in liquid sulfur dioxide is in equilibrium with the dipolar ionic structure III, and that the



III

rate of migration of the proton is such as to result in a considerably broadened line[4] which would probably be undetected because of the small concentration of this species of proton.

Acknowledgment. All spectra were obtained with a Varian model 4311 high resolution NMR spectrometer operating at 56.4 mc. We should like to thank the Purdue Research Foundation, E. I. du Pont de Nemours and Co., and the National Science Foundation for grants which made the purchase of this equipment possible. We also wish to thank Professor H. C. Brown for calling this problem to our attention and providing the compounds.

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(4) See J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, New York, 1959, p. 63.

Potential Anticancer Agents.[1] XXI. 2-(Alkylthio)cyclopentene-1-carboxylic Acids and Derivatives

LEONARD O. ROSS, LEON GOODMAN, AND B. R. BAKER

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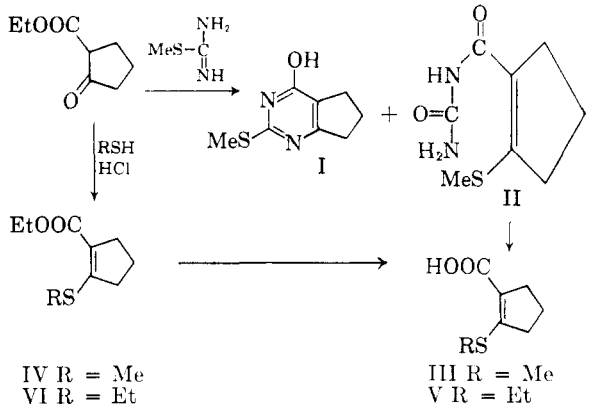
An earlier paper in this series[2] described the condensation of 2-methyl-2-thiopseudourea and 2-carbethoxycyclopentanone in aqueous alkali which led to the isolation of the expected 4-hydroxy-2-(methylthio)-5,6-trimethylenepyrimidine (I) and a product to which structure II was tentatively as-



IV R = Me
VI R = Et

III R = Me
V R = Et

signed. Some further work, which is reported in this note, has placed the structural assignment of II on firmer ground.

Alkaline hydrolysis of the compound assigned structure II gave a carboxylic acid which had strong ultraviolet absorption at 287 mμ, in good agreement with the absorption expected for compound III.[3] For comparison, the acid (III) was synthesized from 2-carbethoxycyclopentanone by the method used by Posner to synthesize 3-(ethylthio)crotonic acid.[4] Methanethiol, in large excess, on reaction with 2-carbethoxycyclopentanone in the presence of concentrated hydrochloric acid, furnished, as the directly isolated product, ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV). The ester IV was saponified to the acid III, which was identical with acid III derived from II as shown by nondepression of the mixed melting point, identical infrared spectra, and the same paper chromatographic behavior. It is interesting to note that the ester IV was the direct product from the reaction of

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* W. A. Skinner, H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) L. O. Ross, L. Goodman, B. R. Baker, paper XVII of this series, *J. Am. Chem. Soc.*, **81**, 3108 (1959).

(3) B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org. Chem.*, **13**, 123 (1948).

(4) T. Posner, *Ber.*, **32**, 2801 (1899).