268. *The Tautomerism of* N-*Hetero-aromatic Amines. Part I.*

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Data and arguments on the tautomerism of α- and γ-amino-*N*-heterocyclic compounds are critically surveyed, and it is concluded that these compounds exist predominantly in the amino-form. A semi-quantitative method for the estimation of the proportion of the tautomers in equilibrium is proposed which consists in comparing the dissociation constants of the amines with those of suitably methylated derivatives in which tautomerism is not possible. In the cases investigated the ratio of amino- to imino-form was found to be greater than $10^3 : 1$.

Amino-compounds of nitrogen-containing aromatic heterocyclic compounds in which the amino-group is in the α- or the γ-position relative to the ring-nitrogen atom, *e.g.*, 2- and 4-aminopyridine, may exist either as amino-derivatives (*e.g.*, I) or as dihydro-imino-compounds (*e.g.*, II) ("amino-" and "imino-form," respectively). Chichibabin (*Ber.*, 1921, **54**, 814; 1924, **57**, 1168, 2093; 1925, **58**, 1704) used the concept of the imino-form extensively to explain the marked differences in chemical behaviour between the potentially tautomeric amines and those which are not capable of such tautomerism, *e.g.*, 3-amino-pyridine (for a tabulation of these differences see Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). Since then it has become customary to assign the imino-structure to any heterocyclic amine whose reactions did not correspond with those expected from an aromatic amine. Chichibabin, 25 years ago, had no other means of explaining the different reactivities than by assuming differences in the molecular structures, *i.e.*, tautomerism. Now, however, these differences can be accounted for by the assumption of different *electron distribution* in the molecules, *i.e.*, by mesomerism. Unfortunately no *N*-heterocyclic amine has been isolated in two tautomeric forms, and there exists no method for the estimation of these tautomers. This problem is therefore still controversial, and only recently two groups of investigators arrived at opposing conclusions. Steck and Ewing (*loc. cit.*), from their study of the absorption spectra of amino-pyridines, -quinolines, and -*iso*quinolines, assigned the imino-structure to these compounds. Anderson and Seeger (*ibid.*, 1949, **71**, 340), who also studied the absorption spectra, found no evidence for the presence of imino-forms in solutions of 2- and 4-aminopyridine. It seems therefore that a critical revaluation of the data is warranted.

(I) (Ia) (II) (IIa)

The potentially tautomeric heterocyclic amines are cyclic amidines or vinylogues of amidines. They will therefore show to some extent the properties of both aromatic amines and amidines. As in all amidines, cation formation will occur by addition of a proton to the doubly-bonded nitrogen atom (Branch and Calvin, "The Theory of Organic Chemistry," New York, 1941, p. 196), *i.e.*, to the ring nitrogen in the amino-forms and to the imino-group in the imino-forms. The resulting ion is stabilised by resonance and a second proton is taken up only at a very low pH or not at all. Because of this resonance stabilisation of the cations the potentially tautomeric amines are stronger bases than their isomers (Albert, Goldacre, and Phillips, *J.*, 1948, 2230). The stronger the amidine character of the amine the greater is this exaltation of the basic strength.

In many cases suggestions that the amines have the imino-structure are based solely on the products of chemical reactions. Such evidence is valueless because the tautomeric form responsible for the reaction may be present in only a minute amount and be formed as the reaction proceeds. Non-occurrence of a reaction expected from one tautomeric form is, however, admissible evidence: it may prove that one of the forms is totally absent. Most of the evidence quoted in favour of the imino-form is of such a nature. The

best evidence is obtained, however, by studying the physical properties of the tautomers in equilibrium.

