

reason to expect geometric isomerization about the C<sub>1</sub>-N bond since the geometric configuration of this bond is already the most favorable, *i.e.*, the C<sub>6</sub>H<sub>5</sub>NH group is *syn* to the hydrogen atom at C-1.

### Experimental

Proton resonance spectra were obtained with a Varian HR-60 spectrometer at 14,100 gauss. Dimethyl sulfoxide [Crowl-Zellerbach Co.] was stored over Linde Molecular Sieve 4A and used without further purification.

The bisphenylhydrazones of biacetyl, cyclopentane-1,2-dione, and cyclohexane-1,2-dione and the phenylosazones of erythrose, arabinose, and glucose were prepared from the reaction of phenylhydrazine on the corresponding carbonyl compound. The observed melting points agreed with those reported in the literature. Glyoxal bisphenylhydrazone was obtained from the reaction of phenylhydrazine and formaldehyde<sup>22</sup> and glyceraldehyde phenylosazone from dihydroxyacetone and excess phenylhydrazine. Glucose 1-methylphenyl-2-phenylosazone was pre-

(22) H. von Pechmann, *Ber.*, **30**, 2459 (1897).

pared by the displacement reaction of glucose methylphenylosazone and 1 equiv. of phenylhydrazine.<sup>23</sup>

**Pyruvaldehyde Bisphenylhydrazone.**—Acetol acetate (2 g.), phenylhydrazine (7 g.), acetic acid (4 ml.), and 80% aqueous ethanol (20 ml.) were warmed on a steam bath for 10 min. On cooling, pale yellow plates, m.p. 145–147°, slowly precipitated (lit.<sup>24</sup> 146–147°).

**3-Acetylglyceraldehyde Phenylosazone.**—Acetic anhydride (1 ml.) was added to a solution of 0.45 g. of glyceraldehyde phenylosazone in 7 ml. of pyridine and the mixture allowed to stand overnight at room temperature. Hydrolysis of the excess acetic anhydride with water followed by ether extraction and recrystallization from ether gave the acetate, m.p. 123–124°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>: C, 65.78; H, 5.85; N, 18.05. Found: C, 66.07; H, 6.14; N, 17.90.

**Acknowledgment.**—The authors wish to thank the Alfred P. Sloan Foundation for financial support of this investigation.

(23) L. L. Engel, *J. Am. Chem. Soc.*, **57**, 2419 (1935); G. Henseke and H. Hantschel, *Chem. Ber.*, **87**, 477 (1954).

(24) H. von Pechmann, *Ber.*, **20**, 2539 (1887).

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## Extrathermodynamic Relationships in Schiff Base Formation

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The rates of reaction of substituted benzaldehydes with *n*-butylamine in dioxane at 25° and with *n*- and *t*-butylamine in methanol at 25 and 45° are reported. The data do not follow the simple Hammett equation, but are correlated approximately by the two-parameter equation  $\log k/k_H = -1.335\sigma^+ + 0.803\sigma^-$  (methanol, 25°). This relationship is probably the result of  $\sigma^+$  dependence for the carbonyl-addition equilibrium and  $\sigma^0$  or  $\sigma^-$  dependence for subsequent equilibria and for the rate-controlling step. Enthalpy-entropy plots are given for these series and for the series of alkylamines previously studied.

Several reasons have been advanced for the non-linearity of Hammett plots of the rates of carbonyl-addition reactions. Some of these, if correct, should cause the curvature to be critically dependent on the solvent. Hemiacetal formation with an alcoholic solvent, for example, while it could in principle decrease the net rate of competing cyanohydrin formation,<sup>2</sup> obviously is not possible in a nonhydroxylic solvent. A shift in rate-controlling step with changing aromatic substituent has been proposed to account for nonlinear  $\rho$ - $\sigma$  plots in condensation reactions<sup>3</sup> and Schiff base formation<sup>4</sup> and is definitely responsible in semicarbazone formation.<sup>5</sup> Such a shift would, like a change in mechanism<sup>6</sup> with substituent or even the diversion of the reaction through a different series of intermediates,<sup>7</sup> almost certainly be so solvent dependent as not to take place at all in a different type of solvent or, at the very least, to change markedly the type of curvature observed.

