quency occurs. The behavior of the 7-substituted 1-naphthylamines recalls the work of Califano and Moccia,[35] and Whetsel, Roberson and Krel,[36] found in the pK_a relations of substituted anilines that the substituents p-CH$_3$, p-OCH$_3$ and p-NH$_2$ lie on lines of slope different from those accommodating the substituents m-NO$_2$, m-CN, m-COOCH$_3$, m-Cl, m-OCH$_3$, p-NO$_2$ and p-Cl.

An interpretation of the varied behavior shown in the pK_a–ν graphs must remain a matter of difficulty until more is known of the mechanism of polar and mesomeric effects on NH bonds. The observation that the greatest divergences occur in quinonoid compounds when the substituents are π-electron-donating suggests that the balance of dipole and mesomeric effects in the bases is not the same as that exercised in the acid–base system where both components are affected.

Acknowledgments.—The author is indebted to Dr. E. Challen for microanalyses, to Dr. R. L. Werner and Mr. I. Reece for help with the spectrophotometric and infrared measurements, to Professors P. E. Verkade and J. Cason for samples of difficultly accessible compounds and finally to Imperial Chemical Industries Dyestuffs Research Laboratories for supplies of dyestuff intermediates.

(35) S. Califano and R. Moccia, *Gazz. chim. ital.*, **86**, 1014 (1956).

(36) K. B. Whetsel, W. E. Roberson and M. W. Krell, *Anal. Chem.*, **30**, 1598 (1958).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF NEW SOUTH WALES, SYDNEY, AUSTRALIA]

The Ionization Constants of 3-Substituted Pyridines, 3-Substituted Quinolines and 4-Substituted Isoquinolines

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Measurement of the pK_a values of 3-bromopyridine, 3-nitropyridine, 3-bromoquinoline, 3-nitroquinoline, 4-bromoisoquinoline and 4-nitroisoquinoline together with published data has enabled a survey to be made of the effects of substituents in the "*meta*" positions in these heterocyclic bases. A statistical analysis shows that 3-substituents in pyridine can be classified into those with $-M$ and $+M$ character, the former giving a regression line passing close to the origin, while the latter give a line cutting the ΔpK_a axis at a negative value, this indicating increased mesomeric effects of the substituents as compared with those in equivalent benzoic acids. The Hammett σ-values are reproduced satisfactorily by a modified Taft equation $\sigma = a\sigma_I + b\sigma_R$ and the parameters a and b can be correlated with electronic structures. The similarity of the behavior of the heterocyclic bases with m-substituted anilines and naphthylamines is demonstrated. The anomalous position of 4-hydroxy-isoquinoline is attributed to its zwitterion structure, and an estimate of the tautomeric constant confirms values found by other methods.

This paper records the determination of the dissociation constants of the heterocyclic bases pyridine, quinoline and isoquinoline substituted in the "*meta*" positions by the groups Br and NO$_2$. This information together with the published data for other substituents enables a comparison to be made of the effects of substituents in these bases and reveals the similarity between their effects in heterocyclic bases and the equivalent aromatic amines, aniline, 1-naphthylamine and 2-naphthylamine.

Experimental

3-Nitropyridine was prepared by the method of de-Hartog and Overhoff.[1] Toward the end of one run when the sulfuric acid had been largely converted to bisulfate, a violent explosion took place apparently as a result of overheating. 3-Nitropyridine was obtained in small yield (less than 5%), the colorless crystals from ether melting at 41° (lit.[1] m.p. 41°).

3-Bromoquinoline and 4-bromoisoquinoline were prepared by published methods,[2,3] and converted to 3-aminoquinoline and 4-aminoisoquinoline by ammonolysis as described by Craig and Cass.[3] 3-Hydroxyquinoline and 4-hydroxyisoquinoline are most easily made by the diazo reaction. The latter substance was prepared as follows: 4-aminoisoquinoline (2 g.) was dissolved in 5 N sulfuric acid (50 ml.), and diazotized with sodium nitrite (1 g.) in 5 ml. of water. The diazo solution was filtered and added to 150 ml. of 2 N sulfuric acid. The temperature was raised to 70° (evolution of nitrogen became vigorous) and held at this value for 15 minutes. The cooled solution was treated with 5 N sodium hydroxide until alkaline and filtered, the filtrate being acidified with acetic acid until precipitation was complete. The precipitate was crystallized from dilute alcohol as colorless crystals of 4-hydroxyisoquinoline, melting with decomposition at 233°, blackening at 200°.

Anal. Calcd. for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.48; H, 4.74; N, 9.83.

3-Hydroxyquinoline prepared by the same method had m.p. 198°, (lit.[4] m.p. 198°).

3-Nitroquinoline was prepared by the condensation of o-aminobenzaldehyde with methazonic acid according to Schofield and Theobald.[5] 4-Nitroisoquinoline has not been reported previously and it was prepared as described: 4-aminoisoquinoline (3 g.) was dissolved in 2 N sulfuric acid (25 ml.), and diazotized with sodium nitrite (1.5 g.) in 5 ml. of water at 5°. The solution was neutralized with calcium carbonate and filtered, the filtrate being added to an aqueous solution of sodium nitrite (25 g.) in 100 ml. of water containing a suspension of 10 g. of cupro-cuproso sulfite and the mixture allowed to stand overnight. The solution was extracted with chloroform, the chloroform removed, and the residue crystallized from aqueous alcohol in pale yellow needles of m.p. 61–64°. Extraction of the material with 0.01 N hydrochloric acid to remove basic impurities and then recrystallization from alcohol gave pure 4-nitroisoquinoline, m.p. 64.5°.

