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STUDIES ON THE CONFORMATIONAL ISOMERS OF 2-ANILINOPYRIDINES AND RELATED COMPOUNDS

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Abstract—Infrared spectra in the N–H stretching region of several nitro-substituted 2-anilinopyridines and related compounds were measured under the conditions in which no intermolecular interaction is probable, and the reasons for the splitting of the N–H bands have been discussed. From the solvent and temperature dependence of the N–H stretching spectra, it is concluded that the splitting is due to the existence of rotational isomers. The assignments of these absorptions are given and some evidence to support the above conclusions is presented.

MANY INVESTIGATIONS have been carried out on the N–H stretching absorptions of arylamines.[1–4] Russel and Thompson[5] reported that benzylaniline has two absorption bands at 3419 cm^{-1} and 3540 cm^{-1}, and assigned them to the two rotational isomers. Schleyer and Trifan[6] showed that N-arylanilines also had two N–H stretching bands, and the band at the lower frequency is assigned to the conformation in which an intramolecular interaction between pi-electrons and the N–H group exists. Ōki and Mutai[7] reported on the N–H absorption bands of benzylaniline derivatives, in which they interpreted the N–H band splitting by assuming the rotational isomers with and without an intramolecular interaction between the N–H group and the pi-electrons. They concluded that the absorption at a lower frequency is due to the N–H --- pi interacted form and that the intensity of the band at the lower frequency is enhanced by the introduction of an electron releasing group in the *para*-position of the aniline nucleus.

As to anilinopyridines, Bell *et al.*[8] reported their IR spectra in the N–H stretching region and discussed the possibility of the existence of a tautomeric equilibria.

In the course of the investigations on 2-anilinopyridine, 2-anilinoquinoline and their nitro derivatives of pharmaceutical interests,[9] the authors measured the N–H stretching absorptions of these compounds and found that they also have two absorption bands in the wave number range between 3300 cm^{-1} and 3450 cm^{-1} of the N–H stretching region. Either of the following mechanism might be realized to cause the splitting of the absorption band: (i) existence of intramolecular or intermolecular hydrogen bonding, (ii) existence of rotational isomers or tautomers, and (iii) coupling with an overtone or combination bands. The authors attribute the splitting of the absorption bands to the rotational isomers by denying the other possi-

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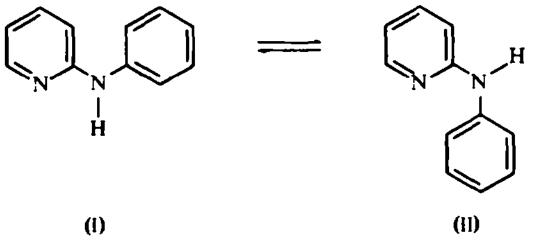
bilities, and conclude that these compounds have two different conformations which can be illustrated by the formulas I and II.



RESULTS AND DISCUSSION

The N–H stretching absorptions of 2-anilinopyridine and 2-anilino-4-methylquinoline, as examples, are illustrated in Fig. 1.

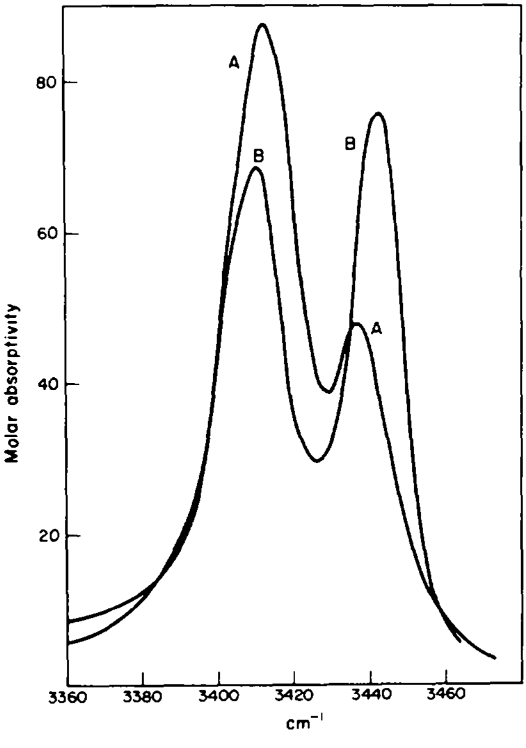


FIG 1. N–H stretching absorptions of 2-anilinopyridine (A) and 2-anilino-4-methylquinoline (B) in $CHCl_3$

The absorption curves of these compounds have two maxima in the wave number range between 3450 cm^{-1} and 3350 cm^{-1}. The N–H stretching absorptions of other compounds are listed in Tables 1 and 2 together with the electron densities on the nitrogen atoms which are calculated by the simple HMO method.