There is, on the other hand, a possible cause of abnormal depression of reactivity for electron-donating *para* substituents which would be more likely to persist from one solvent to another. Resonance of such substituents with the carbonyl group could give rise to a

$\sigma^+$  dependence of one step of the reaction which, combined with a  $\sigma^-$  dependence for other steps, would yield a nonlinear Hammett plot with no change in rate-controlling step.

We have therefore measured the rates of reaction of a series of substituted benzaldehydes with *n*-butylamine both in methanol<sup>4</sup> and in dioxane. In order to study the superposition of structural effects in the amine<sup>8</sup> and the aldehyde, we have also determined the corresponding rates with *t*-butylamine in methanol at 25 and 45°.

### Experimental

**Materials.**—Reagent-grade methanol (Mallinckrodt) was used without purification. Dioxane was refluxed over several portions of sodium hydroxide pellets. Concentrated hydrochloric acid was then added and the solution boiled in contact with air. After drying with sodium hydroxide and sodium wire, the dioxane, b.p. 101.1–101.2°, was distilled under nitrogen and used immediately. Liquid aldehydes were also freshly vacuum distilled under nitrogen. *p*-Nitrobenzaldehyde and *p*-dimethylaminobenzaldehyde were recrystallized from water, *p*-chlorobenzaldehyde from ethanol-water; this last aldehyde also sublimes well.

**Procedure.**—The kinetic runs were made as previously described.<sup>4</sup> When dioxane was the solvent the reaction was carried out under nitrogen and protected from light. The concentrations of both aldehyde and amine were generally 0.005–0.05 *M*. Each 1-ml. sample regardless of solvent was diluted with methanol to a concentration suitable for the Beckman Model DU spectrophotometer. Except in runs involving *m*- and *p*-nitrobenzaldehydes, hydrochloric acid was added to the diluent to convert the Schiff bases to their conjugate acids, ArCH=N<sup>+</sup>HR, and unreacted aldehydes to acetals.

(1) Du Pont Teaching Assistant, 1959–1960.

(2) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, pp. 347–351.

(3) D. S. Noyce, A. T. Bottini, and S. G. Smith, *J. Org. Chem.*, **23**, 752 (1958).

(4) G. M. Santerre, C. J. Hansrote, Jr., and T. I. Crowell, *J. Am. Chem. Soc.*, **80**, 1254 (1958).

(5) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

(6) H. H. Jaffé, *Chem. Rev.*, **53**, 236 (1953).

(7) D. S. Noyce and L. R. Snyder, *J. Am. Chem. Soc.*, **81**, 620 (1959).

(8) R. L. Hill and T. I. Crowell, *ibid.*, **78**, 2284 (1956).

TABLE I  
 SPECTRA<sup>a</sup> OF PROTONATED SCHIFF BASES ArCH=NH<sup>+</sup>R

Ar	$\lambda_{\max}$ , m $\mu$	R = <i>n</i> -C <sub>4</sub> H <sub>9</sub>		R = <i>t</i> -C <sub>4</sub> H <sub>9</sub>	
		$10^{-4} \epsilon$	$10^{-4} \epsilon$	$\lambda_{\max}$ , m $\mu$	$10^{-4} \epsilon$
<i>p</i> -(CH <sub>3</sub> ) <sub>2</sub> N	393 <sup>b</sup>	4.92 <sup>b</sup>		391	4.91
<i>p</i> -OCH <sub>3</sub>	320 <sup>b</sup>	2.89 <sup>b</sup>			
<i>p</i> -CH <sub>3</sub>	288 <sup>b</sup>	2.14 <sup>b</sup>			
<i>m</i> -CH <sub>3</sub>	279	1.94			
H	275 <sup>b</sup>	1.71 <sup>b</sup>	274		2.08
<i>m</i> -OCH <sub>3</sub>	281	1.46			
<i>p</i> -Cl	286 <sup>b</sup>	1.82 <sup>b</sup>	285		2.22
<i>m</i> -Cl	272	1.08	271		1.63
<i>m</i> -NO <sub>2</sub>	235 <sup>b,c</sup>	2.65 <sup>c</sup>			
<i>p</i> -NO <sub>2</sub>	281 <sup>b,c</sup>	1.65 <sup>c</sup>	281 <sup>c</sup>		1.94 <sup>c</sup>

<sup>a</sup> Solvent methanol. <sup>b</sup> Ref. 4. <sup>c</sup> Unprotonated Schiff base.

