lated benzylboron dichloride from these reactions or from the pyrolysis of the chloroborate. In the absence of details of their work we cannot account for the difference in products, but the isolation of 84.5% tropenium and recovered cycloheptatriene in our cyclohexane reaction indicates that aromatization is not a major factor under our conditions.

(19) American Chemical Society-Petroleum Research Fund Scholar, 1960.

DEPARTMENT OF CHEMISTRY KENNETH M. HARMON
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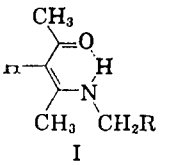
RECEIVED JUNE 19, 1961

A NUCLEAR MAGNETIC RESONANCE STUDY OF KETO-ENOL EQUILIBRIA IN SCHIFF BASES. II

Sir:

A recent paper[1] presented evidence from proton magnetic resonance that bases derived from the 2:1 condensation of a β-diketone and a diamine are present in solution to an extent ≥95% in the ketamine form with only a small dependence of the equilibrium on solvent. The –NH–R structure was inferred from spin-spin splitting of the R methylene protons (J = 6 cps.) by N–H. This study now has been extended to bases derived from other monoamines and β-diketones in order to explore further the apparently high stability of the ketamine over the enol-imine tautomer.

Bases formed from monoamines and simple β-diketones such as acetylacetone give rise to proton resonance spectra similar to those derived from diamines. When R = H, CH_3, C_6H_5 the compounds in $CDCl_3$ or CCl_4 solution exist in the ketamine form I as indicated by the vinyl signal at ~4.9 ppm.[1] and the splitting of the methyl or methylene protons into a doublet with $J \approx 5$–6 cps.

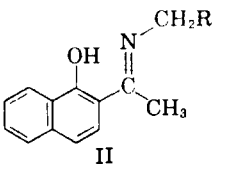


I

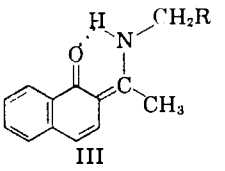
The benzyl base of dibenzoylmethane behaves similarly. No other signals attributable to the N-substituent were observable (concn. ~0.4 M) so that structure I is present to an extent ≥95%. There is no apparent solvent effect upon the equilibrium ($CDCl_3$, C_6H_6, pyridine).

These results, together with corroborative infrared studies on the above and related compounds,[2] offer further evidence of the greater stability of the ketamine form in aliphatic compounds as compared to either the ketimine or enol-imine tautomers. Accordingly, a search was made for other systems in which an alternate tautomer would be of comparable stability.

Derivatives of *o*-hydroxynaphthones were investigated. The tautomers II and III are possible for the base derived from 1-hydroxy-2-naphthone and a monoamine.



II



III

When R = C_6H_5 the proton resonance spectrum in $CDCl_3$ has a sharp methyl signal at 2.37 ppm., complex aromatics at ~7 ppm., and at 16.5 ppm. the broad signal from the acidic proton (the acidic proton in acetylacetone enol is at 15.3 ppm. in C_6H_{12}[3]). At 4.67 ppm. there is a field invariant doublet which collapses to a singlet upon deuteration of the acidic proton and is thus ascribable to the benzyl methylene group split by N–H with J = 4.8 cps. When R = H the spectrum in either pyridine or $CDCl_3$ is analogous to that of the benzyl base. In $CDCl_3$ the methyl doublet is at 3.08 ppm. with J = 4.4 cps. In both compounds the stability of the keto-amine form with its chelated hydrogen-bonded ring (inferred in both cases from the presence of a highly unshielded proton) is sufficient to destroy the aromatic structure of one of the naphthalene rings. These results present some of the most direct physical evidence for such an effect. Previously, similar tautomerism in certain arylazonaphthols had been inferred from ultraviolet and infrared spectra.[4,5,6] As expected, salicylalbenzylamine shows an unsplit methylene signal at 4.77 ppm. in $CDCl_3$.

Preliminary studies of similar bases derived from 2-hydroxy-1-naphthone and 2-hydroxy-1-naphthaldehyde indicate that the phenol-imine form predominates. When R = H in the former the N-methyl signal is a sharp singlet at 3.21 ppm. in $CDCl_3$. The benzyl base of the aldehyde exhibits at 4.73 ppm. in $CDCl_3$ a broadened methylene resonance which persists in CCl_4 and pyridine.

These and other bases derived from *o*-hydroxynaphthaldehydes and *o*-hydroxylnaphthones are presently under investigation and detailed results will be reported in the future.

Spectra were taken on a Varian HR-60 (at 60 or 15.1 Mc./sec.) or A-60 spectrometer using tetramethylsilane as an internal zero of reference. Bases were formed from the carbonyl compound and amine by standard procedures. Compounds were characterized by melting point or in the case of new compounds by elemental analysis. Financial support from the National Science Foundation is acknowledged.

