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Reaction of Aromatic *N*-Oxides with Dipolarophiles. VIII.[1a] Carbamation Products of 2-Anilinopyridine Derivatives

TAKUZO HISANO,* KAZUNOBU HARANO, TOSHIKAZU MATSUOKA, FUMIHIRO SUEMATSU, and NORIHIDE OHIZUMI

Faculty of Pharmaceutical Sciences, Kumamoto University, 5–1 Oe-hon-machi, Kumamoto 862, Japan

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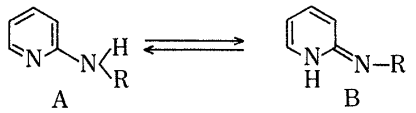
In the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with phenyl isocyanates, we have isolated 1,5-sigmatropy products of the primary cycloadduct and carbamation products of 2-anilinopyridines. In connection with the tautomerism of 2-anilinopyridines, the structure of the carbamation products is discussed in detail based on kinetic, molecular orbital calculation and spectral data. A comparison of the spectral data with those of structurally related compounds indicated that the carbamation does not occur at the ring nitrogen but at the exocyclic one.

Keywords——tautomerism; 2-anilinopyridine; molecular orbital theory; carbamation; phenyl isocyanate; 2-pyridone-imine; 1,3-dipolar cycloaddition; pyridine *N*-oxide; 2-(*N*-phenylcarbamoyl-anilino)pyridine

The tautomeric structure of heterocycles has been attracting the attention of many research groups, as it is of practical and theoretical importance; in particular, the degree of aromaticity has been discussed in connection with their chemical reactivities.[2] Over the past decade, the development of spectral methods has made possible detailed research on the nature of heteroaromatic tautomerism, as has the progress of reliable quantum-mechanical calculation methods, assisted by the rapid development of powerful computers.



A B

Chart 1

In the course of our studies on the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with phenyl isocyanates,[3] we encountered the problem of the tautomerism (A⇌B) of 2-anilinopyridine derivatives (**1**).[4] In the reaction, we isolated a small amount of a pair of ureas (**2a** and **3b**) which might have arisen from the reaction of excess phenyl isocyanate with 2-anilinopyridine derivatives (**1a**, **b**) formed by the decarboxylation of 1,5-sigmatropy products (D and D′). Both types of products (**2a** and **3b**) could, at first glance, be formally considered to be formed from the tautomeric equilibrium between the amino and the imino forms of the 2-anilinopyridines.

Focusing on the tautomerism of 2-anilinopyridines (**1**), we studied the reaction of phenyl isocyanates with 2-anilinopyridines (**1**) and reported that the reactions of 2-anilinopyridine (**1c**) and 5-methyl-2-anilinopyridine (**1b**) with phenyl isocyanate exclusively afforded the corresponding 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridines (**3**), whereas the reactions of 3-methyl and 3,5-dimethyl-2-anilinopyridines (**1a** and **1d**) with phenyl isocyanate afforded 2-(*N*-phenylcarbamoylanilino)pyridine derivatives (**2**).[4] The former imino de-

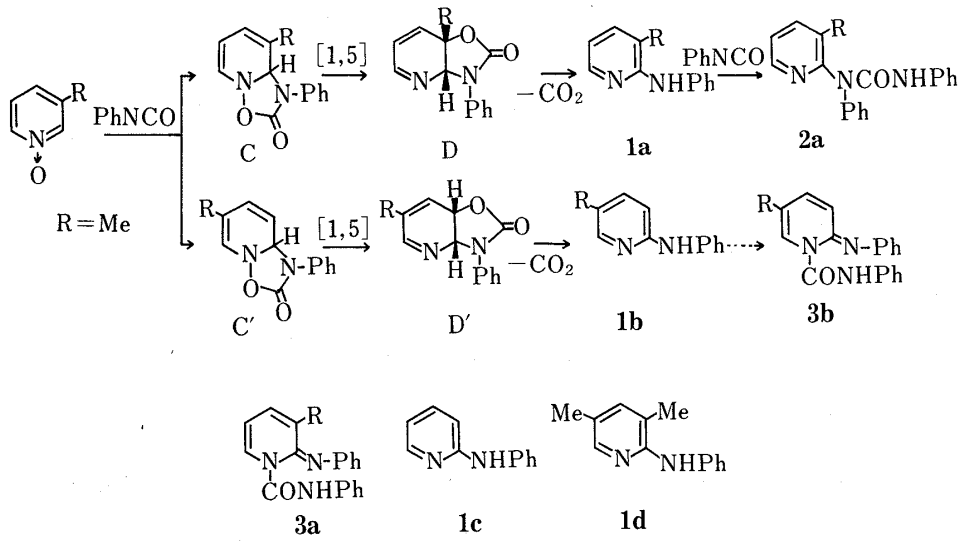


Chart 2

TABLE I. Calculated Geometries of 2-Amino-3-methylpyridine (**4**) and 3-Methyl-2-pyridoneimine (**5**)