The spectra of the Schiff bases were simply obtained from reaction mixtures known (by the invariance of  $\epsilon$  with excess amine concentration) to have gone to completion. The absorptivities used for analysis are given in Table I. Several were obtained from measurements on Schiff bases actually isolated.<sup>4</sup>

### Results

**Dioxane.**—Schiff base formation in this solvent is subject to strong catalysis by acids and peroxides. By scrupulously excluding these impurities we obtained the rate constants  $k$  in Table II.

 TABLE II  
 RATE CONSTANTS,  $k$  (L./MOLE-SEC.), FOR REACTION OF *n*-BuNH<sub>2</sub> WITH XC<sub>6</sub>H<sub>4</sub>CHO IN DRY DIOXANE

X	$10^4 k$	No. of detns.	a.d., %
3,4-CH <sub>2</sub> O <sub>2</sub>	0.272	10	11
<i>p</i> -CH <sub>3</sub> O	3.0	4	5
H	11.1	4	9
<i>p</i> -Cl	7.8	7	13
<i>p</i> -NO <sub>2</sub>	3.4	6	5

The sensitivity of the reaction to acid catalysis is accurately expressed by the equation  $k' = k + k_c[C]$ ; the values of  $k_c$ , the catalytic constant for the catalyst C, are 1.07 l.<sup>2</sup>/mole<sup>2</sup>-sec. (acetic acid, piperonal) and 33 l.<sup>2</sup>/mole<sup>2</sup>-sec. (benzoic acid, benzaldehyde). The reaction seemed less sensitive to traces of water: 0.17 M H<sub>2</sub>O, added in one experiment, raised the  $k$ -value for piperonal to  $3.8 \times 10^{-5}$  l./mole-sec.

The effect of benzoyl peroxide was more complex. If added initially to a reaction mixture of piperonal and *n*-butylamine in dioxane, the peroxide caused a gradual acceleration to a rate corresponding to a  $k_c$  of about 5 l.<sup>2</sup>/mole<sup>2</sup>-sec. However, a solution of peroxide and amine in dioxane, after standing 16 hr., contained no peroxide as determined by iodide titration, yet this spent solution was an effective catalyst for Schiff base formation.

The reaction was very markedly accelerated by exposing the Pyrex reaction vessel in the thermostat to white light.

**Methanol.**—The rate constants for Schiff base formation in methanol are given in Table III, which includes values from our earlier work. Each reaction was run at least once with added sodium methoxide to make sure that the rate was independent of pH in the range used. Only *p*-nitrobenzaldehyde showed a progressive decrease in rate constant with increasing pH: at 25°  $k$  was linear in the molarity of sodium methoxide, from  $1.88 \times 10^{-3}$  l./mole-sec. with no added NaOCH<sub>3</sub> to  $7.7 \times 10^{-4}$  l./mole-sec. at 0.15 M NaOCH<sub>3</sub>. We did

 TABLE III  
 RATE CONSTANTS (L./MOLE-SEC.) FOR SCHIFF BASE FORMATION IN METHANOL

X	<i>n</i> -BuNH <sub>2</sub>		<i>t</i> -BuNH <sub>2</sub>	
	25°	45°	25°	45°
<i>p</i> -Me <sub>2</sub> N	0.0158 <sup>a</sup>		0.000375	0.00112
<i>p</i> -CH <sub>3</sub> O	.0465 <sup>a</sup>			
3,4-CH <sub>2</sub> O <sub>2</sub>	.0337 <sup>a</sup>		.00115 <sup>b</sup>	.00299 <sup>b</sup>
<i>p</i> -CH <sub>3</sub>	.085 <sup>a</sup>			
<i>m</i> -CH <sub>3</sub>	.094			
<i>m</i> -OH	.090 <sup>a</sup>			
H	.104 <sup>a</sup>		.00310	.0071
<i>m</i> -OCH <sub>3</sub>	.093			
<i>p</i> -Cl	.080 <sup>a</sup>		.00327	.0079
<i>m</i> -Cl	.083		.00316	.0098
<i>m</i> -NO <sub>2</sub>	.0352 <sup>a</sup>			
<i>p</i> -NO <sub>2</sub>	.0328 <sup>a</sup>		.00188	.0064

<sup>a</sup> Ref. 4. <sup>b</sup> Ref. 8.

not investigate this effect except to show that these concentrations of methoxide do not change the spectra of solutions of the aldehyde itself.