In these tables, band I and II refer to the absorption bands at the higher and the lower

TABLE 1. THE N–H ABSORPTIONS OF NITRO-SUBSTITUTED 4-METHYL-2-ANILINOQUINOLINES IN CHLOROFORM

Substituent	Frequency (cm^{-1})	Intensity	Electron Anilino-N	Density Ring-N	Intensity Ratio
H	3411	68	1·825	1·250	1·12
	3442·5	77			
6-NO_2	3405	85·5	1·809	1·237	1·38
	3437·5	118			
5-NO_2	3403·5	61·5	1·823	1·216	1·97
	3439	121			
8-NO_2	3404	34·5	1·812	1·226	2·13
	3439	73·5			
4'-NO_2	3405	34	1·787	1·242	4·20
	3437	143			
3'-NO_2	3409	25·5	1·807	1·255	4·43
	3442	113			
2'-NO_2	3342·5	94·5			
2',4'-$(NO_2)_2$	3331	97			
8,2'-$(NO_2)_2$	3337	62·5			
8,2,'4-$(NO_2)_3$	3324	136			

frequencies, respectively, and the notations I and II will be related to the conformations I and II in the further discussion.

The symmetric and asymmetric N–H stretching frequencies of the substituted anilines tend to increase as the electron attracting character of the substituents increase, and hence the electron densities on the anilino-nitrogen atoms decrease. On the contrary, the O–H stretching frequencies of the substituted phenols tend to decrease as the electron densities on the phenolic oxygen atoms decrease.[13] In the present investigation, the N–H stretching frequencies of the 2-anilinopyridine and

TABLE 2. THE N–H ABSORPTIONS OF NITRO-SUBSTITUTED 2-ANILINOPYRIDINES IN CHLOROFORM

Substituent	Frequency (cm^{-1})	Intensity	Electron Anilino-N	Density Ring-N	Intensity Ratio
H	3413	88	1·831	1·210	0·44
	3437	48			
H (inCCl_4)	3417	98			0·29
	3444	48			
5-NO_2	3410	174	1·816	1·207	0·31
	3428	79			
3'-NO_2	3411	59	1·831	1·210	0·93
	3438	88·5			
4'-NO_2	3406	66	1·816	1·208	1·22
	3431·5	115			
5,3'-$(NO_2)_2$	3398	70·5	1·816	1·207	1·30
	3427	113			
5,4'-$(NO_2)_2$	3397	50·5	1·802	1·205	1·20
	3424	111			
3-NO_2	3357	85	1·812	1·210	
2'-NO_2	3346	63	1·813	1·208	
2',4'-$(NO_2)_2$	3328	72	1·800	1·206	

2-anilinoquinoline series tend to shift to lower frequencies when the electron densities on the anilino-nitrogen atoms decrease. This behaviour resembles with that of phenols, and might arise from the higher acidic character of the amino-hydrogen in these compounds. When the electron densities on the nitrogen atoms in the hetero-aromatic nuclei increase, the frequencies of the band I are apt to shift to the higher wave numbers, and the N–H stretching absorptions seem to be dependent on the electron densities of the hetero-aromatic nitrogen atoms. This may be an indication of the existence of some interaction between the N–H group and the nitrogen atom of the quinoline nucleus in conformation I.

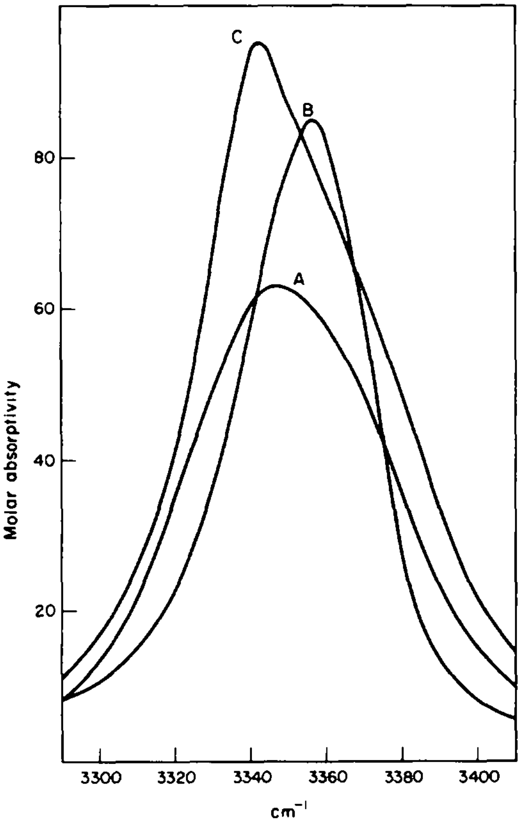


FIG 2. N–H Stretching absorptions of 2'-nitro-2-anilinopyridine(A), 3-nitro-2-anilinopyridine(B) and 2'-nitro-2-anilino-4-methylquinoline(C).