Compound	**4**	**5**
Heat of formation (kcal/mol)	13.092	17.419
HOMO (eV)	7.796	7.510
Bond length (Å)		
1–2	1.353	1.405 (1.405)[a]
2–3	1.411	1.501 (1.477)[a]
3–4	1.405	1.382 (1.365)[a]
4–5	1.404	1.443 (1.446)[a]
5–6	1.411	1.371 (1.371)[a]
1–6	1.353	1.362 (1.365)[a]

a) Values in parentheses for 2-pyridoneimine.

rivatives (**3**) are assumed to have resulted from attack of phenyl isocyanate on the ring nitrogen atom of the imino tautomer.

However, later, doubts arose regarding our previous structure assignment of the reaction products (**3**) on the ground of mechanistic considerations based on the aromaticity[5] of the 2-anilinopyridines and a perturbation calculation[6] for the reaction in question. Therefore, we decided to reinvestigate the carbamation of 2-anilinopyridines (**1**) with phenyl isocyanate not only by molecular spectrometry but also from a theoretical point of view.

First of all, as a part of a study of the application of molecular orbital calculations to the practice of organic chemistry,[1,7] we performed a molecular orbital calculation on the reactants and evaluated the interaction energies according to the perturbation theory.

The calculations reported here were carried out by the CNDO/2 and MINDO/3 methods.[8] The molecular geometries of the parent molecules were determined by means of semiempirical SCF-MO calculations based on the MINDO/3 approximation combined with geometrical optimization by the Fletcher–Powell method. The optimized structures for 2-amino-3-methylpyridine (**4**) and 3-methyl-2-pyridoneimine (**5**) are shown in Table I.

In compound **4**, the aminopyridine moiety was calculated to be planar. The imino

TABLE II. Calculated Reactivity of Phenyl Isocyanate toward Tautomers of 2-Anilinopyridine

Compound	Interaction distance (Å)	Energy changes (eV)		
		Coulombic term (II)	Frontier term (III)	ΔE[a] (eV)
Amino-form	1.75	0.292	0.583	0.875
	3.00	0.171	0.010	0.181
Imino-form	1.75	0.223	0.315	0.538
	3.00	0.130	0.006	0.136

a) ΔE=(II)+(III). See ref. 6.

tautomer (**5**) shows the alternation of long and short bonds, indicating that the aromaticity is considerably decreased by the tautomerism, whereas the bonds of compound **4** are more nearly equal, reflecting the aromatic nature of the ring. The difference in the calculated aromatic resonance energy among the tautomers (4.3 kcal/mol) is somewhat smaller than the experimental value in the case of 2-aminopyridine (8.5 kcal/mol), estimated by Katritzky *et al.* based on the tautomeric equilibrium constants of the corresponding saturated compounds.[9] The resulting geometries were then used for the calculation of 2-anilino-3-methylpyridine (**1a**).

For simplicity, the reactivity described in this paper was calculated using the planar conformations based on the perturbation equation of chemical reactivity derived by Klopman and Salem,[6] with the assumption that the two components might approach with molecular angles of 0° and with a bonding distance of from 1.75 Å, which corresponds to the distance of maximum sigma-type overlap of the carbon and nitrogen *p*-atomic orbitals, to 3.00 Å, for which van der Waals repulsion is not serious.[10]

As it is generally accepted that the third term of the perturbation equation, especially the frontier orbital term, is adequate for the purpose of brief discussion, in this study, calculations of the coulombic interaction term (the second term) and the frontier orbital interaction term were performed[11] for the reaction of 2-anilinopyridine (**1c**) and phenyl isocyanate using the CNDO/2 method. The results are summarized in Table II.