Table IV shows the energies and entropies of activation calculated from the rate constants at 25 and 45°.

 TABLE IV  
 ENERGY (KCAL./MOLE) AND ENTROPY (CAL./MOLE-DEG. AT 25°) OF ACTIVATION FOR SCHIFF BASE FORMATION

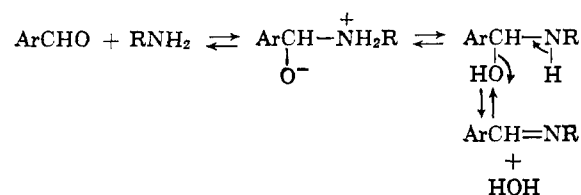
X	<i>n</i> -BuNH <sub>2</sub> <sup>a</sup>		<i>t</i> -BuNH <sub>2</sub>	
	$E_a$	$\Delta S^*$	$E_a$	$\Delta S^*$
<i>p</i> -Me <sub>2</sub> N	8.0	-41.9	10.3	-41.7
3,4-CH <sub>2</sub> O <sub>2</sub>	7.0	-44.0	9.6 <sup>b</sup>	
H			7.7	-46.3
<i>p</i> -Cl	7.3	-41.3	8.3	-44.3
<i>m</i> -Cl			10.6	-36.7
<i>p</i> -NO <sub>2</sub>	10.0	-33.7	11.8	-33.5

<sup>a</sup> Ref. 4. <sup>b</sup> Ref. 8. The enthalpies  $\Delta H^*$  in these references were calculated by subtracting 0.600 kcal. from the experimental activation energies  $E_a$ .

### Discussion

**Mechanism in Aprotic Solvents.**—The most detailed studies of organic reaction mechanisms have dealt with acid-base catalysis in aqueous or alcoholic solutions. These studies have been encouraged both by the applicability of buffered aqueous solution conditions to biochemical reactions and by the remarkable insight into consecutive reaction steps obtainable by varying buffer concentration and pH.

The problem of the mechanism of Schiff base formation in such aprotic solvents as dioxane,<sup>9</sup> benzene, and ether should nevertheless not be neglected. It was recognized by Kresze and Goetz,<sup>9</sup> who suggested the zwitterion ArCH(O<sup>-</sup>)NH<sub>2</sub>R<sup>+</sup> as an intermediate. Assuming that our  $k$ -values represent minimum rates with practically no catalysis by acid impurities, the simplest mechanism is one in which the proton transfers after the initial addition are intramolecular. Acid or base catalysis either by butylamine or by another substrate molecule is inconsistent with the kinetics.

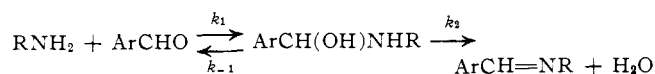


(9) G. Kresze and H. Goetz, *Z. Naturforsch.*, **106**, 370 (1955); **126**, 45 (1957).

Although we observed peroxide catalysis, we cannot yet conclude that it means a free-radical mechanism of Schiff base formation. The increase in rate as the peroxide concentration decreases and the experiment with spent solution both suggest a reaction of the amine with benzoyl peroxide to form some other, probably acidic, species which acts as a catalyst. A similar reservation must be made with regard to the observed photoacceleration.

**Effect of Substituents.**—In both dioxane and methanol, benzaldehyde was the most reactive aldehyde studied. Tables II and III and Fig. 1, in which the rate constants for methanol at 25° are plotted *vs.*  $\sigma$  as a familiar frame of reference, show a maximum in  $k$  near  $\sigma = 0$ . This similarity in the results in two such different solvents almost certainly rules out solvent-substrate interaction, including hemiacetal formation, as a cause of the maximum. The rate is much more sensitive to substituent in dioxane than in methanol.