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.06; H, 3.48; N, 16.09. Found: C, 62.41; H, 3.33; N, 15.98.

Determination of pK_a Values.—pK_a values were determined in all cases by the spectrophotometric method described in a previous paper,[6] acetate and chloroacetate buffers being used for pK_a values between 2 and 5. For the nitro-substituted compounds whose pK_a values lie between 1 and 1.5, the procedure was the same with the exception that the bases were converted to the acid form with

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(1) H. J. de Hartog and J. Overhoff, *Rec. trav. chim.*, **49**, 552 (1930).

(2) R. R. Renshaw and H. L. Friedman, THIS JOURNAL, **61**, 3321 (1939).

(3) J. J. Craig and W. E. Cass, *ibid.*, **64**, 783 (1942).

(4) W. H. Mills and W. H. Watson, *J. Chem. Soc.* **97**, 753 (1910).

(5) K. Schofield and R. S. Theobald, *ibid.*, 395 (1950).

(6) A. Bryson, THIS JOURNAL, **82**, 4862 (1960).

20% sulfuric acid, and solutions of intermediate composition obtained with 0.1 *N* and 0.05 *N* sulfuric acid. The correction for ionic strength in these cases was taken as −0.20. For the remaining bases the correction of −0.06 used in previous work[6] was applied.

Experimental Results

Table I gives a summary of pK_a values available from the literature or determined in this investigation. The figures have been corrected as far as possible for ionic strength.

Discussion

Substituted Pyridines.—The only systematic discussion to date on the behavior of substituents in heterocyclic bases is that of Jaffé and Doak[7] who examined the available data for substituted pyridines, and concluded that the Hammett equation was obeyed, the regression line passing through the origin with a slope of 5.71. The present investigation suggests a pattern somewhat different from that of Jaffé and Doak, and this may arise partly from the choice of substituent constants in the two treatments. Since a comparison with equivalent benzoic acids is the basis of the Hammett equation, it is desirable to select σ-values based on the dissociation constants of these acids, and a critical survey of the available data has been made recently by McDaniell and Brown.[8] Based on this, the following σ_m values have been selected for the regression analysis: NO_2, 0.71; Cl, 0.37; Br, 0.39; I, 0.35; F, 0.34; OCH_3, 0.11_5; OH, 0.10; $COCH_3$, 0.37; COOH, 0.35; CN, 0.64; CH_3, −0.07; and NH_2, −0.07. Of the values chosen, perhaps only that for *m*-NH_2 needs justifying. The generally used Hammett value of −0.161 was not originally derived from *m*-aminobenzoic acid, the relevant dissociation constant of which is rendered uncertain by the tautomerism of the acid. A discussion of the acid–base equilibria in *m*-aminobenzoic acid has been given previously[6] from which a σ-value of −0.07 is obtained for the *m*-NH_2 group. This value fits the regression lines for substituted anilines and phenols much better than does the value of −0.161 (ΔpK_a values of *m*-phenylenediamine and *m*-aminophenol are −0.07 and +0.06, the former being corrected for the statistical effect[9]). The regression analysis[10] has been carried out using: a, the substituents 3-NO_2, 3-CN, 3-$COCH_3$, 3-COOH, 3-CH_3 and 3,5-di-CH_3 all of which apart from the CH_3 group have −I, −M properties (the methyl group is included since its effects are also cumulative being weakly +I, +M); b, the substituents 3-Cl, 3-Br, 3-I, 3-F, 3-OCH_3 and 3-NH_2 which have −I, +M character (the OH group is ignored since tautomerism is present in 3-hydroxypyridine); and c, all the foregoing substituents. For the linear regression equation $\Delta pK_a = \sigma\rho + c$ the values of ρ, *c* and the correlation coefficient *r* are shown in the following table, the ΔpK_a values used being the average of those quoted in Table I.

Table I

pK_a Values (H_2O at 25°) of 3-Substituted Pyridines, 3-Substituted Quinolines and 4-Substituted Isoquinolines[w]

Substituent	Pyridines		Quinolines		Isoquinolines	
	pK_a	ΔpK_a	pK_a	ΔpK_a	pK_a	ΔpK_a
H	$5.18^{a,n}$	..	4.88^a	..	5.41^a	..
	5.17^b	..	4.80^d	..	5.35^f	..
	5.16^c	..	4.79^e	..	5.36^r	..
		..	4.90^f	..		
	5.22^u	..	4.96^v			
	5.23^s	..				
	5.29^q	..				
	5.12^t	..				
3-NO_2	0.81^g	4.36	1.03^g	3.85	...	..
3-CN	1.45^q	3.84	...	..	...	..
3-F	2.97^b	2.20	2.46^e	2.33	...	..
3-Cl	2.84^b	2.33	2.46^c	2.33	...	..
3-Br	2.84^b	2.33	2.61^k	2.27	...	..
			2.69^g	2.19	...	..
3-I	3.25^b	1.92	...	..	...	..
3-COOH	3.13^j	2.04	$(4.62)^o$	..	...	
3-COO^-	$4.77^{j,q}$	0.52	...	..	...	..
	$4.72^{l,m}$	.45				
3-OH	4.75^a	.43	4.27^a	0.61	...	..
	4.86^q	.43	4.18^g	0.70	...	..
3-OCH_3	4.83^a	.35	...	..	...	..
	4.91^n	.27				
3-$COCH_3$	3.18^b	1.99	...	..	...	..
3-NH_2	5.92^h	− .74	4.89^h	−0.01	...	..
	6.09^q	− .80				
3-CH_3	5.68^b	− .51	$(4.38)^k$	..	...	..
	5.52^n	− .34	5.14^d	−0.26		
	5.82^q	− .53	5.17^v	−0.21		
	5.63^u	− .41				
3,5-di-CH_3	6.15^u	− .93	...	..	...	..
4-NO_2	...		...		1.35^g	4.03
4-Br	...		...		3.31^g	2.07
4-OH	...		...		4.80^p	0.58
					4.70^g	0.68
4-NH_2	...		...		6.23^f	−0.85

