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# Studies on the Tautomerism of 2-Anilinopyridine and Related Heterocycles. II. 2-Anilino-5-nitropyridine and 2-Anilinopyrimidine

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The tautomeric behavior of 5-nitro-2-anilinopyridine and 2-anilinopyrimidine was studied. 2-(*N*-Methylanilino) and 1-methyl-2-(phenylimino)-1,2-dihydro derivatives were prepared as models for the amino and imino tautomers, respectively, and their spectra were compared. The results and the assumed tautomeric equilibrium constants strongly suggest the equilibria to be favorable to the amino tautomers, the $K_t$ values being considerably smaller than that of the parent 2-anilinopyridine.

Tautomeric equilibria of aminopyridines have been discussed by several investigators. From experimental evidences and theoretical consequences[1–5] it was concluded that the amino tautomers are considerably more stable than the imino tautomers. As regards 2-anilinopyridines, however, Bell *et al.*[6] and Rud'ko *et al.*[7] claimed the presence of a measurable amount of the imino tautomer on the basis of the splitting of their N–H stretching bands. Cook *et al.* discussed the tautomeric behavior from the ultraviolet spectra.[8] Studies were made on this problem and it was concluded that the tautomeric equilibria by far favor to the amino tautomer[9–10] and that the splitting of the N–H stretching bands is due to the presence of rotational isomers.[11] The tautomeric behavior of the title compounds was studied, since the introduction of the electron-withdrawing group, especially on the pyridine nucleus, might contribute to stabilize the imino tautomers.

## Experimental

*Preparation of Materials.* 2-Anilino-5-nitropyridine (**1**) and 2-anilinopyrimidine (**4**) are known compounds and were prepared by condensing 2-chloropyrimidine and 2-chloro-5-nitropyridine with aniline. *N*-Methylanilino derivatives **2** and **5** were prepared similarly with use of *N*-methylaniline. 1-Methyl-5-nitro-2-(phenylimino)-1,2-dihydropyridine (**3**) and 1-methyl-2-(phenylimino)-1,2-dihydropyrimidine (**6**) are new compounds, and were prepared by the method previously reported.[10] **2**, mp 101 °C. Found: C, 62.80; H, 4.98; N, 18.15%, M+, 229. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33%; M+, 229. **3**, mp 119—120 °C. Found, C, 62.61; H, 5.10; N, 19.14%; M+, 229 (an isomer of **2**). **5**, bp 125—126 °C/11 mmHg. Found C, 71.53; H, 6.16; N, 22.75%; M+, 185. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69% M+, 185. **6**, mp 88—90 °C. Found: C, 71.80; H, 5.84; N, 22.51%; M+, 185 (an isomer of **5**)

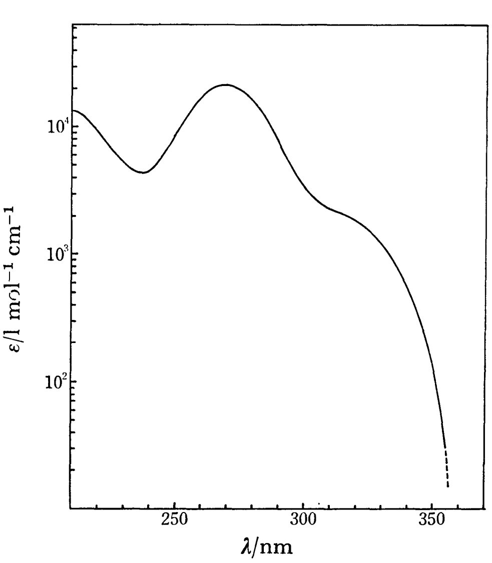
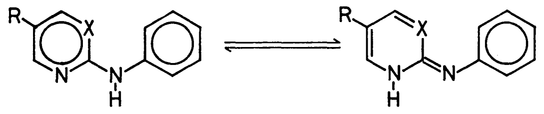


Fig. 1. Ultraviolet spectrum of **4** in aqueous ethanol (1:1).