The rate constants in methanol could be rather poorly approximated by a smooth curve (not shown in Fig. 1) by assuming that  $k_1$  and  $r$  (where  $r = k_2/k_{-1}$ ) both follow Hammett plots with appropriate values of  $\rho_1$  and  $\rho_r$ . If the steady-state method is used for the given consecutive reaction scheme, it can be shown<sup>10</sup> that, if  $\rho_r < 0$



$< \rho_1$  and  $|\rho_r| > \rho_1$ , a maximum in rate as a function of  $\sigma$  will appear when  $r = |\rho_r/\rho_1| - 1$  as the rate-controlling step shifts from addition at low  $\sigma$  to dehydration at high  $\sigma$ .

However, there are three serious objections to this interpretation of our results: the fact that the circles in Fig. 1 do not fall on a smooth curve; the demonstration by Cordes and Jencks,<sup>11</sup> in an excellent investigation of Schiff base hydrolysis, that dehydration is probably rate controlling at the high pH of our experiments; and, most directly, the unlikelihood that a shift in rate-controlling step would occur at the same  $\sigma$ -value in both solvents.

Discarding these explanations, we find a more satisfactory one in the use of  $\sigma^+$  in our correlation equation.<sup>12</sup> The simple equation  $\log k/k_H = \rho^+ \sigma^+$  is not sufficient, but the Yukawa-Tsuno equation,<sup>12,13</sup>  $\log k = -1.92\sigma + 1.36\sigma^+ - 0.957$ , fits the data with an average deviation of 0.08 log unit (SP/S = 0.120). The third term,  $-0.957$ , is the result of considering  $\log k_H$  an adjustable parameter; the observed  $\log k$  for benzaldehyde,  $-0.983$ , together with its  $\sigma$ -value of 0.000, was used merely as one experimental value in the least-squares solution for the coefficients.

A somewhat better fit (a.d. = 0.06, SP/S = 0.085) is obtained by the use of  $\sigma^\circ$ , the normal substituent constant,<sup>14</sup> instead of the Hammett  $\sigma$ . The coefficients are shown in eq. 1.

(10) T. I. Crowell, in "The Chemistry of the Alkenes," S. Patai, Ed., John Wiley and Sons, Inc., New York, N. Y., 1964, p. 266.

(11) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963). We are indebted to Professor Jencks for a discussion of his results before publication.

(12) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(13) (a) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 211; (b) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan*, **32**, 971 (1959).

(14) Reference 13a, p. 215.

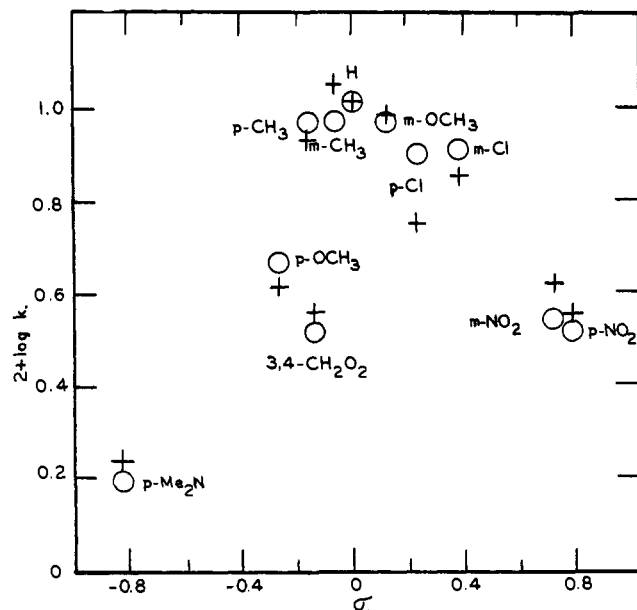


Fig. 1.—Plot of  $\log k$  *vs.*  $\sigma$ , showing lack of  $\rho\sigma$  correlation: O, experimental points; +, calculated by eq. 3.

$$\log k = -1.335\sigma^\circ + 0.803\sigma^+ - 0.983$$

$$\log k/k_H = -1.335\sigma^\circ + 0.803\sigma^+ \quad (1)$$

In this case the calculated constant is equal to the observed  $k_H$ , so that the two equations shown are numerically equivalent. The crosses in Fig. 1 mark the  $\log k$  values calculated by eq. 3. Apparently this type of correlation accounts approximately for the maximum in the simple Hammett plot and the deviations from a smooth bell-shaped curve.