When a nitro-group is introduced at the 3 or 2'-position, only an unsymmetrical N–H band appears at a fairly lower wave number (3300–3350 cm^{-1}). This is because the intramolecular hydrogen bond is formed between the N–H and the nitro groups. In this case two conformations (III and IV) may exist. Judging from the unsymmetrical absorption envelope, the band is likely to be an overlap of more than one symmetrical bands.

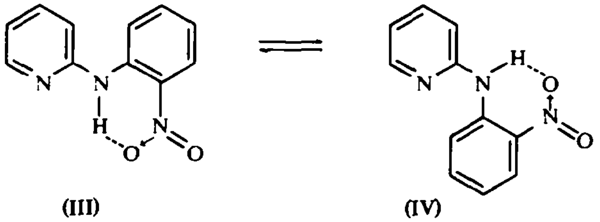
To obtain information on the solvent effect, the authors have measured the N–H stretching absorptions in several aprotic solvents of varying dielectric constants. The results are given in Table 3. The change in intensity ratios shows the fact that band II

TABLE 3. THE N-H STRETCHING ABSORPTIONS OF 4-METHYL-2-ANILINOQUINOLINE(H) AND ITS 6-NITRO DERIVATIVE (6-NO_2) IN SEVERAL SOLVENTS

Compd		N-H Stretching Frequency (cm^{-1}) and Intensity									Dipole Moment[b]
		in CCl_4 ($\varepsilon_D = 2{\cdot}238$)			in $CHCl_3$ ($\varepsilon_D = 4{\cdot}806$)			in CH_2Cl_3 ($\varepsilon_D = 7{\cdot}77$)			Calc.
		ν	ε	$\varepsilon_{II}/\varepsilon_I$[a])	ν	ε	$\varepsilon_{II}/\varepsilon_I$[a]	ν	ε	$\varepsilon_{II}/\varepsilon_I$[a])	
H	I	3415	69	1·12	3411	53	1·56	3404	43	2·37	1·30 D
	II	3447	77	(0·62)	3443	83	(0·83)	3434	102	(1·34)	2·36 D
6-NO_2	I	3409	64	1·51	3405	86	1·37	3397	62	2·37	3·53 D
	II	3443	97	(0·73)	3437	118	(0·77)	3428	147	(1·39)	4·78 D

[a] Integrated intensity ratios (A_{II}/A_I) are also listed in parentheses.

[b] The dipole moment values of pyridine, diphenylamine and nitrobenzene in ref. 14 were employed in this calculation.



(III) (IV)

tends to be more intense as the polarity solvent increases. From the dipole moment values calculated by the addition of the group moments, conformation II is estimated to be more polar than conformation I (Table 3). Thus, the N–H stretching absorption at the lower frequency is assigned to conformation II and the one at the higher frequency to conformation I. This assignment is also in accordance with the existence of N–H---N interaction in conformation II, since its N–H stretching frequency is considerably lower than that assigned to conformation I. However, further investigation is required to affirm the interaction.

Next, the authors have measured the spectra of 4-methyl-2-anilinoquinoline over a range of temperatures in CCl_4. The temperature dependence of the intensity ratio $\varepsilon_I/\varepsilon_{II}$ is shown in Fig. 3. The $\log_{10}(\varepsilon_I/\varepsilon_{II})$ values are linear with 1/T and the energy difference between the two conformations is estimated to be 0·8 kcal/mole from the slope of the straight line in Fig. 3. The temperature dependency of the intensity ratio implies that the mechanical coupling, such as Fermi resonance, might not be responsible for the band splitting.

On the basis of the above data, it is concluded that the 2-anilino-pyridines and -quinolines exist as mixtures of some rapidly interconvertible isomers. However, whether the splitting of the absorption band is due to the rotational isomer or due to the tautomers (V) still remains unsettled.