As can be seen in Table II, relatively large coulombic attractions (the second term energy) contribute to the stability of both transition states, which can be attributed to the highly polarized structures of both reactants. This suggests that the reactivity might be, at least in part, determined by the coulombic interaction in the initial stage of the reaction in addition to the FMO interaction. This result may be consistent with recent observation on the reaction of alcohols and phenyl isocyanate.[12]

Both interaction terms are larger in the amino-type derivative formation than in the imino derivative formation, suggesting that carbamation at the exocyclic nitrogen is more favorable, while the imino-type product formation (attack at the ring nitrogen) is energetically unfavorable.

Taking into consideration these calculation data together with the difference in aromaticity among the tautomers, we reinvestigated the possible existence of imino-form products by carrying out the reactions under various conditions using various types of 2-anilinopyridines, including a reexamination of previously reported reactions.

For the clarification of the substituent effect on the reaction rate, we have investigated the reaction of 3- and 5-methyl substituted 2-anilinopyridines (**1a** and **1b**) with phenyl isocyanate. The reactions were carried out without solvent by heating at 90 °C for 3 h. The structures of the products were determined by comparison of the spectral data [infrared (IR) and nuclear magnetic resonance (NMR)] with those of structurally related compounds. The results are

TABLE IIIa. Yields and Physical Properties of Products of Carbamation of 2-Anilino-5-methylpyridines

Compd.	R	mp (°C)	Appearance (Recryst. solvent)	Formula
2i	*m*-Me	132—134	Colorless needles (*n*-hexane)	$C_{20}H_{19}N_3O$
2j	*p*-Me	128—130	Colorless needles (*n*-hexane)	$C_{20}H_{19}N_3O$
2h	*m*-Cl	124—126	Colorless needles (*n*-hexane)	$C_{19}H_{16}ClN_3O$
2l	*p*-Cl	140—141	Colorless needles (*n*-hexane)	$C_{19}H_{16}ClN_3O$
2b	H	130—131	Colorless plates (ether–acetone)	

Compd.	Analysis (%) Calcd (Found)			Yield (%)	IR (KBr) cm^{-1} (C=O)
	C	H	N		
2i	75.69 (76.14)	6.03 (6.03)	13.24 (13.26)	80	1683
2j	75.69 (75.64)	6.03 (6.11)	13.24 (13.15)	83	1680
2h	67.56 (67.68)	4.77 (4.83)	12.44 (12.20)	73	1680
2l	67.56 (67.99)	4.77 (4.79)	12.44 (12.50)	77	1680
2b				95[a]	1670

Compd.	NMR (in $CDCl_3$, 60 MHz)				MS (*m/e*)
	C_5–Me	C_3–H	C_6–H	–NH–	
2i	2.27	6.38	8.17	12.57	317 (M^+), 197 ($M^+ - CONHC_6H_5$)
2j	2.25	6.30	8.15	12.60	317 (M^+), 197 ($M^+ - CONHC_6H_5$)
2h	2.25	6.24	8.17	12.52	338, 340 (M^+), 218, 220 ($M^+ - CONHC_6H_5$)[b]
2l	2.28	6.27	8.17	12.58	338, 340 (M^+), 218, 220 ($M^+ - CONHC_6H_5$)[b]
2b					

a) Known compound. *b*) Relative intensity 3 : 1.

summarized in Tables IIIa and IIIb.

In the reaction of various 2-(*o*-, *m*- or *p*-substituted anilino)-5-methylpyridine with phenyl isocyanate, 2-(*N*-phenylcarbamoyl)-anilino-5-methylpyridine derivatives were exclusively obtained in high yields, irrespective of the position and the nature of the substituent on the anilino moiety.

On the other hand, in the case of 2-anilino-3-methylpyridine derivatives, the yields were markedly influenced by the position of the substituent on the anilino moiety. As shown in Table IIIb, the yield decreases in the order of *p*- > *m*- > *o*-. In particular, 2-anilino-3-methylpyridine derivatives bearing an *o*-chloro or *o*-methyl substituent on the anilino moiety hardly reacted with phenyl isocyanate. These reaction properties may be due to steric hindrance around the reaction site.

