[CONTRIBUTION FROM THE VENEREAL DISEASE EXPERIMENTAL LABORATORY, U. S. PUBLIC HEALTH SERVICE, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA]

Tautomeric Equilibria. I. Substituted Pyridines and their 1-Oxides

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RECEIVED SEPTEMBER 27, 1954

A method is developed for the use of the Hammett equation in the elucidation of tautomeric equilibria. The method is applied to the equilibria between 4-hydroxypyridine 1-oxide and 1-hydroxy-4-pyridone, between 4-(and 3-)-ammoniopyridine 1-oxide ion and 4-(and 3-)-amino-1-hydroxypyridinium ion, and between the neutral and zwitterion forms of nicotinic and isonicotinic acids.

Tautomeric equilibria have long been of interest to chemists, and many such equilibria have been studied in great detail. Numerous methods have been used to elucidate the equilibrium position,[2,3] and the demonstration of the zwitterion nature of aminoacids was a triumph of the combination of all the available methods.[3] In spite of the availability of this variety of experimental methods, numerous recent papers have relied almost exclusively on the interpretation of ultraviolet absorption spectra for the determination of the equilibrium position. This fact is particularly unfortunate because quantitative predictions of the effects of substituents on absorption spectra still cannot generally be made with assurance.

A knowledge of the acid (or base) dissociation constants of a pair of tautomers permits an estimation of the equilibrium constants for the tautomeric equilibrium.[2] In the present paper we shall show that it is possible to use the Hammett equation[4] in the estimation of the relevant dissociation constants when dealing with aromatic compounds. All the compounds which we shall discuss have two functional groups (X and Y), both of which are capable of participating in acid–base equilibria. In the acid–base reactions of such compounds, we must consider the following equilibria

$$\begin{tikzcd}
 & \text{X—R—Y}\quad\text{I} \arrow[d, shift left, "H^+"] & \\
\text{HX—R—Y} \arrow[rr, shift left] & \arrow[u, shift left, "OH^-"] \arrow[d, shift left, "H^+"] & \text{X—R—YH} \arrow[ll, shift left] \\
\text{II} & \text{HX—R—YH}\quad\text{IV} \arrow[u, shift left, "OH^-"] & \text{III}
\end{tikzcd}$$

Here R is some biradical carrying both the functional groups X and Y, and all charges have been omitted. Theoretical estimation of equilibrium constants, either for the process II ⇄ I and III ⇄ I, or IV ⇄ II and IV ⇄ III permits estimation of an equilibrium constant for the tautomeric equilibrium II ⇄ III and also allows comparison with the experimentally determined equilibrium constants for the processes II + III ⇄ I and IV ⇄ II + III. In the latter comparisons, corrections for the tautomeric equilibrium must be made[5] unless it can be shown that such corrections are negligible. An equilibrium constant (K) for the equilibrium II ⇄ III of 20 leads to a correction of only 0.02 in the pK, so that the tautomeric equilibrium may be neglected if $K \geqslant 20$, and in this case the measured pK's may be identified with the equilibria IV ⇄ III and III ⇄ I directly. If $K \geqslant 100$ it may be said that only III is present in appreciable quantity (>1% of the mixture). Similar statements, with II replacing III, are of course valid if $K \leqslant 1/20$ and $\leqslant 1/100$, respectively.

In the preceding paper we have shown that the Hammett equation is applicable to the basicities of 3- and 4- substituted pyridines and their 1-oxides.[6] We shall now illustrate the principles discussed above by use of some of these compounds in which the substituent is an acidic or basic functional group. All the relevant experimental pK's are listed in Table I. In several of these cases no information concerning the position of tautomeric equilibrium was previously available, and in at least two cases incorrect conclusions were reached on the basis of spectral evidence alone.