(1) G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099 (1961).

(2) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, *ibid.*, **71**, 3337 (1949).

(3) L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

(4) A. Burawoy and A. R. Thompson, *J. Chem. Soc.*, 1443 (1953).

(5) E. Sawicki, *J. Org. Chem.*, **22**, 743 (1957).

(6) K. J. Morgan, *J. Chem. Soc.*, 2151 (1961), and references therein.

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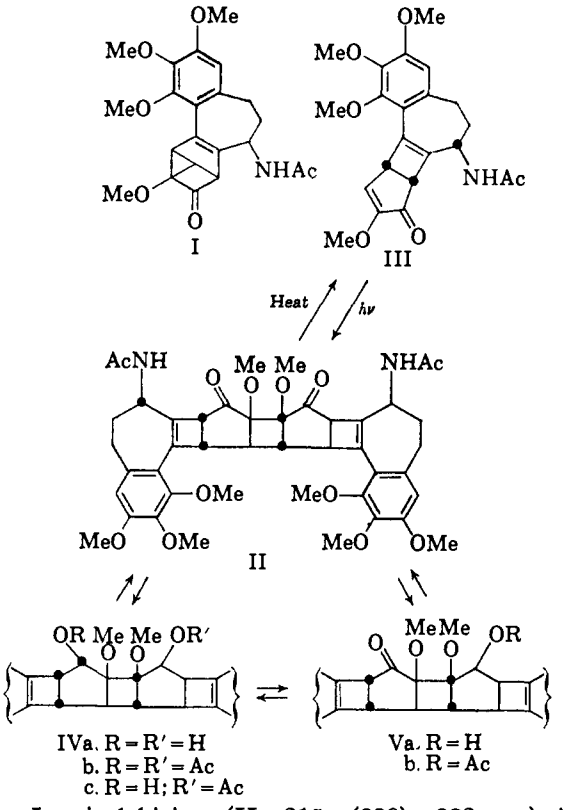
RECEIVED AUGUST 16, 1961

THE STRUCTURE OF α-LUMICOLCHICINE—SOME EXAMPLES OF DIAMAGNETIC SHIELDING BY THE CARBON–OXYGEN DOUBLE BOND

Sir:

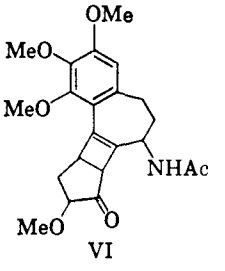
α-Lumicolchicine, which is formed with β-lumicolchicine and γ-lumicolchicine in the irradia-

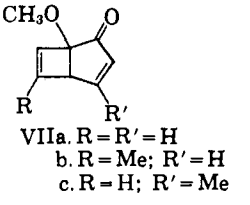
tion of colchicine,[1,2,3] has remained a structural enigma although structures were assigned to β-lumicolchicine and γ-lumicolchicine several years ago.[3,4] The recent suggestion that α-lumicolchicine is I[5] prompts a description of our results which are in substantial disagreement with the formulation I and which lead unambiguously to structure II for α-lumicolchicine. A central feature in the establishment of structure II was the demonstration that α-lumicolchicine is a dimer rather than a monomer.[6]



α-Lumicolchicine (II, 215, (230), 282 mμ) is quantitatively converted to β-lumicolchicine (III) on heating to the melting point or heating above 100° in solution. Conversely, α-lumicolchicine (II) can be obtained by irradiation of III in Pyrex vessels. α-Lumicolchicine is inert to hydrogen under conditions in which β-lumicolchicine absorbs two equivalents of hydrogen.[1] α-Lumicolchicine fails to give carbonyl derivatives[1] but does show a strong 5.78μ band in the infrared. The head to head dimer structure (II) is required by the facile thermal reversion to III and by the nuclear magnetic resonance spectra of II, IVa,b,c, and Va,b which also require that the head to head dimer be *trans*-fused and specifically eliminate the head to tail dimer. Reduction of α-lumicolchicine with excess sodium borohydride in aqueous tetrahydrofuran gives a diol (IVa; mol. wt., 850 (Rast), 788 (Signier); 227, 278 mμ) which gives a diacetate (IVb; mol. wt., 786; 5.73 μ; 228, 280 mμ) and a monoacetate (IVc, mol. wt., 810; 5.74 μ; 228, 279 mμ; C-methyl, 5.13%, calcd. 5.34%). Oxidation of diol IVa regenerates II. Reduction of α-lumicolchicine with one equivalent of sodium borohydride gives a keto-alcohol (Va, 5.82 μ[7]; 217, (228). 279 mμ) which gives a ketoacetate (Vb, 5.74, 5.84 μ[7]; mol. wt., 748; 217, (228), 281 mμ). Oxidation of the keto-alcohol (Va) gives II and reduction of Va gives diol IVa. Oxidation of the monoacetate (IVc) gives the ketoacetate (Vb). *The formation of a monoacetate, a ketoalcohol and a ketoacetate can only be interpreted in terms of a dimeric structure for α-lumicolchicine.*