The Case for the Imino-forms.—(1) *Alkylation.* In the first paper (Chichibabin, Konowalowa, and Konowalowa, *Ber.*, 1921, **54**, 814) of a series entitled "The Tautomerism of 2-Aminopyridine," Chichibabin found that methyl iodide reacted with the ring-nitrogen atom of bases such as 2- and 4-aminopyridine. He did not claim this as evidence that the bases exist in the imino-form (as later authors did, cf. Steck and Ewing, *loc. cit.*) but only stated that they react in this form. However, from our knowledge that amidines are methylated on their doubly-bound nitrogen atom (Pyman, *J.*, 1923, 3359) and from a consideration of the electron distribution in these compounds (cf. dipole moments, below) it is now obvious that the ring-nitrogen atom will be methylated in the *amino-*, not in the imino-, form. It has been shown (Angyal, *Austral. J. Sci. Res.*, in the press) that acylating agents also attack the ring-nitrogen atom. Nevertheless this argument for the imino-form is still sometimes used: *e.g.*, Albert and Ritchie (*J.*, 1943, 458), who found that the ring-nitrogen atom is methylated by methyl iodide in 5-aminoacridine whereas it does not react in the other aminoacridines, state that "the usually unreactive tertiary ring nitrogen is reacting as a secondary amine because of tautomerism." The tautomeric imino-form would, undoubtedly, be methylated on the imino-group. The enhanced nucleophilic reactivity of the ring-nitrogen atom is probably due to the strong resonance in 5-amino-acridine which causes high electron density on the ring-nitrogen atom.

Equally unconvincing is the assignment of the imino-structure to 9-amino-phenanthridine (Morgan and Walls, *J.*, 1932, 2227) on the basis of its acetylation which appears to give a ring-acetyl derivative.

(2) *Diazotisation.* The potentially tautomeric *N*-hetero-aromatic amines are not diazotised by nitrous acid in dilute solutions of acids (Marckwald, *Ber.*, 1894, **27**, 1317; Albert and Ritchie, *loc. cit.*; Morgan and Walls, *loc. cit.*) but only in concentrated acid solution (Königs, Kinne, and Weiss, *Ber.*, 1924, **57**, 1172). Diazonium salts, however, cannot be obtained but the corresponding hydroxy-compounds are formed. These facts have sometimes been used as arguments for the imino-form but can be explained without invoking it. Resonance (I $\leftrightarrow$ I*a*) causes low electron density on the amino-nitrogen atom, insufficient for reaction with the but weakly electrophilic dinitrogen trioxide molecule (Ingold, Hughes, and Ridd, *Nature*, 1950, **166**, 642) In concentrated acid solutions, however, the strongly electrophilic nitrosonium ion is present and will react. The case is analogous to that of polynitro-substituted anilines. The instability of the diazonium salts is similarly explained: aromatic diazonium salts are stabilised by resonance involving electrons from the aromatic ring (Dewar, "The Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 182). In the *N*-hetero-aromatic series the strong electron attraction of the ring-nitrogen atom prevents this resonance and therefore the diazonium compounds are as unstable as the aliphatic ones.

(3) *Hydrolysis.* Many potentially tautomeric amines are hydrolysed by acid or alkali to the corresponding hydroxy-compounds; this has often been taken as an indication for their existence in the imino-form (Morgan and Walls, *loc. cit.*; Marshall and Walker, *J.*, 1951, 1004). It is true that compounds which definitely have the imino-structure, such as 1 : 4-dihydro-4-imino-1-methylpyridine, are readily hydrolysed by alkalis. However, 5-amino-, 5-methylamino-, and 5-dimethylamino-acridine are all hydrolysed to acridone, the last—which *cannot* exist in the imino-form—the most easily (Albert and Ritchie, *loc. cit.*).

The ease of hydrolysis probably indicates low electron density on the carbon atom to which the amino-group is attached rather than the presence of an imino-form. This is borne out by a comparison of 4-amino-quinoline, -cinnoline, and -quinazoline (Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104); only the last-named compound is hydrolysed by acids and in this compound the electron density on $C_{(4)}$ is particularly low.