TABLE I

THE pK'S OF THE COMPOUNDS DISCUSSED (FROM REF. 6)

Compound	pK_1	pK_2
4-$HOC_5H_4N^+OH$	2.36	5.80
4-$H_3N^+C_5H_4N^+H$	−6.77	9.17
3-$H_3N^+C_5H_4N^+H$	−1.3	6.09
4-$H_3N^+C_5H_4N^+OH$	−6.27	3.65
3-$H_3N^+C_5H_4N^+OH$	−2.1	1.47
4-$HOOCC_5H_4N^+H$	1.80	4.90
3-$HOOCC_5H_4N^+H$	2.09	4.77
4-$HOOCC_5H_4N^+OH$	−0.48	2.86
3-$HOOCC_5H_4N^+OH$	0.09	2.73

4-Hydroxypyridine 1-Oxide.—Shaw[7] has demonstrated by spectroscopic means that 2-hydroxypyridine 1-oxide actually does not exist in aqueous solution, but that instead the tautomeric 1-hydroxy-2-pyridone is present. He was, however, unable to determine by the same method whether the species present in aqueous and alcoholic solutions is 4-hydroxypyridine 1-oxide (VI) or the tautomeric 1-hydroxy-4-pyridone (VII) since the spectra of the isomeric benzyloxy derivatives were too similar. This uncertainty about the species present in solution led us to state that the value $\sigma^* = 1.88$ derived for the $\geqslant N^+—O^-$ group was a minimum value.[8] In order to decide which of the tautomeric species is present in solution, we shall examine the equilibrium VI ⇄ VII, together with the

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[1] Department of Chemistry, University of Cincinnati, Cincinnati 21, Ohio.

[2] G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1946, p. 31.

[3] D. I. Hitchcock, in C. L. A. Schmidt, "The Chemistry of Aminoacids and Proteins," Charles C. Thomas, Springfield, Illinois, 2nd Ed., 1944, Chapter XI; J. T. Edsall, Chapter XVI, Section I.

[4] (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[5] Ref. 2, p. 198; however, the smaller one of a pair of such corrections can never exceed a factor of 2, *i.e.*, 0.3 in the pK.

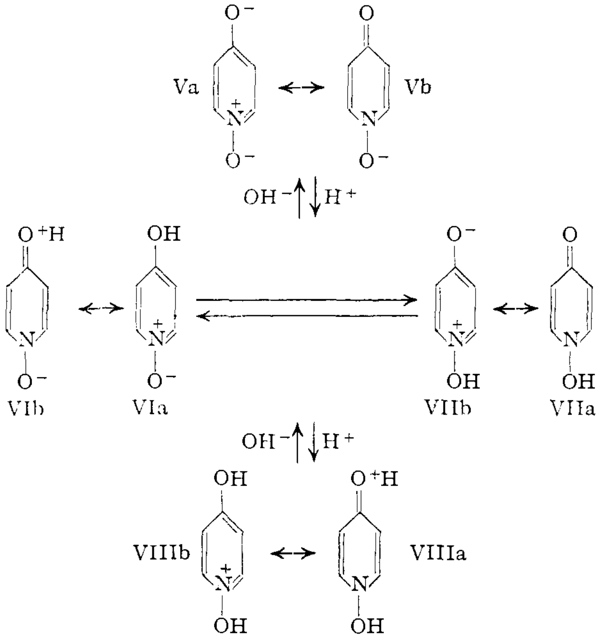
[6] H. H. Jaffé and G. O. Doak, THIS JOURNAL, **77**, 4441 (1955).

[7] E. Shaw, *ibid.*, **71**, 67 (1949).

[8] H. H. Jaffé, *ibid.*, **76**, 3527 (1954).

acid base equilibria of these compounds with V and VIII.

We can use the Hammett equation, with $\sigma(p\text{-OH}) = -0.357$,[4b] and $\rho = 2.088$,[6] to estimate $pK = 1.68$