[a] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956). [b] H. C. Brown, D. H. McDaniell and O. Häfliger, "Determination of Organic Structures by Physical Methods," ed. Braude and Nachod Academic Press Inc., New York, N. Y., p. 597. [c] E. F. G. Herington, *Disc. Faraday Soc.*, **9**, 26 (1950). [d] W. A. Felsing and B. S. Biggs, This Journal, **55**, 3624 (1933). [e] W. K. Miller, S. B. Knight and A. Roe, *ibid.*, **72**, 4763 (1950). [f] A. R. Osborn, K. Schofield and L. N. Short, *J. Chem. Soc.*, 4191 (1956). [g] This research. [h] A. Albert, R. Goldacre and J. N. Phillips, *J. Chem. Soc.*, 2240 (1948). [j] R. W. Green and H. K. Tong, This Journal, **78**, 4896 (1956). [k] S. B. Knight, R. H. Wallick and J. Bowen, *ibid.*, **76**, 3780 (1954); also S. B. Knight, R. H. Wallick and C. Balch, *ibid.*, **77**, 2577 (1955). [l] R. F. Evans. E. F. G. Herington and W. Kynaston, *Trans. Faraday Soc.*, **49**, 1284 (1953). [m] H. R. Stephenson and H. Sponer, This Journal, **79**, 2050 (1957). [n] R. K. Murman and F. Basolo, *ibid.*, **77**, 3484 (1955). [o] R. C. Elderfield and M. Siegel, *ibid.*, **73**, 5624 (1951). [p] S. F. Mason, *J. Chem. Soc.*, 5010 (1957); 674 (1958). [q] H. H. Jaffé and G. O. Doak, This Journal, **77**, 4441 (1955). [r] R. Karrer and H. Schmid, *Helv. Chim. Acta*, **29**, 1853 (1946). [s] A. Gero and J. J. Markham, *J. Org. Chem.*, 16, 1835 (1952). [t] E. B. Hughes, H. H. G. Jellinek and B. A. Ambrose, *J. Phys. Chem.*, **53**, 410 (1949). [u] R. J. L. Andon, J. D. Cox and D. F. G. Herington, *Trans. Faraday Soc.*, **50**, 918 (1954). [v] R. Ricardi and M. Bresesti, *Ann. chim.* (*Rome*), **48**, 826 (1958). [w] ΔpK_a values were determined using the pK_a values of the parent bases where specified; otherwise these values were used: pyridine, 5.18; quinoline, 4.88; isoquinoline, 5.38; corrections of −0.06 for an ionic strength of 0.6 *M* are applied to the values in reference *h*. pK_a values in references *a*, *h* and *p* are at 20°.

The degree of correlation between ΔpK_a and σ-values is higher for the individual groups a and b than for all substituents taken together. This may be taken as evidence (see statistical appendix) for the contention that substituents in 3-substituted

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[7] H. H. Jaffé and G. O. Doak, This Journal, **77**, 4441 (1955).

[8] H. D. McDaniell and H. C. Brown, *J. Org. Chem.*, **23**, 120 (1958).

[9] R. Kuhn and A. Wasserman, *Helv. Chim. Acta*, **11**, 3 (1928).

[10] C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," John Wiley and Sons, Inc., New York, N. Y., 1956.

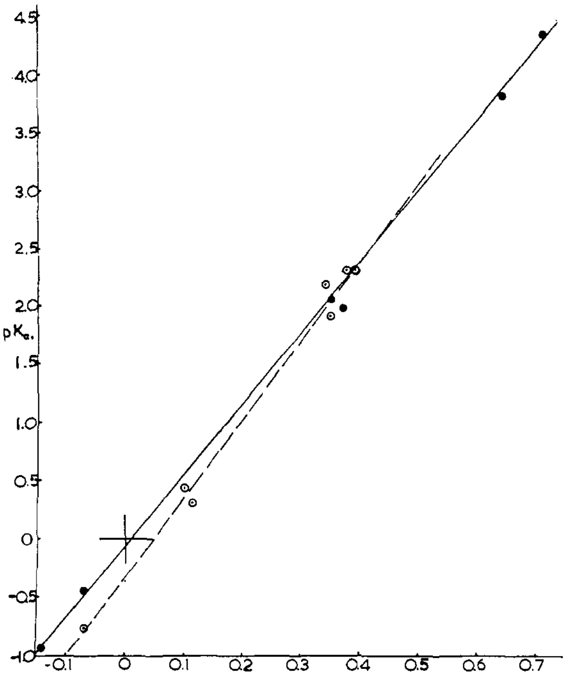

Fig. 1.—3-Substituted pyridines: —●—, −M; —⊙—, +M.

pyridines exercise distinctive effects depending on their −M or +M properties and the appropriate regression lines are drawn in Fig. 1. It will be noticed that the substituents with −M properties fall

	ρ	c	r	n
Group a	6.18	−0.09	0.998	6
Group b	7.00	− .36	.994	6
Group c	6.36	− .17	.970	12

on a line passing close to the origin, while the +M group define a line cutting the pK_a axis at a negative value. This is interpreted to indicate greater mesomeric effects by the latter substituents presumably as a result of the closer proximity of the mesomeric moment of the substituent to the NH^+ pole of the acid.