The nuclear magnetic resonance spectra of α-lumicolchicine and its derivatives not only confirm the assigned structures but provide rare examples of diamagnetic shielding by a carbon–oxygen double bond. Theory[8] predicts that protons in a roughly conical area above and below the plane of a carbon–oxygen double bond will experience diamagnetic shielding while protons in the vicinity of the carbonyl group but outside this conical area experience paramagnetic shielding (*e.g.*, the paramagnetic shift of aldehydic protons). The nuclear magnetic resonance spectrum of α-lumicolchicine is remarkably similar to that of β-lumicolchicine; the most notable differences are the absence of the 3.32 τ doublet from the olefinic hydrogen of III and the shift of one methoxyl resonance from 6.28 to 6.98 τ. Methoxyl groups α- to ketones usually appear in the 6.4-6.6 τ region (VI, 6.60τ; VIIa, 6.40τ; VIIb, 6.58τ; VIIc, 6.57τ).[9] The resonance at 6.98 τ is beyond even the value for dimethyl ether (6.76τ). This shift must result from diamagnetic shielding within the molecule. The shielding cannot arise solely from the carbonyl adjacent to the methoxyl group (*cf.* VI and VII) and thus must involve the ketonic carbonyl in the other half of the dimer. This would not be possible in a head to tail dimer or in a *cis*-fused head to head dimer but is accounted for neatly by structure II (see stereoformula VIII). The rotating methoxyl groups α- to the ketone carbonyls must pass directly over the ketone carbonyl of the other half of the dimer. Evidence that diamagnetic shielding is responsible for the observed





(1) R. Grewe and W. Wulf, *Ber.*, **84**, 621 (1951). The α-lumicolchicine which we prepared was identical with a sample provided by Professor R. Grewe.

(2) F. Šantavý, *Biol. Listy*, **31**, 246 (1950).

(3) E. J. Forbes, *J. Chem. Soc.*, 3864 (1955).

(4) P. D. Gardner, R. L. Brandon and G. R. Haynes, *J. Am. Chem. Soc.*, **79**, 6334 (1957).

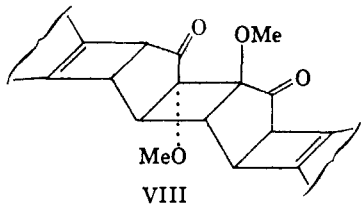
(5) G. O. Schenck, H. J. Kuhn and O.-A. Neumüller, *Tetrahedron Letters*, No. 1, 12 (1961).

(6) α-Lumicholchicine has been reported to give monomeric molecular weight.[5]

(7) This carbonyl absorption is at slightly higher wave length than that of II, but rearrangement is precluded by the interconversion of Va and II and Va and IVa and the oxidation of IVc to Vb.

(8) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, pp. 122-124.

(9) W. G. Dauben, K. Koch, O. L. Chapman and S. L. Smith, *J. Am. Chem. Soc.*, **83**, 1768 (1961).



VIII

shift comes from examination of the resonance positions of the methoxyl protons in diol IVa (normal, 6.75 τ), ketoalcohol Va (normal 6.81 and shifted 6.90τ) and ketoacetate Vb (normal 6.75 and shifted 6.88τ). *The duality of the methoxyl resonance in Va and Vb offers unequivocal evidence of the dimeric nature of these compounds.* The N–H resonance in the diol IVa is strongly shifted to low field (1.95 τ) from the N–H resonance in II (3.28 τ). This shift is shown by all derivatives of II which possess an hydroxyl group and is the result of hydrogen bonding between the acetamido nitrogen and the nearest hydroxyl group. This is possible only if these groups are *cis*- thus defining the stereochemistry of IVa,b,c and Va,b. The duality of the N–H resonance in the monoacetate (1.76, 3.37 τ), the ketoalcohol (1.95, 3.60 τ) and the ketoacetate (3.15, 3.86 τ) emphasizes again the dimeric nature of these compounds.