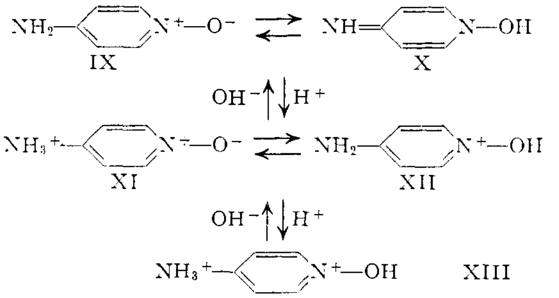


for the equilibrium VIII $\rightleftarrows$ VI. This value is probably somewhat of an underestimate, since $\sigma(p\text{-OH})$ opposite the strongly electron attracting $\geqslant\text{N}^+\text{—OH}$ group should probably be smaller (more negative) than -0.357.[6] This estimated value is in reasonable agreement with the experimental value, although the latter is somewhat larger than the calculated one.[6] In an equilibrium of the type IV $\rightleftarrows$ II + III, it can be shown that the observed pK, ignoring a tautomeric correction which cannot exceed 0.3,[5] must be the smaller of the two pK's applicable to the partial reactions IV $\rightleftarrows$ II and IV $\rightleftarrows$ III. Hence, the fact that the estimated pK (VIII $\rightleftarrows$ VI) = 1.68 is somewhat smaller than the experimental value of 2.36 indicates that the tautomeric equilibrium VI $\rightleftarrows$ VII cannot be in favor of VII.

We have no reliable substituent constant for the O^--group,[4b] and hence cannot estimate the pK for the process VII $\rightleftarrows$ V. The other two pK's, corresponding to the equilibria VI $\rightleftarrows$ V and VIII $\rightleftarrows$ VII cannot readily be estimated; the equilibrium VI $\rightleftarrows$ V would require a σ for the $\geqslant\text{N}^+\text{—O}^-$group, which we are attempting to derive from this equilibrium. The equilibrium VIII $\rightleftarrows$ VII can hardly be treated from the point of view of the Hammett equation, since the change in resonance energy between VIIIa $\longleftrightarrow$ VIIIb and VIIa $\longleftrightarrow$ VIIb has little relation to the corresponding change in phenols.

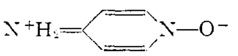
Thus, we conclude that the pK, in Table I, applies to the equilibrium VIII $\rightleftarrows$ VI, and hence the pK reported previously[8] applies to the equilibrium VI $\rightleftarrows$ V. Accordingly, the value $\sigma^* = 1.88$ for the $\geqslant\text{N}^+\text{—O}^-$ group may now be accepted as the true value.

4-Aminopyridine 1-Oxide.—We have previously determined the basicity of 4-aminopyridine 1-oxide (IX) by potentiometric titration. On the basis of the assumption that the first proton adds to IX at the amino group to give 4-ammoniopyridine 1-oxide ion[9] (XI), we calculated a value $\sigma^* = 0.37$ for the $\geqslant\text{N}^+\text{—O}^-$-group. Since this value was not only much smaller than the σ^*-value calculated from the pK of 4-hydroxypyridine 1-oxide, but also much smaller than the normal σ-value calculated from the pK of isonicotinic acid 1-oxide we concluded that the proton must add at the oxygen atom, to give 4-amino-1-hydroxypyridinium ion (XII).[8] This assignment was in agreement with the one made by Hirayama and Kubota.[10] With the additional information now available, it will be possible to confirm this assignment unequivocally. We have to consider the equilibria



Using the same line of reasoning as above for the equilibrium VI $\rightleftarrows$ VII, and using $\sigma(p\text{-NH}_2) = -0.660$, $\rho = 2.088$, we obtain for the equilibrium XII $\rightleftarrows$ XI $pK_a = 2.22$, which again is probably somewhat of an underestimate due to the uncertainty of the σ-value for the amino group.[6] On the other hand, the σ^*-value of $+1.88$ for the $\geqslant\text{N}^+\text{—O}^-$ group, together with known ρ-values for the pK's of anilinium ions ($\rho = 2.767$),[4b] permits us to estimate for the equilibrium XI $\rightleftarrows$ IX $pK_a = -0.64$. The difference between these two quantities leads to an equilibrium constant for XI $\rightleftarrows$ XII of about 10^3, and consequently the equilibrium is vastly in favor of XII.

The fact that the experimental pK for the equilibrium XII $\rightleftarrows$ IX agrees reasonably with the calculated value, and, if anything, is too large, indicates that X cannot be appreciably more stable than IX. We cannot rule out at this time that 4-aminopyridine 1-oxide is actually an equilibrium mixture of IX and X. However, it appears unlikely that X should be as stable as IX. Two factors seem to favor greater stability of IX: the larger bond energy of NH compared to OH bonds, as indicated by the relative acidities of OH and NH_2 groups, and the greater resonance energy in IX, arising not only out of the Kekulé structures, but enhanced by a contribution from structure XIV.[8] The only



XIV

factor favoring the greater stability of X compared to IX is the existence of a *partial* charge separation

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(9) The group H_3N^+- will be designated by the prefix ammonio, as suggested by J. F. Bunnett, F. Draper, Jr., P. R. Ryason, P. Noble, Jr., R. J. Tonkyn and R. E. Zahler, THIS JOURNAL, **75**, 642 (1953).