Exactly the opposite argument was used by Goodall and Kermack (*J.*, 1936, 1546). Observing that 5-aminoacridines containing disubstituted amino-groups are more readily hydrolysed by acids to acridones than are those with only one *N*-substituent, they concluded that the compounds with tertiary amino-groups are in the amino-forms but those with

secondary amino-groups exist in the imino-form. There seems to be no logical basis for this argument. 5-Dimethylaminoacridine is also hydrolysed by acids (Albert and Ritchie, *loc. cit.*). The most probable explanation is steric hindrance of resonance; the disubstituted amino-group cannot become coplanar with the aromatic rings and therefore the resonance stabilisation in this compound will be less than in the mono-substituted derivatives. The reduced resonance is clearly visible in the smaller exaltation of the basic strength: 5-amino-, -methylamino-, and -dimethylamino-acridine have pK_a 9·45, 9·77, and 7·53, respectively, whereas 2-amino- and 2-dimethylamino-acridine have practically identical pK_a values, there being no steric hindrance (Albert and Goldacre, *J.*, 1946, 706; Albert, "The Acridines," Edward Arnold & Co., London, 1951, p. 122).

(4) *Schiff's bases.* Some *N*-hetero-aromatic amines do not condense with aldehydes. Thus 5-aminoacridine does not react with benzaldehyde or salicylaldehyde (Albert and Ritchie, *loc. cit.*), and 4-aminopyrimidines do not react with sugars (Baddiley, Lythgoe, and Todd, *J.*, 1943, 571). In both cases the conclusion was drawn that the amines behave like imino-compounds. The more probable explanation again involves the low electron density on these amino-nitrogen atoms which will prevent nucleophilic addition to the carbonyl carbon atom of the aldehyde. Tables of calculated electron densities (Longuet-Higgins and Coulson, *J.*, 1949, 975: Pullman, *Rev. Sci.*, 1948, **86**, 219) show that at $C_{(4)}$ in pyrimidine and at $C_{(5)}$ in acridine the electron density is particularly low; this effect would be transmitted to an attached amino-group. 2-Aminoacridine occupies an intermediate position: it does not react with benzaldehyde but condenses with the more reactive salicylaldehyde (Albert and Ritchie, *loc. cit.*).

The Case for the Amino-forms.—(1) *Resonance energy.* The energetics of the amino–imino tautomeric system have apparently not been considered. The amino-forms have a fully aromatic structure and benefit by the aromatic resonance energy; the imino-forms, however, have a quinonoid structure in which some of the aromatic resonance energy has been lost. In consequence one would expect the amino-form to have the lower energy, and therefore to be more stable, in all the hetero-aromatic amines (unless substituents which have a strong influence on electron densities interfere).

Also, the analogy with the corresponding hydroxy-derivatives is often emphasised. For these compounds the pyridone, quinolone, acridone, etc., structures are well established (see, *e.g.*, Mosher in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1950, Vol I, p. 435). The two classes of compounds, however, are not analogous. Branch and Calvin (*op. cit.*, p. 289) have calculated from Pauling's bond-energy values that in the amide–imidol tautomeric system, $\cdot NH\cdot C{:}O \rightleftharpoons \cdot N{:}C\cdot OH$, the former tautomer is the more stable to the extent of about 10 kcal./mole. This gain in bond energy may compensate for the loss of resonance energy in the tautomerisation from hydroxypyridine to pyridone. But in the amino-compounds the tautomeric system is that of amidines, $\cdot NH\cdot C{:}N\cdot \rightleftharpoons \cdot N{:}C\cdot NH\cdot$ in which there is no change in bond energies; there is nothing therefore to compensate for the loss of resonance energy.

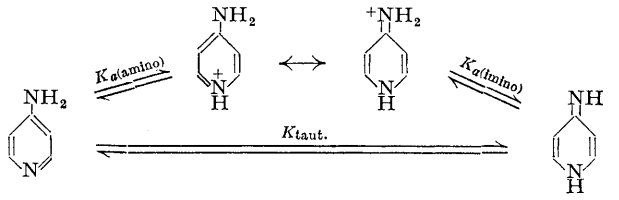
(2) *Dipole moments.* The evidence based on dipole moments is not conclusive. Leis and Curran (*J. Amer. Chem. Soc.*, 1945, **67**, 79) have reported that the dipole moment of 4-aminopyridine is somewhat larger than that calculated by combining the values for pyridine and aniline. This is concordant with the amino-form (I) with a resonance contribution from (I*a*). According to these authors the imino-form (II) cannot be present in any significant amount since it would have a very low moment. It seemed to us, however, that the structure of the imino-form would have a very considerable contribution from (II*a*), owing to its strong tendency to revert to the aromatic system, and therefore would be strongly rather than weakly polar. Accordingly we tried to measure the moment of 1 : 2-dihydro-4-imino-1-methylpyridine—a compound which can have only the imino-structure—but were prevented by its low solubility in benzene and dioxan. However, the measurements were carried out in the quinoline series: 4-aminoquinoline was found to have a moment of 4·4 D—the same as 4-aminopyridine—and 1 : 4-dihydro-4-imino-1-methyl quinoline a moment of 5·1 D. A high dipole moment is, therefore, no evidence for the amino-form.