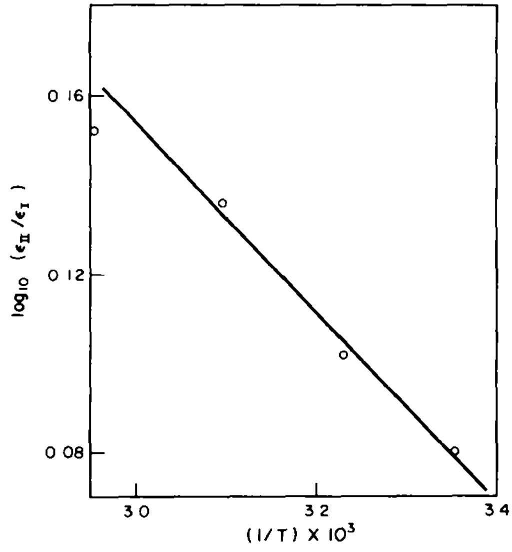


FIG 3. Temperature dependence of the intensity ratio $(\varepsilon_{II}/\varepsilon_I)$ 2-anilino-4-methylquinoline.

TABLE 4. HMO π-ELECTRON ENERGY (β) OF 2-ANILINOPYRIDINES[a]

Tautomeric Form	2-Anilinopyridines							2-PhNH-4-Me-Quinoline
	H	4-NO_2	5-NO_2	6-NO_2	2'-NO_2	3'-NO_2	4'-NO_2	
Amino Form	20·4174	27·6474	27·6788	27·6502	27·6876	27·6664	27·6474	31·6823
Imino Form	20·0670	27·4762	27·3440	27·3558	27·3506	27·3145	27·3440	31·4881
ΔE_{pi}	0·3504	0·1712	0·3348	0·2944	0·3370	0·3519	0·3034	0·1942

[a] $N\alpha$ is omitted, where N is the number of the π-orbitals.

(I) or (II) (V)

Several investigations were reported concerning the stability of the tautomeric forms of the aminopyridines and related compounds.[15-18] Bodor *et al.*[15] recently studied the tautomerism of several amino-derivatives of hetero-aromatic compounds by employing the SCF-MO method, and concluded that the amino-tautomer of the aminopyridines is by far the more stable. This is in agreement with available experimental evidence. The authors have also calculated the pi-electron energies of the anilinopyridine and the pyridine-anil forms of 2-anilinopyridines by the HMO method. The results are given in Table 4. From these data, the pi-electron energy differences between the two tautomers are apt to decrease and the tautomerization is easier when nitro groups are introduced. However, the pi-electron energy differences indicate that the amino form is, on the whole, more stable than the corresponding imino form.

TABLE 5. THE UV SPECTRA OF 2-ANILINOPYRIDINE AND RELATED COMPOUNDS

Compounds	Solvent	λ_{max} (nm)	ε_{max}
2-Anilinopyridine	n-Hexane	276	9800
	MeOH	275	9800
	MeCN	274	13100
Diphenylamine[19]	EtOH	285	20250
5-Nitro-2-anilino-pyridine	n-Hexane	250	—[a]
		348	—
	Ether	252	10000
		373	15400
	MeOH	253	11300
		382	14800
	MeCN	253	11300
		380	16400
4-Nitrodiphenylamine[19]	EtOH	257	10300
		390	21200

[a] Saturated solution

A study has been made on the UV absorptions of 2-anilinopyridine and its 5-nitro derivative: the latter is expected to take the imino form more easily than its parent compound. The absorption curves in some solvents of different polarity are presented in Fig. 4 and Table 5. The intensities, locations of the maxima and contours of the bands are very similar in all solvents employed, and this may give support to the estimation that the anilinopyridines are not in tautomeric equilibria. When compared with the spectra of the corresponding diphenylamines, which are incapable of adopting the imino tautomeric forms, the spectra are quite similar in location and intensity of the absorption maxima, and the anilinopyridine forms (I) are again supported.

Further, 3-carboline has been prepared from 2-chloropyridine and *o*-phenylene-

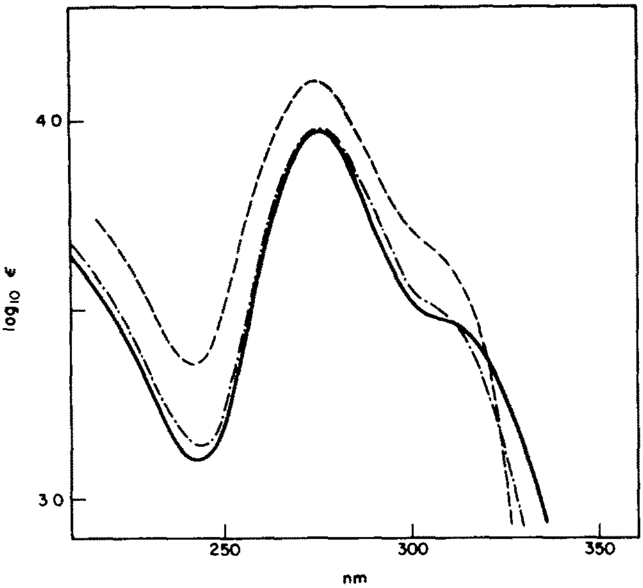


Fig 4a. –·–·– in n-Hexane, – – – – – – in MeCN, ——— in MeOH.