(10) H. Hirayama and T. Kubota, *J. Pharm. Soc., Japan*, **73**, 140 (1953).

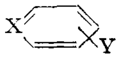
in the latter structure. Spectroscopic evidence[11] also is consistent with the assumption that only IX is present at equilibrium. Thus, it may be concluded that the equilibrium IX $\rightleftarrows$ X is definitely not in favor of X, and quite probably strongly in favor of IX.

Finally, the equilibrium XIII $\rightleftarrows$ XII merits some attention. Hirayama and Kubota[10] have reported $pK_a = -6.27$ for XIII. This compares with $pK_a = 4.58$ for anilinium ion, so that the $\geqslant N^+$—OH group increases the acid strength of anilinium ion about 10^{11} fold. The same authors also report $pK_a = -6.55$ for 4-aminopyridinium ion. From these data we may calculate, at least formally, the σ^*-values of $\geqslant N^+$—OH and $\geqslant N^+$—H given in Table II. These extremely large values may not have any precise significance, but they are given here as an indication of the tremendous electron attracting power of these groups.

3-Aminopyridine 1-Oxide.—If the above reasoning is applied to 3-aminopyridine 1-oxide, one may estimate the following pK's (where the symbols 3-IX, etc., refer to the 3-isomer of IX, etc.): 3-XI $\rightleftarrows$ 3-IX, $pK = +0.35$; 3-XII $\rightleftarrows$ 3-IX, $pK = +1.27$; 3-XIII $\rightleftarrows$ 3-XI, $pK = 0.39$, and hence for the equilibrium 3-XI $\rightleftarrows$ 3-XII, $K \sim 10$. Accordingly, 1-hydroxy-3-aminopyridinium ion and 3-ammoniopyridine 1-oxide ion exist in aqueous solution as an equilibrium mixture in which the former tautomer predominates. The experimental pK of this tautomeric mixture is in reasonable accord with the predictions. The pK of 1-hydroxy-3-ammoniopyridinium ion (3-XIII), neglecting the tautomeric correction, leads to the $\sigma(\geqslant N^+OH)$ listed in Table II.

TABLE II

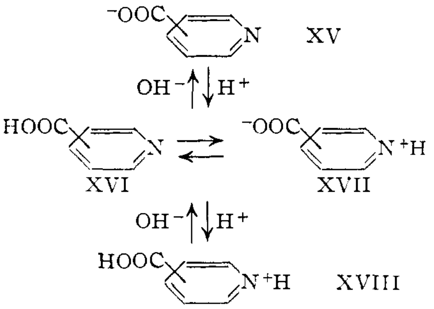
SUBSTITUENT CONSTANTS FOR THE $\geqslant N^+H$ AND $\geqslant N^+OH$ GROUPS FROM THE pK OF



Y =	σ_{meta}	σ_{para}	σ^*_{para}
	a. X = N^+H		
COOH	2.1	2.3	..
NH_3^+	2.1	..	4.0
	b. X = N^+OH		
NH_3^+	2.3	..	3.9

Nicotinic and Isonicotinic Acids.—Another interesting problem concerns the tautomeric equilibria between the neutral and zwitterion forms of nicotinic and isonicotinic acids. By a spectrographic method, Hughes, Jellinek and Ambrose[12] have determined the acidity and basicity of nicotinic acid, and assigned $pK_1 = 3.60$ to the pyridinium group and $pK_2 = 4.88$ to the carboxylic acid function. Evans, Herington and Kynaston[13] have repeated the same measurements by a spectrophotometric method and have obtained $pK_1 = 2.09$, and a pK_2 value in substantial agreement with the work of Hughes, Jellinek and Ambrose.[12] We have redetermined both values by potentiometric titration and find values in excellent agreement with the values of reference 13.