(3) *Absorption spectra.* Conclusions have been often drawn on the tautomerism of

N-heterocyclic amines from the study of absorption spectra. These conclusions are unreliable, however, unless information is available about the bands occurring in the spectra of both the amino- and the imino-forms.* Since replacement of a hydrogen atom by a methyl group causes only minor changes in the spectrum, such information can be obtained from the spectra of methylated derivatives in which tautomerism has been eliminated. By this method, Anderson and Seeger (*loc. cit.*) have shown that the characteristic band of the imino-form does not appear in the spectra of 2- and 4-aminopyridines and consequently the imino-form, if it exists at all, can be present in very small proportion only.

(4) In two cases, those of melamine (Knaggs and Lonsdale, *Proc. Roy. Soc.*, 1940, **177**, A, 140; Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737) and of 4-amino-2 : 6-dichloropyrimidine (Clews and Cochran, *Acta Cryst.*, 1950, **3**, 76), the amino-structure was proved by *X*-ray analysis.

From this survey it appears that the amino-form is the more stable and therefore predominates in the *N*-hetero-aromatic amines. But all the above-mentioned information on the tautomeric equilibrium is only qualitative. Yet there exists a simple method, based on the determination of the basic strength, which yields quantitative values for the tautomeric equilibrium constant, with a certain approximation (cf. Branch and Calvin, *op. cit.*, p. 301). Since both the amino- and the imino-form give the same mesomeric cation by the addition of a proton, the following equilibria coexist :



in this scheme $K_{a(\text{amino})}$ and $K_{a(\text{imino})}$ are the acid dissociation constants of the cation as the conjugate acid of the amino- and the imino-form, respectively, and $K_{\text{taut.}}$ is the tautomeric equilibrium constant. Since

$$K_{a(\text{amino})} = [\text{amino}][H^+]/[\text{cation}]$$

and

$$K_{(a)\text{imino}} = [\text{imino}][H^+]/[\text{cation}]$$

it follows that

$$K_{\text{taut.}} = [\text{amino}]/[\text{imino}] = K_{a(\text{amino})}/K_{a(\text{imino})} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

i.e., the tautomeric equilibrium constant can be calculated from the two dissociation constants. This relation is generally valid for all tautomeric equilibria where the two tautomers give the same cation (or anion); in a qualitative sense it requires the less prevalent tautomer to be the stronger base (or acid). Many examples could be quoted; thus imino-esters are stronger bases than amides; *iso*ureas and *iso*thioureas are stronger bases than ureas and thioureas, respectively; the nitroalkanes are weaker acids than their *aci*-forms, and simple enols are stronger acids than the corresponding ketones [although equation (1) indicates that the unknown *cyclo*hexa-2 : 4-dienone, the ketonic tautomer of phenol, must be a stronger acid than phenol].

Application of this simple relation is restricted by the difficulty of determining the dissociation constants of both tautomeric forms. Apparently this has been achieved

* A recent example of an unjustified conclusion from spectra is the assignment of the imino-structure to 4-aminoquinoline and 4-aminocinnoline (Hearn, Morton, and Simpson, *J.*, 1951, 3318) on the basis of the resemblance of their spectra to those of 4-quinolone and 4-cinnolone, respectively. There is no reason, however, why the *O*- and the *N*-derivatives should absorb at the same wave-length. In fact, comparison of the ultra-violet spectra of 2- and 4-ethoxypyridine and 2- and 4-pyridone on the one hand (Specker and Gawrosch, *Ber.*, 1942, **75**, 1338), and the corresponding aminopyridines and dihydroimino-*N*-methylpyridines on the other (Anderson and Seeger, *loc. cit.*) shows that in all cases the *N*-derivatives absorb at a longer wave-length than the analogous *O*-derivatives.

only in the case of the nitroalkanes (Turnbull and Maron, *J. Amer. Chem. Soc.*, 1943, **65**, 212) where the tautomeric equilibrium constants have been calculated according to equation (1).