Substituted Quinolines.—There are fewer results available for the 3-position in the quinoline ring, the values being restricted in aqueous solution to NO_2, Br, OH, NH_2 and CH_3. The values for quinoline-3-carboxylic acid (ref. *o*) and 3-methylquinoline (ref. *k*) have been ignored, the first because it relates to a 50% methanol solution, and the second because the value is inadmissible since it conflicts with the more plausible values in references *d* and *v*. The pK_a values for 3-F and 3-Cl from reference *e* were determined in 10% ethanol solution and, though strictly inapplicable, confirm the trends shown in aqueous solution. The value for 3-OH is admissible, for it has been shown,[11] and confirmed in this work, that 3-hydroxyquinoline exists in aqueous solution almost completely as the non-zwitterion form. A single regression line can be drawn from these values, but it is equally plausible to draw two lines, one through the points for the groups NO_2 and CH_3 passing close to the origin, and the other through the remaining points cutting the ΔpK_a axis at a positive value. More data are required to confirm this contention, but it is at least consistent with the established behavior of the 3-substituted 1-naphthylamines.[6] Figure 2 illustrates the comparison between the two systems, only the points for the −I, +M substituents being shown (NO_2 excepted).

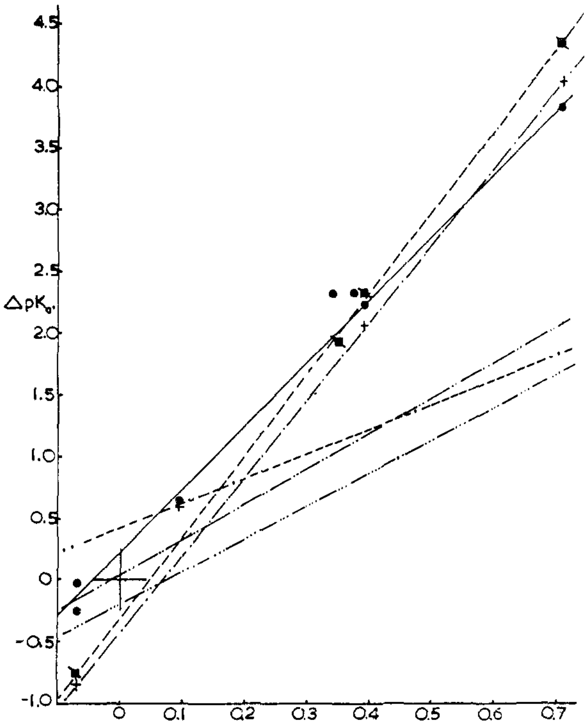

Fig. 2.——●—, 3-substituted quinolines; ——■——, 3-substituted pyridines; —·—+—·—, 4-substituted isoquinolines; ----, 3-substituted 1-naphthylamines; —··—··—, 3-substituted anilines; —···—···—, 4-substituted 2-naphthylamines (+M substituents).

Substituted Isoquinolines.—Only four points are available for this series, one of which is inadmissible since the compound 4-hydroxyisoquinoline has been shown to exist in aqueous solution very largely as the zwitterion[11] and the experimental ΔpK_a value for the 4-OH group refers mainly to the equilibrium

$$OHC_9H_6NH^+ \rightleftharpoons {}^-OC_9H_6NH^+ + H^+$$

The remaining three points define a line shown in Fig. 2 lying below that of the +M substituents in the pyridine series. The similarity between the 4-substituted isoquinolines and 4-substituted 2-naphthylamines is evident and indicates that factors of a parallel nature operate in the control of acid–base equilibria in these compounds.

Evaluation of σ-Values and Application of the Taft Equation.—It has been shown[6] that the experimentally derived σ-values for substituted anilines and naphthylamines can be adequately reproduced by a modification of the Taft equation involving additional parameters, *viz.*, $\sigma = a\sigma_I + b\sigma_R$, and that these parameters can be correlated with the factors considered to be significant in acid–base equilibria in aromatic bases. It is of interest to

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[11] F. S. Mason, *J. Chem. Soc.*, 5010 (1957); 674 (1958).

TABLE II

COMPARISON OF CALCULATED AND EXPERIMENTAL σ-VALUES FOR 3-SUBSTITUTED PYRIDINES, 3-SUBSTITUTED QUINOLINES AND 4-SUBSTITUTED ISOQUINOLINES

Substituent	σ_I[a]	σ_R[a]	3-X-Pyridine Calcd.	3-X-Pyridine Exptl.	3-X-Quinoline Calcd.	3-X-Quinoline Exptl.	4-X-Isoquinoline Calcd.	4-X-Isoquinoline Exptl.
NO_2	0.63	0.16	0.71	0.72	0.62	0.64	0.66	0.67
CN	.58	.10	.63	.64	..	..	..	..
$COCH_3$	.28	.15	.34	.33	..	..	..	..
CH_3	− .05	− .06[c]	−0.08	− .07	− .06	− .04	..	..
F	.52	− .44	.35	.36	..	..	..	..
Cl	.47	− .24	.38	.39	..	..	..	..
Br	.45	− .22	.37	.39	.37	.36	.34	.34
I	.39	− .11	.35	.34	..	..	..	..
OCH_3	.26	− .51	.056	.05	..	..	..	..
OH	.26	− .60	.02	.07[d]	.10	.11	.02	.12[d]
NH_2	.17[b]	− .76	− .14	− .13	− .02	.00	− .12	− .13