We have also determined the acidity and basicity of isonicotinic acid: $pK_1 = 1.80$ and $pK_2 = 4.90$.[14] In order to make the assignments we shall consider the equilibria



The Hammett equation permits estimation of the pK's for three out of the four possible equilibria. and these estimates are given in Table III. Unfortunately, substituent constants for the $\geqslant$N-group are not sufficiently well established[7] to evaluate equilibrium constants for the tautomeric equilibrium XVI $\rightleftarrows$ XVII with certainty. However, the data clearly indicate that in both cases the equilibrium constant for this equilibrium lies somewhere between 10 and 40. Consequently, both acids exist predominantly as zwitterions (XVII), although the uncharged forms (XVI) contribute around 5% (2–10%) to the equilibrium mixture. The experimentally determined pK's actually apply to this equilibrium mixture, and should be corrected for the tautomeric equilibrium before they are applicable to any of the individual equilibria listed.[4] The corrections involved are of the order of 0.01 to 0.04 pK unit, and have been neglected.

TABLE III

pK'S ESTIMATED BY USE OF THE HAMMETT EQUATION FOR THE VARIOUS EQUILIBRIA POSSIBLE IN THE DISSOCIATION OF NICOTINIC AND ISONICOTINIC ACID

Process	Nicotinic acid	Isonicotinic acid
XVI-XV	3.6	3.7
XVII-XV	4.7	4.5
XVIII-XVI	3.3	3.8

An independent check of the data is possible. The difference in free energy between IV and I + $2H^+$ must be independent of the path by which one goes from reactants to products. Hence, $pK_1 + pK_2$ must be a constant, independent of which isomer is assumed for AH, and this sum must agree with the sum of the experimentally determined pK's. For both nicotinic and isonicotinic acids, $pK_1 + pK_2 \sim 7.1$ when AH is assumed to have the form XVI, and the experimental values found in this investigation are 6.9 and 6.7, respectively, in reasonable agreement with the calculated values.

The above discussion indicates that the pK_1 values apply to equilibria XVIII $\rightleftarrows$ XVII. These values then permit the calculation, at least form-

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(11) H. H. Jaffé, THIS JOURNAL, **77**, 4451 (1955).

(12) E. B. Hughes, H. H. G. Jellinek and B. A. Ambrose, *J. Phys. Colloid Chem.*, **53**, 414 (1949).

(13) R. F. Evans, E. F. G. Herington and W. Kynaston, *Trans. Faraday Soc.*, **49**, 1284 (1953).

(14) These results are in good agreement with the spectrophotometric results of ref. 13, and with data recently reported by H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.*, **58**, 548 (1954). This latter paper, however, assumes that isonicotinic acid is *not* a zwitterion.

ally, of σ-values for the *m*- and *p*- $\geqslant N^+$—H groups, which are indicated in Table II, where they can be compared with values derived from the aminopyridines.

Similar tautomeric equilibria, of course, arise in the 1-oxides of nicotinic and isonicotinic acid, in 3-hydroxypyridine and in the aminopyridines. These cases are not further discussed here since there appears to exist no question about the assignment of the *pK*'s to the various possible equilibria. Arguments of the type described in this paper lead to the assignments indicated in the preceding paper,[6] and are in agreement with expectations.

NOTE ADDED IN PROOF.—Since this paper was accepted for publication, Metzler and Snell[15] have reported an investigation of the tautomeric equilibrium between 3-hydroxypyridine and the corresponding zwitterion. Their data present a gratifying verification of the validity of the method proposed in the present paper. Let us denote 3-hydroxypyridine by 3-VI′, its zwitterion by 3-VII′, and its conjugate acid and base, respectively, by 3-VIII′ and 3-V′, in analogy with the similar compounds V–VIII. The method presented in this paper, together with known σ and ρ values,[16] then leads to the following *pK* values: 3-VIII′ $\rightleftharpoons$ 3-VI′, 5.30; 3-VIII′ $\rightleftharpoons$ 3-VII′, 5.42 and 3-VI′ $\rightleftharpoons$ 3-V′, 8.54. These values compare with 5.44, 5.37 and 8.26, respectively, reported by Metzler and Snell; the agreement is seen to be excellent, considering the uncertainties involved in the Hammett equation in general, and its application to heterocyclic compounds in particular. Metzler and Snell's value for the tautomeric equilibrium constant, K = 1.17, also compares favorably with our calculated value, K = 0.76. The data quoted are particularly gratifying since they seem to suggest that the substituent constants for groups such as 3-$\geqslant N^+H$ appear to have real significance. The data further permit calculation, for the *m*-O^--group, of a value $\sigma = -0.54$, which seems very reasonable.