*Measurement of Spectra.* Ultraviolet and infrared spectra were measured with Hitachi EPS-3T and Hitachi 225 recording spectrophotometers, respectively. NMR spectra were obtained with a JEOL JNM C60-H spectrometer and, when necessary, Eu(fod)$_3$ was used to separate the overlapping signals. Details of the spectral measurement were imilar to those previously reported.[10]

## Results and Discussion

*Ultraviolet Spectra.* The ultraviolet spectra of 2-anilino-5-nitropyridine (**1**), 2-anilinopyrimidine (**4**) and their *N*-methyl derivatives are given in Table 1. The spectra of **1** and **4** resemble considerably those of the corresponding *N*-methylanilino derivatives **2** and **5**, differing a great deal from those of the corresponding 1-methyl-2-(phenylimino)-1,2-dihydro derivatives **3** and **6**. Even when the measurements were carried out in highly polar solvents, **1** and **4** showed no absorption bands in the longer wavelength region in which the characteristic absorption bands of the pyridoneimine chromophores appear (Fig. 1). This suggests that **1** and **4** exist almost exclusively as the amino tautomer. Measurement in several other solvents also gave similar results.



(I) (II)

In order to estimate the tautomeric equilibrium constants of **1** and **4**, the dissociation constants ($K_a$) of the amino (**2** and **5**) and the imino (**3** and **6**) model compounds were determined by means of the pH

Table 1. Ultraviolet spectra

| Compound | $\lambda_{max}$/nm ($\varepsilon_{max}$/l·mol$^{-1}$·cm$^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| | in $C_6H_{12}$ | | in $CH_3CN$ | | in $C_2H_5OH$ | |
| **1** | 247 | (11500) | 250 | (15500) | 215 | (14700) |
| | 348 | (19400) | 377 | (21500) | 378 | (19300) |
| **2** (amino) | 220 | (13600) | 216—230 | (12600) | 218—233 | (14400) |
| | 350—353 | (21500) | 373 | (19000) | 365 | (19300) |
| **3** (imino) | 217 | (15900) | 216 | (15800) | 215 | (14300) |
| | 350—354 | (14500) | 356—362 | (13800) | 350—356 | (13000) |
| | 376 | (12000)* | 375—392 | (13000)* | 394 | (10300)* |
| **4** | 270 | (25800) | 270 | (28800) | 273 | (21300) |
| | 300—310 | ( 2500)* | 310—315 | ( 2500)* | 308—310 | ( 2300)* |
| **5** (amino) | 227 | (13800) | 234 | (11500) | 229 | (12700) |
| | 265 | (12300) | 254 | (12300) | 265 | (14100) |
| | 290—300 | ( 2800)* | 265—273 | (11700) | 300—320 | ( 2400)* |
| | | | 300—305 | ( 3300)* | | |
| **6** (imino) | 271 | ( 7800) | 280 | ( 8900) | 275 | ( 7200) |
| | 361 | ( 1100)* | 370 | ( 1500) | 367 | ( 1400) |

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Table 2. The dissociation constants and tautomeric equilibrium constants

| Compound | p$K_a$ | $K_t$[a] |
|---|---|---|
| **1** | 0.59 | $8.0\times10^3$ |
| **2** | 0.76 | |
| **3** | 4.66 | |
| **4** | 5.20 | $5.5\times10^2$ |
| **5** | 5.26 | |
| **6** | 8.00 | |

a) $K_t$=[amino tautomer]/[imino tautomer].

Table 3. NMR spectra (in $CDCl_3$)

| Compound | H(3) | H(4) | H(5) | H(6) | N-$CH_3$ |
|---|---|---|---|---|---|
| **1** | 6.92 | 8.22 | — | 9.03 | — |
| **2** | 6.25 | 7.87 | — | 8.95 | 3.55 |
| **3** | 6.30 | 7.48 | — | 8.42 | 3.61 |
| **4** | — | 8.34 | 6.65 | 8.34 | — |
| **5** | — | 8.28 | 6.53 | 8.28 | 3.51 |
| **6** | — | 8.07 | 5.80 | 8.07 | 3.47 |

Table 4. Infrared NH stretching absorptions (in $CCl_4$)