[a] Reference 14. [b] The σ_I value of 0.10 for NH_2 recommended by Taft gives low results for all three series and for *m*-phenylenediamine. A figure of 0.17 gives consistent results throughout and is used here. [c] The σ_R value for CH_3 gives results which are too negative in all cases. A figure of −0.06 has been used. [d] Experimental are higher than calculated values owing to tautomerism.

decide whether similar applications and correlations are possible for heterocyclic bases, and for this purpose the relevant Hammett substituent constants must be evaluated. Since for comparative study, the same reaction constant should be used for pyridines, quinolines and isoquinolines, we choose a value of 6.00 which corresponds closely to the ΔpK_a-σ_m relation for the −I, −M substituents in the 3-substituted pyridine series; σ-values for the substituents are derived from the relation $\sigma = \Delta pK_a/6.0$ and are shown in Table II. It is found that the equations (1), (2) and (3) reproduce these values very satisfactorily

$$\text{3-substd. pyridines, } \sigma = 1.02\sigma_I + 0.40\sigma_R \qquad (1)$$

$$\text{3-substd. quinolines, } \sigma = 0.93\sigma_I + 0.23\sigma_R \qquad (2)$$

$$\text{4-substd. isoquinolines, } \sigma = 0.95\sigma_I + 0.38\sigma_R \qquad (3)$$

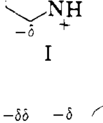
Calculated and derived values are shown in Table II.

Although the data are limited in the quinoline and isoquinoline series and thus restrict the precision with which the parameters *a* and *b* may be determined, the extent of the range of ΔpK_a values (from 4.4 to −0.85) units encourages a belief that these constants have some quantitative significance. A comparison with the equations for the *m*-substituted anilines and naphthylamines[6] is instructive for it reveals the similarities between the aromatic and heterocyclic series. The equations are: *m*-anilines, $\sigma = 1.05\sigma_I + 0.33\ \sigma_R$; 3-X-pyridines, $\sigma = 1.02\sigma_I + 0.40\sigma_R$; 3-X-1-naphthylamines, $\sigma = 0.95\sigma_I + 0.12\sigma_R$; 3-X-quinolines, $\sigma = 0.93\sigma_I + 0.23\sigma_R$; 4-X-2-naphthylamines, $\sigma = 0.78\sigma_I + 0.40\sigma_R$; 4-X-isoquinolines, $\sigma = 0.95\sigma_I + 0.38\ \sigma_R$.

The significant features are: (a) In a comparison of *m*-anilines and 3-substituted pyridines, the mesomeric component of the inductive effect is greater in the pyridine series. (b) The transmission of the polar effect to the reaction site is less efficient in the bicyclic compounds than in the benzene or pyridine series. (c) The mesomeric contributions to the substituent effect are appreciably lower in 3-substituted 1-naphthylamines and 3-substituted quinolines than in the other comparable series.

An attempt has been made[6] to account for these characteristics in the aromatic bases on the basis of electronic structure, and the behavior of the heterocyclic series suggests that similar explanations may hold for these. It has been postulated[6] that four factors may be of significance in the control of acid–base equilibria in substituted aromatic bases, the relevant terms being: (a) potential energy increments I_a and I_b due, respectively, to the effect of the substituent dipole on the NH_3^+ pole of the acid and on the delocalization of the lone pair electrons of the amino group of the base; (b) potential energy increments M_a and M_b due to the interaction of the mesomeric moment of the substituent with the NH_3^+ pole of the acid in one case, and with the process of delocalization of the unbonded electrons in the base in the other. In the case of the heterocyclic bases the terms I_b and M_b may be disregarded since delocalization is not significant, hence the ΔpK_a values are principally the result of the potential energy changes in the conjugate acids.

Consider now the acids I, II, III and IV. It is a reasonable assumption that the changes in π-electron densities in the aromatic rings produced by the delocalization of the amino nitrogen electrons will be similar to those produced by the same substituents in the naphthalene ring,[6] being denoted by the symbols $-\delta$ and $-\delta\delta$, the latter denoting a smaller increment of negative charge. The significant features are: (a) the similarity between I and II, and (b) the relatively low increments of π-electron density at positions *ortho* to the NH^+ pole in III. Of the terms I_a and M_a, I_a might be expected to be equal for I, II and III since the substituent and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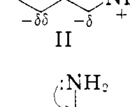
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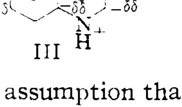
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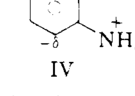