In previous papers,[4] we have considered that the carbamation products formed from 2-anilinopyridine (**1c**) and 2-anilino-5-methylpyridine (**1b**) are the imino-form compounds (**3**). This conclusion was mainly based on the facts that the ^{1}H-NMR spectra of these compounds commonly show a characteristic absorption in the nonaromatic region between δ 6.00 and δ 6.40 and that the chemical shifts are roughly consistent with that of the C_3-H proton of a representative imino-form derivative, 1-methyl-2-pyridone phenylimine (**6**).[13] However, this

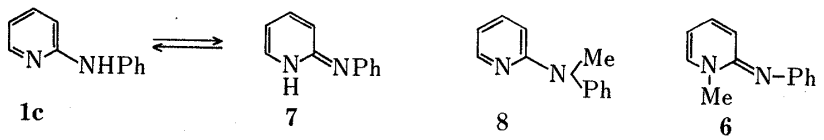
TABLE IIIb. Yields and Physical Properties of Products of Carbamation of 2-Anilino-3-methylpyridines[a]

Compd.	R	mp (°C)	Appearance (Recryst. solvent)	Formula
2e	*m*-Me	129—130	Colorless prisms (*n*-hexane)	$C_{20}H_{19}N_3O$
2f	*p*-Me	88—90	Colorless prisms (*n*-hexane)	$C_{20}H_{19}N_3O$
2g	*m*-Cl	115—116	Colorless prisms (*n*-hexane)	$C_{19}H_{16}ClN_3O$
2h	*p*-Cl	115—117	Colorless prisms (*n*-hexane)	$C_{19}H_{16}ClN_3O$
2a	H	134—135	Colorless needles (ether–acetone)	

Compd.	Analysis (%) Calcd (Found)			Yield (%)	IR (KBr) cm^{-1} (C=O)
	C	H	N		
2e	75.69 (75.86)	6.03 (6.10)	13.24 (13.02)	54	1680
2f	75.69 (75.77)	6.03 (5.92)	13.24 (13.04)	78	1683
2g	67.56 (67.89)	4.77 (4.83)	12.44 (12.48)	48	1680
2h	67.56 (67.49)	4.77 (4.58)	12.44 (12.13)	77	1683
2a				93[b]	1660

Compd.	NMR (in $CDCl_3$, 60 MHz)		MS (*m/e*)
	C_3–Me	C_6–H	
2e	2.27	8.36	317 (M^+), 197 ($M^+ - CONHC_6H_5$)
2f	2.28	8.37	317 (M^+), 197 ($M^+ - CONHC_6H_5$)
2g	2.22	8.38	338, 340 (M^+), 218, 220 ($M^+ - CONHC_6H_5$)[c]
2h	2.20	8.37	338, 340 (M^+), 218, 220 ($M^+ - CONHC_6H_5$)[c]
2a			

a) The products of the *o*-Me and *o*-Cl derivatives were inseparable from diphenyl urea. *b*) Known compound. *c*) Relative intensity 3 : 1.



1c **7** **8** **6**

Chart 3

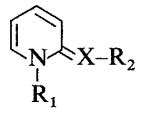
assumption seems to be questionable.

The ^{1}H-NMR spectral data for a closely related series of compounds are given in Tables IV and V. It can be readily seen from the examples quoted in Table IV that, as a general trend, C_5-H resonates at δ 5.9—6.4, *i.e.* upfield from other protons.

As regards the tautomerism of 2-anilinopyridine (**1c**), a considerable decrease in aromaticity was predicted for the heterocyclic part of the imino tautomer (**7**).[13] The heterocyclic protons of the imino-form compound (**6**) were found to resonate at remarkably higher field: the high field shifts in **6** reach 0.95 ppm on average, indicating the loss of ring current corresponding to 41% of the induced ring current of benzene.

The lack of this characteristic signal due to the nonaromatic proton in the carbamation

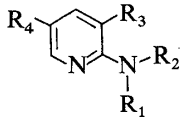
TABLE IV. ^{1}H-NMR Spectral Data for 2-Imino-Type Compounds



Compd. No.	R_1	R_2	X	NMR (in $CDCl_3$, 60 MHz)		
				C_3–H	C_5–H	C_6–H
6	Me	Ph	N	6.35	5.69	7.16
9	Ts[a)]	Ts[a)]	N	>6.90	6.49	8.37
10	Me	PhNHCO	C	>6.80	6.13	8.66
11	$PhCH_2$	PhNHCO	C	>6.60	5.97	8.60
12	H		O	6.57	6.15	7.31

a) Ts=*p*-Me–$C_6H_4SO_2$–.