Since the tautomeric forms of the heterocyclic amines are not known, their ionisation constants cannot be directly determined. As an approximation, however, the corresponding constants of their known methylated derivatives can be substituted. The error introduced is not large since methyl substitution usually increases pK_a by about 0·2 unit only (Hall and Sprinkle, *ibid.*, 1932, **54**, 3469; see also Albert and Goldacre, *loc. cit.*, 1946). Thus the dissociation constant of the dihydro-imino-*N*-methyl compound can be substituted for $K_{a(\text{imino})}$; and, since—as the results show—the amino-form predominates considerably, the experimentally determined constant of the heterocyclic amine, K_a, will be nearly identical with, and can be used instead of, $K_{a(\text{amino})}$. In other cases, where the equilibrium is not one-sided to such an extent, it will be necessary to substitute the dissociation constant of the corresponding dimethylamino-compound for $K_{a(\text{amino})}$.

This method has apparently been applied only once to tautomeric equilibria: by Tucker and Irvin (*ibid.*, 1951, **73**, 1923) to 4-quinolone. Independently of the American authors we have investigated (C. L. Angyal, Thesis, Sydney, 1951) some heterocyclic amines; our results, together with published data on melamine, are shown in the Table.

	pK_a	$pK_{a(\text{Me})}$ *	$K_{\text{taut.}}$ †	ΔF (kcal./mole)
2-Aminopyridine	6·86 ‡	12·20 §	2×10^5	7·3
4-Aminopyridine	9·17 ‡	12·5 §	2×10^3	4·5
4-Aminoquinoline	9·17 ‡	12·4 §	2×10^3	4·5
2-Aminothiazole	5·39 ‡	9·65 §	2×10^4	6·0
Melamine (2 : 4 : 6-triamino-1 : 3 : 5-triazine)	5·16 ‡	10·54 ‖	2×10^5	7·3

* pK_a of the corresponding dihydro-imino-*N*-methyl compound.
† Calculated from equation (1), with K_a instead of $K_{a(\text{amino})}$, and $K_{a(\text{Me})}$ instead of $K_{a(\text{imino})}$.
‡ Albert, Goldacre, and Phillips, *loc. cit.* § Present work.
‖ Value for ethyl*iso*melamine, Dudley, *J. Amer. Chem. Soc.*, 1951, **73**, 3007.

The imino-compounds derived from the amino-pyridines and -quinoline show a basic strength typical of amidines (*e.g.*, acetamidine, pK_a 12·52; Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162), and 1 : 4-dihydro-2-imino-3-methylthiazole has a strength comparable to that of *S*-methyl*iso*thiourea (pK_a 9·83, Albert, Goldacre, and Phillips, *loc. cit.*). The imino-forms of other heterocyclic amines would presumably show the same non-aromatic basic strength, and since all the heterocyclic amines so far measured have considerably lower pK_a's, they probably all exist in the amino-form.

The last column of the Table gives the difference of the free energies of the tautomers, calculated from the equation $\Delta F = -\boldsymbol{R}T \ln K_{\text{taut.}}$. Since the bond energies of the tautomers are equal, this difference in the free energies is mainly due to resonance and is therefore a measure of the loss of aromatic resonance energy in the change from the amino- to the imino-form.

The above conclusions are valid only for the dilute aqueous solutions in which the pK_a values were determined; but the ΔF values are sufficiently large to make it unlikely that the position of the equilibrium would be reversed by a change of solvent. It is worth mentioning that the absorption spectra of 2- and 4-aminopyridine are the same in water and in ether (Anderson and Seeger, *loc. cit.*).