IV

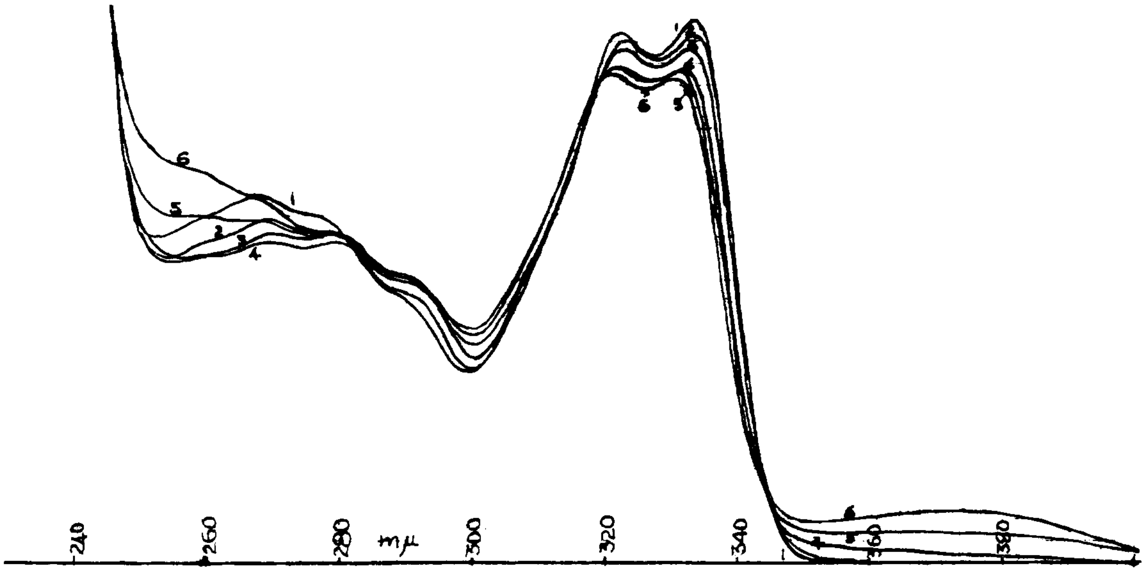
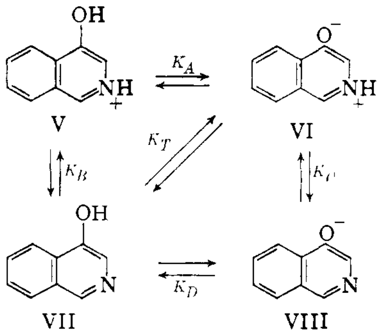


Fig. 3.—3-Hydroxyquinoline in water–dioxane solutions, concentration 0.0004 *M:* 1, dioxane; 2, 75% dioxane; 3, 50% dioxane; 4, 25% dioxane; 5, 10% dioxane; 6, water.

NH$^+$ poles are in spatially equivalent positions. However, the values of *a* reveal that the polar effect is rather less in quinolines and isoquinolines than in pyridines, and this may indicate variations in dipole orientation or in dielectric constant. On the other hand, the mesomeric terms M_a, which are determined by the π-electron densities, should form the sequence I $\approx$ II > III, and this is the experimental order, the low value for the 3-substituted quinolines being analogous to that found for 3-substituted 1-naphthylamines. A comparison between I and IV shows that the mesomeric effect will be proportionately greater than the polar effect in the pyridines since the mesomeric moment is closer to the functional group in these compounds.

Tautomeric Equilibria.—Acid–base equilibria in the hydroxy compounds of the heterocyclic bases are complicated by the presence of tautomerism as shown by reference to 4-hydroxyisoquinoline where the cation V can dissociate to produce both the zwitterion VI and the phenol VII with further dissociation to the anion VIII occurring at higher *p*H values. Of the equilibria involved, only the constants K_A, K_B, and K_T are of interest here, and these are related by the equation



$$K_T = \frac{\text{(zwitterion)}}{\text{(enol)}} = \frac{K_A}{K_B} \qquad (1)$$

The measured dissociation constant K_0 is given by the equation

$$K_0 = \frac{\text{(zwitterion + enol)} \times (\text{H}^+)}{\text{(acid)}}$$

from which may be derived the relations

$$K_B = \frac{K_0}{1 + K_T} \text{ or } pK_B = pK_0 + \log(1 + K_T) \qquad (2)$$

and

$$K_A = \frac{K_0}{1 + 1/K_T} \text{ or } pK_A = pK_0 + \log(1 + 1/K_T) \qquad (3)$$

It has been shown[11] recently that 3-hydroxyquinoline in aqueous solution exists almost entirely as the non-dipolar form, while 4-hydroxyisoquinoline in the same solvent is present very largely as the zwitterion VI. These conclusions have been verified in the present work by examination of the absorption spectra of the two bases in water–dioxane mixtures. The curves which are shown in Figs. 3 and 4 reveal a marked difference in the behavior of the two substances, 3-hydroxyquinoline showing little change with increasing dioxane, whereas 4-hydroxyisoquinoline shows a progressive change of molecular type as the dielectric strength is lowered by the addition of dioxane. Published work[11,12] also indicates that 3-hydroxypyridine exists in aqueous solution partly as the zwitterion and the tautomeric constant has been estimated as approximately 1. Only the pK_a value of 3-hydroxyquinoline is therefore admissible, and the ΔpK_a values of the remaining compounds should lie above the regression lines for the +M group of substituents. This is found to be the case and it is further possible to make assessments of the tautomeric constants from the known pK_0 and estimated pK_B values. Thus the pK_0 value of 4-hydroxyisoquinoline is 4.70, and the ΔpK_B values read from the regression line in Fig. 2 or calculated from Table II are 0.18 and 0.12 from which an average pK_B may be given as 5.23, and the value of K_T from eq. 2 found to be 2.39. The aqueous solution therefore

[12] D. E. Metzler and E. E. Snell, THIS JOURNAL, **77**, 2431 (1955).