A simple interpretation of eq. 3 is that one step in the mechanism (probably the equilibrium addition to the carbonyl group) is correlated by  $\sigma^+$  and the subsequent equilibria and rate-controlling dehydration, most of which involve atoms insulated from the benzene ring by at least one intervening atom, by  $\sigma^\circ$ . Thus there can be a mechanistic basis for the Yukawa-Tsuno equation.

The insertion of a third parameter, though not justified by our limited set of data, into eq. 1 gives  $\log k = 0.482\sigma - 1.646\sigma^\circ + 0.649\sigma^+ - 0.995$ , but the correlation is not improved.

The observed value for *p*-chlorobenzaldehyde is 0.15 log unit above the calculated value (see Fig. 1). This may be related to the deviation of *p*-chlorobenzaldehyde from a linear rate-equilibrium relationship<sup>5</sup> in semicarbazone formation, which led Leffler and Grunwald to suggest that the measurement was in error.<sup>15</sup> The value for piperonal, calculated by assuming the 3,4-methylenedioxy group equivalent to 3,4-dimethoxy and adding the terms in  $\sigma$  and  $\sigma^+$  for both methoxyl groups, is in good agreement with the observed rate constant.

**Structure of the Amine.**—The rates of reaction of *t*-butylamine with the series of substituted benzaldehydes show a dependence upon substituent similar to that discussed above for *n*-butylamine, but the rates are depressed by 1.2 to 1.6 log units, the sensitivity to the structural change increasing slightly with decreasing  $\sigma$ .

(15) Reference 13a, p. 161.

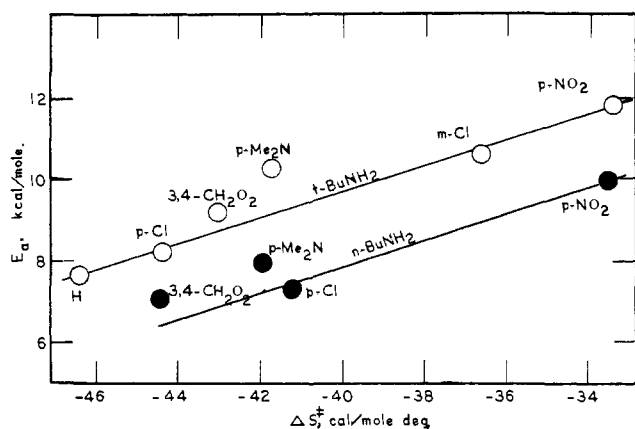


Fig. 2.—Enthalpy-entropy plots for substituted benzaldehydes with *n*- and *t*-butylamine.

In the enthalpy-entropy diagram<sup>16</sup> in Fig. 2, a straight line is drawn through four points of the *t*-butyl series, the slope corresponding to an isokinetic temperature of 316°K. The points for piperonal and *p*-dimethylaminobenzaldehyde are above the line, possibly because of the strong resonance interaction associated with highly negative  $\sigma^+$  values. If a line of the same slope is passed through the *p*-nitrobenzaldehyde point in the *n*-butylamine series the few available points show similar behavior.

Another extrathermodynamic relationship in Schiff base formation is seen in Fig. 3, an enthalpy-entropy plot of our earlier data<sup>8</sup> for the reaction of piperonal with all the primary aliphatic amines through  $C_4H_9NH_2$ . If a line of slope 415° is drawn through the point for ethylamine, the points for the other amines are dis-

(16) Reference 13a, Chapter 9.