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RECEIVED AUGUST 2, 1961

CONFIGURATIONAL ANALYSIS OF 4-FORMYL-1-METHYLPYRIDINIUM IODIDE OXIMES AND ITS RELATIONSHIP TO A MOLECULAR COMPLEMENTARITY THEORY ON THE REACTIVATION OF INHIBITED ACETYLCHOLINESTERASE

Sir:

Wilson[1,2] has offered the hypothesis that chemotherapeutic activity of 2-formyl-1-methylpyridinium iodide oxime in the treatment of "nerve gas" poisoning depends both on its ability to associate with inhibited enzyme at the site of phosphorylation and a proper orientation of the reactive oximino function for enzyme reactivation by nucleophilic displacement of the phosphate grouping. The *anti* configuration in the 2(and 4)-formyl-1-methylpyridinium oximes satisfied geometrical dispositions defined for the displacement reaction[2]; support for the contribution of geometric conformation regarding the reactivation rates of inhibited acetylcholinesterase was obtained from observations of enhanced activity of the "oximes" of the "anti" configuration.[2] Only 2-formyl-1-methylpyridinium iodide oxime was claimed sufficiently stable in the "*syn*" series for study and was not found active in reactivating inhibited acetylcholinesterase.[2] Subsequently, it was discovered that the unstable "*syn*" series compounds were carbinolamines, not oximes.[3]

Recent studies in these Laboratories have established that both geometrical isomers of isonicotinaldehyde oxime may be isolated.[4] The *syn* isomer

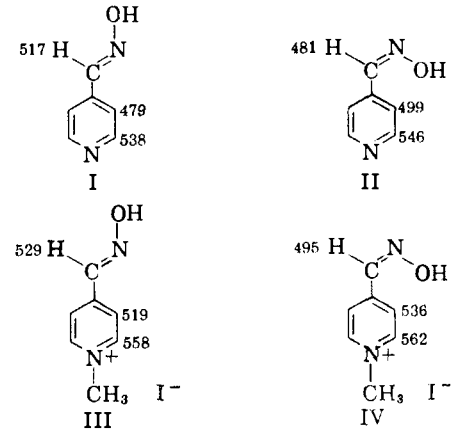

Fig. 1.—Nuclear magnetic resonance peaks (c.p.s.) of isonicotinaldehyde oximes and 4-formyl-1-methylpyridinium iodide oximes from spectra obtained by Varian Associates in deuterium oxide at 60 Mc. The ring proton resonances refer to doublets. Tetramethylsilane was used as internal reference at 0 with respect to observed resonance.

of isonicotinaldehyde oxime, I, m.p. 132–133°, was reported previously.[5] The other geometrical isomer, II, m.p. 165–167° (*Anal.* Found for $C_6H_6N_2O$: C, 58.8; H, 4.9; O, 13.3) was isolated in yields of less than 5% from isonicotinaldehyde and hydroxylamine in basic aqueous media at 10–15° by fractional crystallization from the *syn* isomer. This procedure was not satisfactory because of inconsistent reproducibility, but a better method was not found. Alkylation of I and II with methyl iodide yielded isomeric 4-formyl-1-methylpyridinium iodide oximes, III (m.p. 182–183°; reported[5] 181–183°, *pKa* 8.6) and IV, m.p. 169–172° (*Anal.* Found for $C_7H_9IN_2O$: C, 32.3; H, 3.3; O, 6.3; neut. equiv., 246; p*K*a 9.0), respectively.

On comparing the nuclear magnetic resonance spectra of I and II it was noted that the signal from the hydrogen on the oximino carbon was shifted chemically to lower field in the spectrum of I. This suggests by analogy with propionaldoxime,[6] that the hydrogen is *syn* to the oxime oxygen (Fig. 1). Additional strength for this assignment is found in the signals from the ring protons *ortho* to the oximino function which are chemically shifted further

(1) I. B. Wilson and S. Ginsburg, *Biochim. et Biophys. Acta*, **18**, 168 (1955).

(2) I. B. Wilson, *Federation Proc.*, **18**, 752 (1959).

(3) E. J. Poziomek, D. N. Kramer, B. W. Fromm and W. A. Mosher, *J. Org. Chem.*, **26**, 423 (1961).

(4) E. J. Poziomek, D. N. Kramer and W. A. Mosher, Abstr. 138th Meeting, Am. Chem. Soc., 1960.

(5) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

(6) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958). Cited by J. A. Pople, W. G. Schreiner and H. J. Berstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 374. To check Phillips' assignment[6a] of the two —CH=NOH multiplets arising from *syn-anti* isomerism, Lustig[6b] examined the spectra of the two *p*-chlorobenzaldoximes in dimethyl sulfoxide solution. The —CH=NOH resonance of the *syn* oxime appeared at lower field and Phillips' assignment[6a] is substantiated. The structures of both isomers of *p*-chlorobenzaldoxime had been determined previously through X-ray diffraction studies.[6c] (b) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961). (c) B. Jerslev, *Nature*, **166**, 741 (1950); **180**, 1410 (1958).