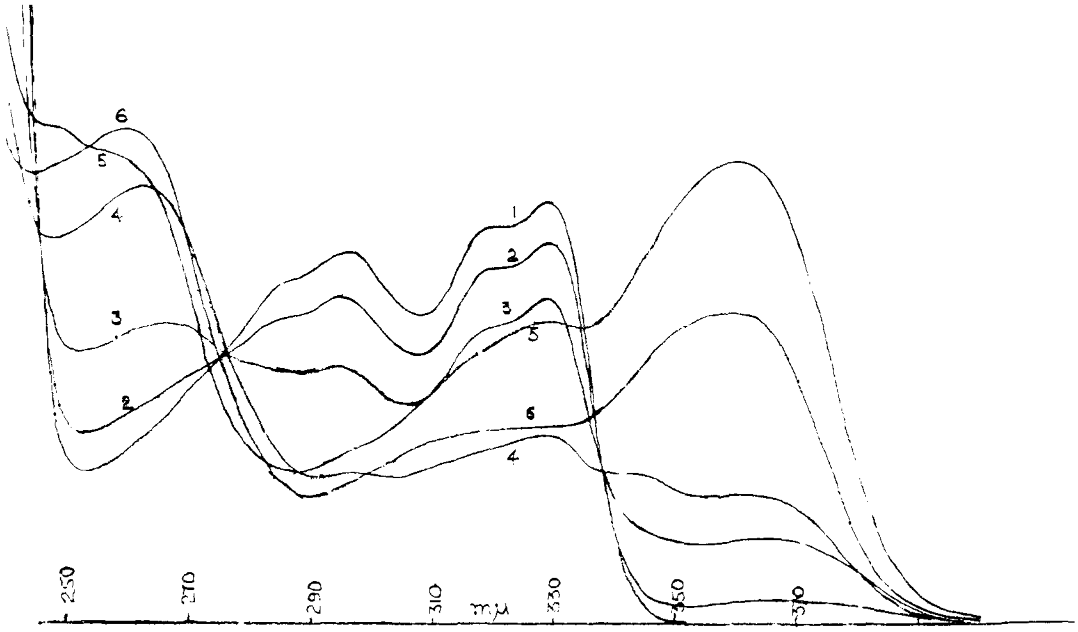
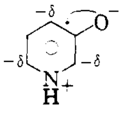


Fig. 4.—4-Hydroxyisoquinoline in water–dioxane solutions, concn. 0.0004 *M*: 1, dioxane; 2, 75% dioxane; 3, 50% dioxane; 4, 25% dioxane; 5, 10% dioxane; 6, water.

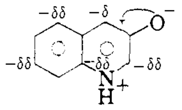
contains 70% of the base as the zwitterion and this may be compared with the estimates of 74 and 79% obtained by Mason from pK_a and spectral data.[11]

For 3-hydroxypyridine the value of pK_B can be estimated as 4.97 from the methoxy compound by adding 0.10 to correct for the difference between the σ_p-values of OCH_3 and OH, or it may be estimated as 5.05 from the calculated value of σ in Table II. Taking an average pK_B value of 5.00 with $pK_0 = 4.75$ we find $K_T = 0.78$ corresponding to 44% zwitterion. This may be compared with other estimates of about 45–50%.[11,12]

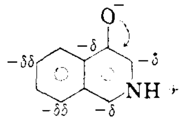
The explanation offered for the effects of substituents in the foregoing should account also for the differences in the tautomeric equilibria of the three hydroxy compounds. The general principle governing such equilibria is expressed by eq. 1 which stated in the form $\log K_T = pK_B - pK_A$ shows that for low proportions of zwitterion, pK_B must be considerably smaller than pK_A and *vice versa*. The pK_B values of 3-hydroxyquinoline and 4-hydroxyisoquinoline are 4.2 and 5.2, these arising from the differing pK_a values of the parent bases coupled with the specific polar and mesomeric effects of the substituents discussed in the previous section. On the other hand, pK_A values are not known, although estimates can be obtained by equating them to the dissociation exponents of the N-methyl derivatives, as has been done by Mason who calculated the tautomeric constants on this basis.[11] The pK_A values so assessed, *viz.*, 4.96 for 3-hydroxypyridine, 4.93 for 4-hydroxyisoquinoline and 5.42 for 3-hydroxyquinoline, can be interpreted structurally in terms of the relative stabilities of the zwitterions IX, X and XI. In these cases the mesomeric effects produced by the delocalization of the $-O^-$ group to the ring will be in the order 3-hydroxypyridine (IX) ≈ 4-hydroxyisoquinoline (XI) > 3-hydroxyquinoline (X), thus accounting for the observed pK_A values of the closely related N-methyl derivatives. It follows that 4-hydroxyisoquinoline exists mainly as the zwitterion, and 3-hydroxyquinoline as the phenol.



IX



X



XI

Acknowledgments.—The author is indebted to Dr. E. Challen for the microanalyses and to Mr. I. Reece for assistance with the spectrophotometric measurements.

Appendix.—The probability that the data for the −M and +M groups of substituents lie on separate regression lines can be determined by evaluating the variance ratio $F = s_{a+b}^2/s^2$ where s^2 is the residual variance for all 12 substituents with 10 degrees of freedom, and s_{a+b}^2 is the combined residual variance of the two separate groups calculated from the individual variances s_a^2 and s_b^2 by the equation $s_{a+b}^2 = (4s_a^2 + 4s_b^2)/8$ and having 8 degrees of freedom. The residual variances are calculated from the equation

$$s^2 = \frac{(I - r^2)\left[\Sigma(\Delta pK_a)^2 - \frac{(\Sigma\Delta pK_a)^2}{n}\right]}{n - 2}$$

where r is the correlation coefficient and n is the sample number.[13,14] The values of s_{a+b}^2 and s^2 are 0.191 and 0.0245, respectively, from which $F_{8,10} = 7.8$ corresponding to a 0.005 significance level, *i.e.*, the probability that the data fall on one rather

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[13] K. A. Brownlee, "Industrial Experimentation," H. M. Stationery Office, London, 1950, pp. 32, 59.

