Communications TO THE EDITOR

Conformational Study of 1,2,2,6,6-Pentamethyl-4-Phenyl-4-Piperidinol[1,2]

Sir:

Compounds having three opposing axial substituents are unknown with cyclohexane derivatives[3]; however, several substituted piperidines having this structural feature have been prepared. Prominent among these are the 1,2,2,6,6,-pentamethyl-4,4-disubstituted-piperidines[4] which, assuming the piperidine ring to be in the chair form, must have three opposing axial substituents due to the geminal substitution on the 2, 4, and 6 positions.

The consequence of this three-way axial interference in the chair form should be a lowering of the energy barrier between the chair and boat forms. The major steric interaction in the boat form of a cyclohexane derivative, *i.e.*, the 1-"flagpole" substituent with the 4-"flagpole" substituent, is missing in the piperidine ring provided the "second substituent" on the nitrogen, the free pair of electrons, interacts with the "flagpole" substituent on the 4-position of the piperidine.

A piperidine derivative having the favorable requirements for the boat form mentioned above is 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (I). The preparation of I hydrochloride has been reported[4b]; however, the reactions of the compound did not indicate any unusual properties of the hydroxyl group. Thus I was reported to be acylated to 1,2,2,6,6-pentamethyl-4-acetoxy-4-phenylpiperidine (II) using conditions no more vigorous than those required for the acylation of 1-methyl-4-phenyl-4-piperidinol (III). This reaction may be contrasted with the unsuccessful attempts to acylate 1,2,2,6-tetramethyl-4-phenyl-4-piperidinol (IV)[5].

A reinvestigation of the properties of I has led to several interesting observations. The reactions of phenyl lithium with 1,2,2,6,6-pentamethyl-4-piperidone gave I, b.p. 130–133° at 0.5 mm., $n_D^{25.5}$ 1.5339 (Calcd. for $C_{16}H_{25}NO$: C, 77.68; H, 10.19. Found: C, 77.43; 9.99) which had not been isolated previously. The ultraviolet and infrared absorption spectra were consistent with this structure and definitely eliminated any possibility that I had undergone dehydration. Unlike III and IV, 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (I) was a thick oil which defied all attempts at crystallization (even standing for periods of greater than one year). The hydrochloride of I was prepared, m.p. 235–236°, lit.[4b] m.p. 234–236°, but analysis did not indicate the six molecules of water of hydration previously reported (Calcd. for $C_{16}H_{26}ClNO$: Cl, 12.5; calcd. for $C_{16}H_{26}ClNO \cdot H_2O$: Cl, 11.8; calcd. for $C_{16}H_{26}ClNO \cdot 6H_2O$: Cl, 9.07. Found: Cl, 11.7). All attempts to form the acetate ester of I failed and only starting material could be isolated. Although the melting point 242–244°, of the hydrochloride from this reaction was higher than that obtained for I hydrochloride, the infrared and ultraviolet absorption spectra of the reaction product were identical with those of I hydrochloride. The higher melting hydrochloride melted with decomposition, perhaps indicating a difference in degree of hydration; however, neither halogen analysis nor infrared absorption spectra show any difference in composition. *Anal.* Calcd. for $C_{16}H_{26}ClNO$: Cl, 12.5. Found: Cl, 11.8.

The physical state of I and the reduced reactivity of the hydroxyl of I suggested the possibility of intramolecular hydrogen bonding between the 1-nitrogen and the 4-hydroxyl group of the boat form of I. This hypothesis was confirmed by the infrared absorption spectra of I in carbon disulfide and carbon tetrachloride solutions at low concentrations (2.20×10^{-2} *M* in 1 mm. path; 1.10×10^{-2} *M* in 2 mm. path; and 5.5×10^{-3} *M* in 4 mm. path). There was no change in the spectrum on dilution: a sharp band at 3555 cm.$^{-1}$ (unbonded) and a broad band at 3350 cm.$^{-1}$ (bonded). For comparison a similar study of 1-methyl-4-phenyl-4-piperidinol (III) was made. At comparable concentrations (1.47×10^{-2} *M* in 2 mm. path and 7.3×10^{-3} *M* in 4 mm. path) the infrared absorption spectra of III showed little or no bonded hydroxyl for it gave only a sharp band at 3565 cm.$^{-1}$ (unbonded). More concentrated solutions of III showed intermolecular hydrogen bonding with a sharp band at 3565 cm.$^{-1}$ (unbonded) and a broad band at 3130 cm.$^{-1}$ (bonded). The 3130-cm.$^{-1}$ band disappears on dilution of the solution.

These data indicate the presence of significant

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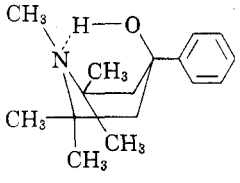
(2) This paper was presented before the Division of Organic Chemistry at the 132nd Meeting of the AMERICAN CHEMICAL SOCIETY at New York, N. Y., September 8–13, 1957.

(3) W. Klyne, *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. I, p. 51.