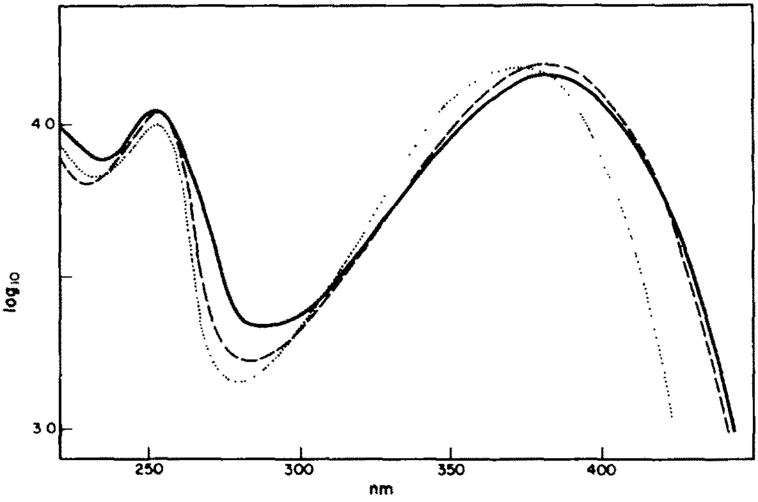


Fig 4b. ······· in diethyl ether, – – – – – in MeCN, ——— in MeOH.

Fig 4. UV spectra of 2-anilinopyridine (Fig. 4a) and its 5-nitro derivative (Fig. 4b) in various solvents.

diamine[20] in order to check the possibility of the tautomeric equilibrium. It can tautomerize but has no freedom of rotation around the C–N bond, so the N–H band splitting can be observed only in the former case. The N–H stretching absorptions of this compound were measured in two solvents and illustrated in Fig. 5. Only one symmetrical band is observed in each spectrum in this figure. This can be interpreted that 3-carboline possesses only one conformation, since it has no freedom of rotation around the C–N bond.

In conclusion, the splitting of the N–H stretching band is attributed to rotational isomerism and the possibility of tautomeric equilibrium is excluded by the UV and IR spectral evidence. The two N–H stretching absorptions of these compounds are also assigned to the two conformers from the solvent effect and other evidence.

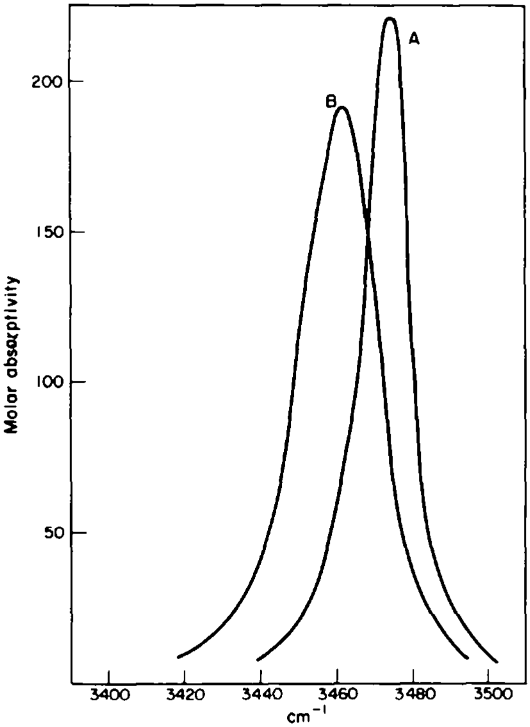


FIG 5. N–H stretching absorption of 3-carboline in CCl_4(A) and in $CHCl_3$(B).

EXPERIMENTAL

The IR spectra were measured with a Perkin–Elmer Model 112-G grating IR spectrophotometer and UV spectra were measured with a Hitachi EPS-3T spectrophotometer. Commercial $CHCl_3$ was carefully purified and freed from alcohol by shaking with H_2SO_4 and by repeated distillation. Commercially available spectro grade solvents were used otherwise. The concentrations of the solutions for IR measurements were about 2×10^{-3} mole/l, at which concentrations the association of solutes is negligible. Preparation of the 2-anilinopyridines and 2-anilino-4-methylquinolines has been reported in other publications of the present authors.[10, 12]

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