[14] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 13; also *Ann. Rev. Phys. Chem.*, **9**, 292 (1958).

than on two lines is under 0.5%, and it may therefore be accepted that the −M and +M groups of substituents show distinctive properties in their $\Delta pK_a - \sigma_m$ relationships.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY, ATLANTA, GA.]

Polar Effects on Rates and Equilibria. III[1]

BY JACK HINE

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It is shown that the Hammett equation can be derived by the assumption that substituents add to the free energy content of a molecule or ion a term, called the free energy of polar interaction of substituents, that is proportional to the product of their polar substituent constants. By use of an analogous assumption for the calculation of the extra resonance energy of interaction between *para* groups, equations are developed that may be used to calculate 99 log (K/K_0) values in four different reaction series with an average deviation of 0.057. The derivation of equations to correlate equilibrium constants for the isomerization of m-XC_6H_4Y to p-XC_6H_4Y, the disproportionation of C_6H_5X to C_6H_6 and $C_6H_4X_2$'s and other reactions is also described, as is an expression for the ratio of the σ-constants for two substituents in terms only of the activity coefficients of certain aromatic compounds.

Introduction

It has been shown previously[2] that within the limits of applicability of the Hammett equation[3] or even a less restrictive but more general Hammett-type equation in which the reaction constants for *m*- and *p*-substituted compounds need not be identical, the reaction constant for an equilibrium process is proportional to the difference in the substituent constants for the two groups being equilibrated. Thus, for example, in the case of these equilibria for two related compounds

$$m\text{-}X_1C_6H_4Y_1 \underset{}{\overset{K_{m-X_1}{}^y}{\rightleftarrows}} m\text{-}X_1C_6H_4Y_2 \qquad (1)$$

$$m\text{-}X_2C_6H_4Y_1 \underset{}{\overset{K_{m-X_2}{}^y}{\rightleftarrows}} m\text{-}X_2C_6H_4Y_2 \qquad (2)$$

we may write

$$\log \frac{K_{m-X_1}{}^y}{K_{m-X_2}{}^y} = \tau_m(\sigma_{m-X_1} - \sigma_{m-X_2})(\sigma_{m-Y_1} - \sigma_{m-Y_2}) \qquad (3)$$

where $K_{m-X_1}{}^y$ and $K_{m-X_2}{}^y$ are the respective equilibrium constants, τ_m is a proportionality constant whose value depends only on the nature of the organic radical (*m*-phenylene in this eq.) to which the substituents are attached, the nature of the reaction medium and temperature, and the σ's are polar substituent constants. A more fundamental but to date perhaps less useful approach to the problem of the effect of structure on rate and equilibrium was initiated by Bjerrum[4] and culminated in the work of Kirkwood and Westheimer.[5] For application to reactions 1 and 2 the Kirkwood–Westheimer equations may be written in the form

$$\log (K_{m-X_1}{}^y/K_{m-X_2}{}^y) = C(\mu_{X_1} - \mu_{X_2})(\mu_{Y_1} - \mu_{Y_2}) \qquad (4)$$

where the μ's are the dipole moments (or the electrical charges in the case of charged groups) and C (whose evaluation was the goal of most of the earlier work) is a constant whose value depends only on the nature of the reaction medium and temperature (which determine the external dielectric constant) and the nature of the organic radical to which the groups are attached (which determines the distance and angle between the groups and the extent and dielectric constant of that part of the molecule between the groups).

Results and Discussion

Development of Equations.—The similarity in form between eq. 3 and 4 suggests a similarity in derivation. Kirkwood and Westheimer have used the accepted physical laws to calculate the contribution to the free energy content of various species due to the interactions of the dipoles and/or electrical charges of substituent groups. I shall assume that from the total free energy of a molecule or ion there may be separated a part to be called the *free energy of polar interaction*, whose magnitude may be calculated from certain properties of the substituent groups called their *polar substituent constants*. Thus, for m-$X_1C_6H_4Y_1$ the free energy of polar interaction of the substituent groups ($F_{p.i.}$) is assumed to be represented

$$F_{p.i.}{}^{m\text{-}X_1C_6H_4Y_1} = 2.3RT\tau_m\sigma_{m-X_1}\sigma_{m-Y_1} \qquad (5)$$

where the σ_m's are polar substituent constants characteristic of the interaction of the substituents with other substituents *meta* to them, τ_m is a proportionality constant describing the efficiency of such *meta* interactions in the solvent and at the temperature under consideration, and the $2.3RT$ has been inserted for convenience in the subsequent use of equilibrium constants. It is assumed that most of the contributions to the total free energy of m-$X_1C_6H_4Y_1$ (the energy of the aromatic ring, the four C–H bond energies, the energy of the group X_1 and of its interaction with the ring) are the same for m-$X_1C_6H_4Y_2$. Hence the free energy change for reaction 1 will include only the differences in free energies of polar interaction

$$F_{p.i.}{}^{m-X_1C_6H_4Y_1} - F_{p.i.}{}^{m-X_1C_6H_4Y_2} = 2.3RT\tau_m\sigma_{m-X_1}(\sigma_{m-Y_2} - \sigma_{m-Y_2})$$

and the differences between the free energy of the Y_1 and Y_2 groups and of their interactions with the ring. Assuming that this latter term will also be the only contributor, aside from the $\Delta F_{p.i.}$ term, to the free energy of reaction 2, it follows that

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[1] For parts I and II see ref. 2 and J. Hine and W. C. Bailey, Jr., THIS JOURNAL, **81**, 2075 (1959).

[2] J. Hine, *ibid.*, **81**, 1126 (1959).

[3] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, chap. VII.

[4] N. Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923).

[5] J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 513 (1938).