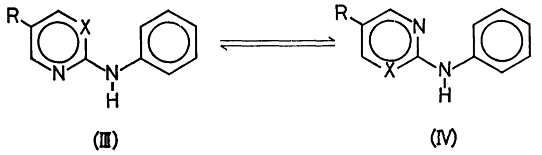
| Compound | $\nu_{NH}$/cm$^{-1}$ ($\varepsilon_{max}$/l mol$^{-1}$ cm$^{-1}$) |
|---|---|
| 2-Anilinopyridine | 3417 ( 98)<br>3444 ( 48) |
| **1** | 3409 ( 84)<br>3438 ( 39) |
| **4** | 3432 (179) |
| 3-Carboline | 3476 (220) |
| Diphenylamine | 3427 |

dependence of their ultraviolet spectra. The tautomeric equilibrium constants obtained from the $K_a$ values by the equation $K_t=K_a(\text{amino})/K_a(\text{imino})$ are given in Table 2. As expected, the $K_t$ value of **1** and **4** is remarkably smaller than that of unsubstituted 2-anilinopyridine. The electron withdrawing nitrogroup on the heterocyclic ring gives rise to the displacement of the unshared electrons on the exocyclic nitrogen atom towards the ring, favoring the imino tautomer. The effects is more pronounced when another carbon atom constituting the ring is substituted by a nitrogen atom. This is due to the electronegative nature of nitrogen atom. From the $K_t$ value obtained, 2-anilinopyrimidine is expected to exist as a tautomeric mixture containing *ca.* 0.2% of the imino tautomer in aqueous ethanol solution. The amount of the imino tautomer corresponds to the apparent molar absorption coefficient of *ca.* 3 l mol$^{-1}$ cm$^{-1}$ in the longer wavelength region, being too low an intensity to be detected by the usual measurement of ultraviolet spectrum.

*NMR Spectra.* The NMR spectra of the heterocyclic ring protons of 2-anilino-5-nitropyridine, 2-anilinopyrimidine, and their *N*-methyl derivatives are given in Table 3.

The assignment of the signals was carried out by comparison with similar compounds, by using their lanthanoid induced shifts by Eu(fod)$_3$, and by the estimation from the electron densities. As has been shown from MO calculations,[10] the imino tautomer is expected to have considerable bond alternation in the heterocyclic part of its molecule. This causes a decrease in aromaticity of the heterocyclic ring, resulting in chemical shifts of the protons on the ring to displace towards higher fields. The effect is observed in the imino model compounds **3** and **6**, which is in line with the case of the imino models of 2-anilinopyridine and 2-anilino-4-methylquinoline. The spectra of **1** and **4** resemble as a whole the corresponding amino model compounds (**2** and **5**), there being no indication of the presence of the imino tautomers. Analogous to the case of unsubstituted 2-anilinopyridine, the hydrogen atom at the 3-position of the heterocyclic ring resonates at a higher field and is attributed to the anisotropy effect caused by the phenyl ring of anilino moiety, since the 3-H is located close on the phenyl ring in one (III) of the two possible rotational isomers. This is reasonable, since the effect is not predominant with **5** which is void of such steric hindrance and the molecule is supposed to be nearly planar.

*Infrared Spectra and the Existence of Rotational Isomers.* Existence of the tautomeric equilibrium is often presumed on the basis of the splitting in the N–H stretching bands of these and related aminopyridines. Surely it can be an indication of the tautomeric equilibria if other possibilities are excluded. However, the presence of rotational isomers (III and IV) has been suggested on several nitro-substituted 2-anilino-pyridines and -quinolines to explain the splitting of N–H absorptions.[11] As regards 2-anilinopyrimidine (**4**), the two rotational isomers are degenerate and the appearance of a single absorption band is predicted if the splitting is caused by rotational isomerism. In accord with this prediction, **4** has actually a single symmetrical absorption band at 3432 cm$^{-1}$ in the N–H stretching region.



(III) (IV)

The imino compounds **3** and **6** exhibit very strong C=N stretching absorptions at 1649 and 1630 cm$^{-1}$, respectively. On the other hand, other compounds including **1** and **4** have no remarkable absorptions when the spectra were measured in carbon tetrachloride solutions.

From the results, the amino tautomers are found to be by far more favorable in the tautomeric equilibria of both **1** and **4**. As expected, the tautomeric equilibrium constants of these compounds are considerably lower than the tautomeric equilibrium constant ($K_t = 2\times10^{-5}$) of the parent 2-anilinopyridine.

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