Acknowledgment.—The author acknowledges the skilled technical assistance of Mrs. Caroline Sasser.

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(15) D. E. Metzler and E. E. Snell, THIS JOURNAL, **77**, 2431 (1955).

(16) See Table II, ref. 6 and H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Tautomeric Equilibria. II. A Molecular Orbital Discussion of the Relative Stabilities of Pairs of Tautomers Involving Benzenoid and Quinoid Structures[1]

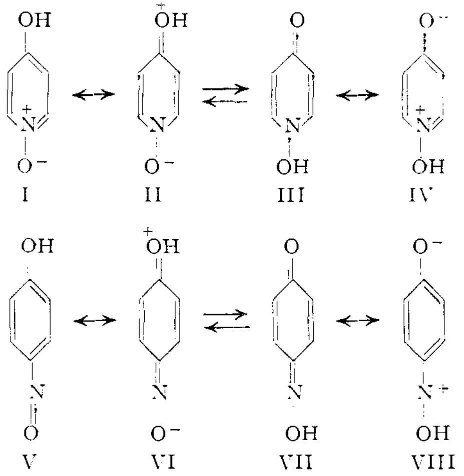
BY H. H. JAFFÉ

RECEIVED JANUARY 28, 1955

The difference in π-electron energy between each of the isomeric hydroxypyridine 1-oxides and the tautomeric N-hydroxypyridones, and between each of the isomeric nitrosophenols and the corresponding benzoquinonone monoximes has been calculated by molecular orbital theory, using a crude perturbation method. The hydroxypyridine 1-oxides and 3-nitrosophenol are found to be more stable than the corresponding N-hydroxy compounds, but *o*- and *p*-benzoquinone monoxime are more stable than the corresponding nitrosophenols. These conclusions are in agreement with experimental facts, as far as is known, with the possible exception of 2-hydroxypyridine 1-oxide.

Tautomerism between a compound involving benzenoid forms and its isomer involving a quinoid form as predominant resonance structures have frequently been discussed.[1,2] Whenever the quinoid compound[3] is found to be the more stable of a pair of tautomers, the question arises what characteristic of the quinoid compound can overcome the difference in resonance energy between benzenoid and quinoid compounds which, in general, is of the order of 20 kcal./mole.[4] As a contribution to this problem the present paper reports an investigation of the benzenoid and quinoid tautomers[3] of the isomeric hydroxypyridine 1-oxides (N-hydroxypyridones) and of the isomeric nitrosophenols (benzoquinone monoximes) by molecular orbital (MO) theory. In spite of its crude nature, the perturbation method of Coulson and Longuet-Higgins is used[5] since it makes the desired treatment especially simple.

The equilibria investigated are represented by formulas I–VIII and by the corresponding isomers in which the two functional groups are in the α and β (or *ortho* and *meta*) positions to each other. It should be noted that the structures written are only those considered most important, and that no



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[1] Presented before the Division of Physical and Inorganic Chemistry at the 127th meeting of the American Chemical Society, Cincinnati, Ohio, April, 1955. For paper I, see H. H. Jaffé, THIS JOURNAL, **77**, 4445 (1955).

(2) *E.g.*, (a) E. Havinga and A. Schors, *Rec. trav. chim.*, **69**, 457 (1950), and references cited there. (b) G. E. Philbrook, paper presented before the Southeastern Section of the American Chemical Society, Birmingham, Alabama, October, 1954.

(3) We shall call "quinoid compound" the tautomer in which the quinoid structure is presumably the predominant resonance structure because it is the only structure not involving separation of charges. The other tautomer, in which the benzenoid structures presumably predominate, will be designated as "benzenoid compound."

(4) G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 69.

(5) C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (*London*), **A191**, 39 (1947); **A192**, 16 (1947).