(4) (a) G. Merling, *Ber. deut. pharm. Ges.*, **6**, 173 (1896); *J. Chem. Soc.*, **72**, 499 (1897). (b) G. M. Badger, *et al.*, Brit. Patent **576,962**, April 29, 1946; *Chem. Abstr.*, **24**, 3782 (1948). (c) Robert R. Chauvette, thesis, University of New Hampshire (1954). (d) W. Steinkopf and W. Ohse, *Ann.*, **448**, 205 (1926). (e) L. Orthner, *Ann.*, **459**, 217 (1927).

(5) G. Badger, J. Cook, and G. Donald, *J. Chem. Soc.*, 197 (1950).

amounts of the boat form of I in the pure state and in solution. This is unique with the monocyclic piperidine derivatives and undoubtedly results from the combination of three factors: (1) extreme steric strain of three opposing axial groups in the chair form, (2) lack of interference between the two "flagpole" substituents in the boat form, but rather (3) stabilization of the boat form by hydrogen bond formation between the two "flagpole" substituents.[6]



I

(6) Added in proof: Barton [*J. Chem. Soc.*, 2907 (1957)] recently reported similar conclusions concerning the conformation of the A ring of 2-β-bromolanostan-3-one.

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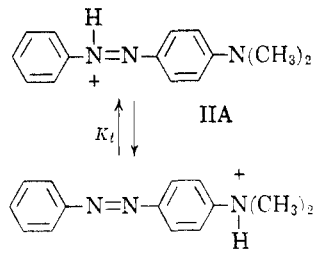
Tautomeric Equilibria. III. The Structure of the Conjugate Acid of *p*-Dimethylaminoazobenzene

Sir:

The structure of the conjugate acid of *p*-dimethylaminoazobenzene has been the subject of considerable discussion and controversy in recent years.[1] We are currently engaged in an extensive program having for one of its aims the unequivocal determination of this structure by a variety of methods. One of the lines of attack has given such a clear-cut decision that we believe preliminary publication in this form is indicated.

We have now determined the pK_a of the conjugate acid of *p*-phenylazo-*N*,*N*,*N*-trimethylanilinium methyl sulfate and of the second conjugate acid of *p*-dimethylaminoazobenzene by a spectrophotometric technique. In the process the spectra of *p*-phenylazo-*N*,*N*,*N*-trimethylanilinium ion (I) and of the first conjugate acid of *p*-dimethylaminoazobenzene (II) were needed. The spectra, in 5% sulfuric acid as solvent, are given in Fig. 1. The spectra are readily explained by the assumption, proposed by earlier workers[1b] that II is an equilibrium mixture of II A and II B.



IIA

IIB

The band at 316 mμ, due to II B, occurs at a lower intensity than the same band in I. The 516 mμ band, then, must be ascribed to II A. The equilibrium appears to shift slightly with solvent composition; with increasing sulfuric acid concentration in the range from 5–30%, the height of the 516 mμ peak increases, and simultaneously the height of the 316 mμ peak decreases. Making the perfectly reasonable assumption that the spectra of I and II B agree exactly, not only in wave length but also in intensity, we calculate an equilibrium constant K_t = [IIA]/[IIB] = 1.2 in 5% sulfuric acid, and K_t = 2.2 in 20% sulfuric acid.

The pK_a measurements confirm the above conclusions. Since no H_+-Scale is available the calculations were based on Hammett's H_0-Scale.[2] Although this procedure may partially invalidate the absolute values found, it is unlikely to have a profound effect on the difference between the pK_a's of the two compounds, which is the only quantity of importance for the present argument. The pK_a values found in this way were: IH^+, −3.65 ± 0.03; IIH^+, −3.04 ± 0.06.

Since

$$pK_a(IH^+) = -\log [I][H^+]/[IH^+]$$

$$pK_a(IIH^+) = -\log [IIA + IIB][H^+]/[IIH^+]$$

$$= -\log [IIB](1 + K_t)[H^+]/[IIH^+]$$

and assuming that the basicities of I and IIB are identical, *i.e.* that the effect of the groups $-\overset{+}{N}(CH_3)_3$ and $-\overset{+}{N}H(CH_3)_2$ on the basicity of azobenzene is the same, it follows that

$$pK_a(IIH^+) = pK_a(IH^+) - \log(1 + K_t)$$

hence K_t = 3.0. Since this value applies to a solution approximately 50% in sulfuric acid, the agreement with the spectroscopic values is excellent.

Thus it appears unequivocally established that the first conjugate acid of *p*-dimethylaminoazobenzene is an equilibrium mixture of IIA and IIB and the value of the equilibrium constant, although solvent dependent, in moderately concentrated sulfuric acid solution is about 1–3. The implications of this finding relating to substituted dimethylaminoazobenzenes will be examined in a later paper.

(1) (a) M. T. Rogers, T. W. Campbell, and R. W. Maatman, *J. Am. Chem. Soc.*, **73**, 5122 (1951); H. H. Jaffé, *J. Chem. Phys.*, **21**, 415 (1953); I. M. Klotz, H. A. Fiess, J. Y. Chen Ho, and M. Mellody, *J. Am. Chem. Soc.*, **76**, 5136 (1954); (b) W. S. McGuire, I. F. Izzo, and S. Zuffanti, *J. Org. Chem.*, **21**, 632 (1956); G. Cilento, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **78**, 1718 (1956); E. Sawicki, *J. Org. Chem.*, **22**, 365 (1957).

(2) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 267.