TABLE V. ^{1}H-NMR Spectral Data for 2-Amino-Type Compounds

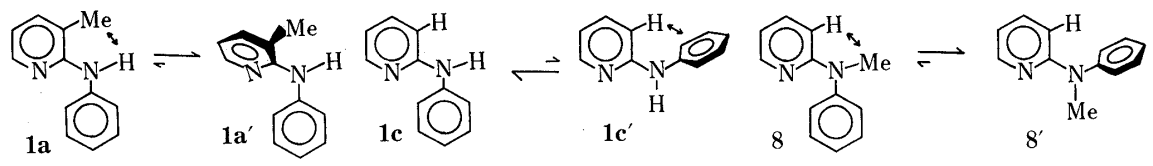


Compd. No.	R_1	R_2	R_3	R_4	NMR (60 MHz)		
					C_3–H	C_5–H	C_6–H
1c	Ph	H	H	H	7.25	6.65	8.14
1a	Ph	H	Me	H		6.80	8.27
1b	Ph	H	H	Me	6.84		8.05
2a	PhNHCO	Ph	Me	H		7.70—6.70	8.30
2b	PhNHCO	Ph	H	Me	6.12		8.15
8	Me	Ph	H	H	6.54	6.47	8.16
13	Ts[a)]	Ts[a)]	H	H	>6.90	>6.90	8.52

a) Ts=*p*-Me–$C_6H_4SO_2$–.

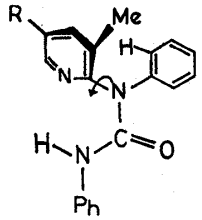
product of 2-anilinopyridine (**1c**) and the presence of the moderately high field signals in the cases of 2-anilinopyridine (**1c**) and 2-anilino-5-methylpyridine (**1b**) suggest that the carbamation products of **1b** and **1c** do not have the imino structure but the amino one, and their C_3-H signals are shifted to higher field by the phenyl ring current effect. This conclusion is supported by the fact that the chemical shifts of the C_3-protons are quite sensitive to small changes in the environment (see Table V).

Hirota *et al.*[13)] suggested that, judging from the ^{1}H-NMR spectrum of 2-anilinopyridine derivatives, 2-anilinopyridine (**1c**) can exist in either of the rotational isomers **1c** and **1c′** and the change of substituent on the exocyclic nitrogen from hydrogen to methyl causes a

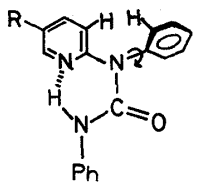


1a **1a′** **1c** **1c′** **8** **8′**

Chart 4



2a: R=H
2d: R=Me



2b: R=Me
2c: R=H

Fig. 1. Stable Conformations of **2**.

conformational change wherein the C_3-H lies above the phenyl ring, resulting in a high field shift because of the diamagnetic effect. In 2-anilinopyridine (**1c**), the rotamer **1c** is more stable than the rotamer **1c'** because of the steric hindrance between the hydrogen atom at the 3-position (C_3-H) and the phenyl group. In 2-(*N*-methylanilino)pyridine (**8**), the interaction between Me and C_3-H in conformation (**8**) prevents the planar arrangement of the pyridine ring and exocyclic nitrogen. This interference may be eliminated by rotation of the pyridine ring about C_2–N. This requires an energetically unfavorable twisted conformation, because the C_2–N bond has a greater double bond character[13] than the N–Ph bond. On the other hand, the conformer (**8'**) can still be coplanar by the sacrifice of the N–Ph coplanarity.

In 2-anilino-3-methylpyridine (**1a**), the situation may be different from the cases of the above two compounds. However, the preferred conformation is easily deduced from the considerations[13] stated above. In either conformation (**1a** and **1a'**), the pyridine ring cannot lie in the plane defined by the urea moiety. Quantitative calculations show that this assumption is reasonable. The total energies indicate that the most stable conformation is the one in which the pyridine ring is rotated about the C_2–N bond at *ca.* 30°.[14]

The considerations hitherto mentioned seem to be applicable to the interpretation of the spectral data of the carbamation products. In compound **2b**, the interaction between C_3-H and the phenylcarbamoyl group is strong and so increases the trend toward the perpendicular disposition of the N–Ph group. In such a conformation, the C_3-H proton is subject to the diamagnetic effect of the phenyl ring which produces a high field shift more efficiently than in the case of compound **8**. Thus, the abnormal high-field shift of C_3-H can be accounted for by the anisotropic effect of the neighboring phenyl ring.

The ^{1}H-NMR spectrum of compound **2b** indicates the existence of a hydrogen bond between the hydrogen atom of the urea group and the nitrogen atom of the pyridine ring. Such a hydrogen bond may stabilize the planar arrangement of the heterocyclic ring and exocyclic nitrogen. In contrast, the hydrogen bond could not be observed in compound **2a**, supporting the existence of the twisted conformation about the exocyclic C_2–N bond as depicted in Fig. 1.