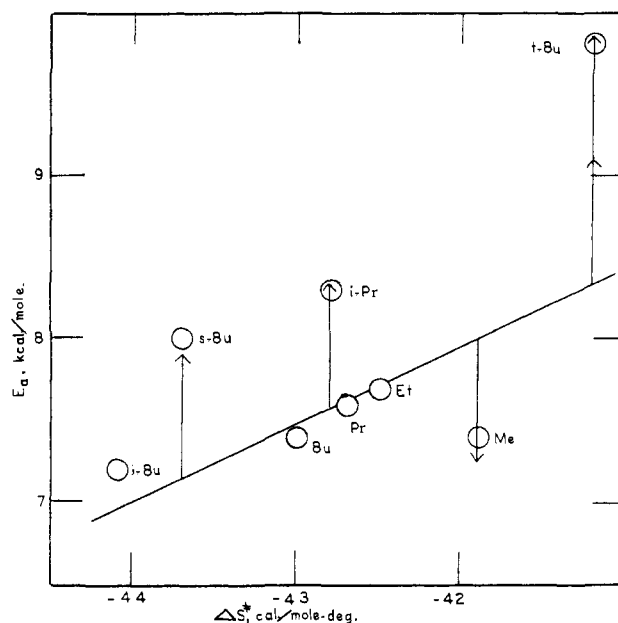


Fig. 3.—Enthalpy-entropy plot for piperonal with primary alkylamines in terms of deviation from a single line caused by  $\alpha$ -substitution.

placed upward from the line by approximately  $0.75(n - 1)$  kcal., where  $n$  is the number of methyl groups attached to the carbon atom bearing the amino group. The data are insufficient to evaluate the effect of chain branching in the  $\beta$ -position as in isobutylamine.

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## The Structure of Amaryllisine

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Amaryllisine has been shown to possess structure III on the basis of close correspondence of infrared, nuclear magnetic resonance, and mass spectra to those of alkaloids of known structure. The failure of combustion analysis is noted.

Although all alkaloids of the *Amaryllidaceae* contain oxygenated aromatic systems, free phenols are seldom isolated.<sup>2</sup> It was therefore of some interest when chromatography of the alkaloid extract from *Brunsvigia rosea* (*Amaryllis belladonna*) over alumina produced a phenolic compound, m.p. 255–258°, which was eluted by chloroform containing ethyl alcohol. Combustion analysis and neutral equivalent of this phenol corresponded to the formula  $C_{17}H_{21}NO_4$ , and analysis showed three methoxyl groups and no  $N-CH_3$ . The compound, which was named amaryllisine, possessed a small positive rotation,  $[\alpha]^{24}_D 2.4^\circ$ , and ultraviolet absorption suitable to a phenol ( $\lambda_{max} 283 \mu$  ( $\epsilon 5900$ )) and shifted by addition of base to  $\lambda 252 \mu$  ( $\epsilon 6600$ ), 297  $\mu$  ( $\epsilon 4080$ ). The infrared spectrum at high dilu-

tion in carbon tetrachloride showed the presence of a hydrogen-bonded hydroxyl ( $3547 \text{ cm.}^{-1}$ ), olefinic hydrogen ( $3032 \text{ cm.}^{-1}$ ), the aromatic system ( $1615$  and  $1590 \text{ cm.}^{-1}$ ), and ether linkages ( $1095$ ,  $1068 \text{ cm.}^{-1}$ ).<sup>3</sup> The methylenedioxy group, which occurs frequently in this family of alkaloids, was absent, for its presence would have been unmistakably revealed by an additional peak near  $965 \text{ cm.}^{-1}$ .<sup>4</sup> The occurrence of three methoxyl groups in the formula  $C_{17}H_{21}NO_4$  allows fourteen carbon atoms and the nitrogen atom to form the basic ring system. However, with a single exception,<sup>5a</sup>

(3) Cf. L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

(4) L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957).

(5) (a) Ismine, 6-(2-methylaminophenyl)piperonyl alcohol, is thought to be a natural degradation product from the series haemanthidine-tazettine-haemanthamine (R. J. Highet, *J. Org. Chem.*, **26**, 4767 (1961)). (b) For a review of the position of norbelladine in the biosynthesis of *Amaryllidaceae* alkaloids, see A. R. Battersby, Tilden Lecture, *Proc. Chem. Soc.*, 189 (1963).

(1) (a) University of California; (b) National Heart Institute.

(2) For recent reviews of the alkaloids of this family, see W. C. Wildman in "The Alkaloids," Vol. VI, R. H. Manske, Ed., Academic Press, Inc., New York, N. Y., 1960, p. 289; H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p. 410.