Experimental

Materials.—4-Aminopyridine and 4-aminoquinoline, as well as their methiodides, were prepared by Mr. N. K. Matheson according to published methods (Chichibabin and Ossetrova, *Ber.*, 1925, **58**, 1709; Claus and Frobenius, *J. pr. Chem.*, 1897, **56**, 184). The methiodide, m. p. 149°, of 2-aminopyridine was made according to Chichibabin, Konowalowa, and Konowalowa (*loc. cit.*). The methiodide of 2-aminothiazole was prepared by boiling a solution of the amine (5 g.) in anhydrous ethanol (5 c.c.) with methyl iodide (7 g.) for 10 minutes and crystallising the yellow precipitate from anhydrous ethanol. It melted at 174°; Nef, who prepared it in a sealed tube at 130°, reported m. p. 175° (*Annalen*, 1891, **265**, 112).

Ionisation Constants.—Approx. 0·01M-aqueous solutions of the hydriodides were titrated

potentiometrically at 21° with 0·1N-potassium hydroxide. The pH values were determined with a Leeds and Northrup Universal pH Potentiometer Assembly (No. 7663-A-1), adjusted to pH 9·16 by comparison with a M/20-borax buffer. The solutions were made in carbon dioxide-free water and were titrated in a stream of nitrogen. The pK_a values were calculated according to the equation, $pK_a = pH - \log\{([B] - [OH^-])/([BH^+] + [OH^-])\}$, where [B] and $[BH^+]$ are the calculated concentrations of the base and its conjugate acid, respectively, corrected for the dilution caused by addition of alkali but not for the activity coefficients or for the potassium-ion error. Above pH 12 the values were not readily reproducible and the error in pK_a may there be as high as 0·2 unit.

Dipole Moments.—Details of procedure and calculations were as recorded by Calderbank and Le Fèvre (*J.*, 1948, 1949; cf. also Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). 1 : 4-Dihydro-4-imino-1-methylquinoline is described as an oil (Claus and Frobenius, *loc. cit.*) but we found that it crystallised on evaporation of its solution in benzene. Because of its extreme sensitivity to oxygen, carbon dioxide, and water, however, it seemed unsuitable for purification, analysis, and weighing. Instead, the base was liberated from a solution of its hydriodide by concentrated sodium hydroxide solution and extracted by chloroform, and the extract dried (Na_2SO_4) and evaporated *in vacuo*. Dry benzene was then added, the whole was evaporated several times to remove all water and chloroform, and the benzene solution was filtered and used directly for dipole moment measurements. The concentration was determined by acidimetric titration (phenolphthalein) of an aliquot. (The base, as it separates from water, is not soluble in benzene probably because of hydrate formation.)

The measurements are tabulated under the usual headings (Calderbank and Le Fèvre, *loc. cit.*).

$10^5 w_1$	ε	d_4	$\alpha\varepsilon_2$	β
4-Aminoquinoline in dioxan at 25°				
0	2·2192	1·0303	—	—
457	2·2990	1·0313	17·46	0·2124
684	2·3342	1·0317	16·81	0·1986
1010	2·3955	1·0321	17·46	0·1731
whence $\alpha\varepsilon_2 = 17·24$ (mean); $\beta = 0·195$ (mean).				

$10^5 w_1$	ε	d_4	$\alpha\varepsilon_2$	β
1 : 4-*Dihydro-4-imino-1-methylquinoline in benzene at* 30°				
0	2·2628	0·86718	—	—
671	2·3835	0·86901	18·00	0·3179
1017	2·4415	0·86988	17·57	0·3062
1261	2·4920	0·87061	18·18	0·3137
whence $\alpha\varepsilon_2 = 17·92$ (mean); $\beta = 0·313$ (mean).				

	M	P_T (c.c.)	$[R_L]_D$	μ (D)
4-Aminoquinoline	144·2	439·4	46·6	4·38
1 : 4-Dihydro-4-imino-1-methylquinoline	158·2	577·0	51·2	5·11

The authors are indebted to Mr. N. K. Matheson for preparative assistance, and to Professor A. Albert for a helpful discussion.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, December 3rd*, 1951.]