Further support for the assignment was provided by carbon-13 nuclear magnetic resonance (^{13}C-NMR) measurements. The resonances of the sp^2 carbons and the sp^3 carbons(methyl) of compounds **2a**, **2b** and **2c** exhibited essentially the same spectral pattern.

Careful inspection of the IR and ultraviolet (UV) spectral data and comparison of them with those of structurally similar compounds indicates that the previously described structure assignment for the series of imino-form compounds was incorrect. The IR spectra of compounds **2a** and **2d** lack a characteristic band for C=N at near 1640 cm^{-1} and the UV absorption bands in the range of 290—300 nm, which were assigned to the π–π^* electronic transitions of the iminodiene chromophores,[4a] are at shorter wavelength than the expected values from the calculation and the observed data of compound **6**.

The products in question did not undergo 1,3-sigmatropic rearrangement to the amino-form compounds, although the rearrangement is thermally allowed[15] and driven by the gain

of aromaticity. The carbamation rate for compound **1a** ($k=0.90\times10^{-3}$) is almost the same as that for compound **1b** ($k=0.59\times10^{-3}$). If the formation of the imino-type compound would occurs in the case of compound **1b**, the latter value would seem to be too large because of the predominance of the amino-form compound which can be deduced from the tautomerism equilibrium constant of 2-anilino-pyridine ($k=2\times10^{-5}$).[13]

The IR and UV spectroscopic analyses of the products and the chemical behavior of **1b** are not straightforward as compared with NMR spectroscopic analyses. However, all the considerations and observations support the conclusion that the carbamation does not occur at the ring nitrogen but at the exocyclic one.

Experimental

All melting points are uncorrected. The ^{1}H-NMR spectra were taken with a Hitachi R-600 and a JEOL JNM-C-60H spectrometer *in ca.* 10% (w/v) solution with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. The ^{13}C-NMR spectra were determined with a JEOL FX-100 and refer to solutions in deuteriochloroform as a concomitant standard, downfield chemical shifts being computed relative to tetramethylsilane. The IR spectra were recorded on a JASCO DS-301 infrared spectrophotometer equipped with a grating. Mass spectra were taken with a JEOL JMS-01SG double-focusing spectrometer operating at an ionization potential of 75 eV. UV spectra were determined with a JASCO UVIDEC-220B digital spectrophotometer.

All the calculations were performed on FACOM M-200 and M-382 computers in the computer center of Kyushu University.

Preparation of Materials——2-Anilinopyridines were prepared by the decarboxylation of 2-oxo-3-phenyl-2,3,3a,7a-tetrahydrooxazolo[4,5-*b*]pyridine derivatives formed from 1,3-dipolar cycloadducts of the corresponding pyridine *N*-oxides and substituted phenyl isocyanates according to the procedures reported previously.[3] Phenyl isocyanates were obtained from commercial suppliers and were used without further purification.

Carbamation of 2-Anilinopyridines——A mixture of 2-anilinopyridine (0.0025 mol) and phenyl isocyanate (0.005 mol) was heated at 90 °C for 3 h with shaking. After cooling, the reaction mixture was dissolved in 50 ml of benzene and then 20 ml of ice-water was added to decompose excess phenyl isocyanate. The precipitated diphenylurea was filtered off and the benzene layer was treated with 20 ml of dil. HCl. The aqueous layer was neutralized with anhydrous powdered Na_2CO_3 and then extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the carbamation product. The products were purified by recrystallization from ether. The results are summarized in Tables III—IV.

1-*p*-Toluenesulfonyl-2-*p*-toluenesulfonylimino-1,2-dihydropyridine (9)——A mixture of 2-aminopyridine (0.01 mol), *p*-toluenesulfonyl chloride (0.02 mol) and potassium carbonate in 10 ml of acetone was refluxed for 1 h. The precipitated colorless solid was collected by suction then washed with cooled acetone and water. The crystals were recrystallized from chloroform–benzene to give colorless prisms, mp 168—170 °C, in 65% yield. IR ν_{max}^{KBr} cm^{-1}: 1632 (C=N). *Anal.* Calcd for $C_{19}H_{18}N_2O_4S_2$: C: 56.70, H; 4.51, N; 6.96. Found: C; 56.93, H; 4.53, N; 6.75.

1-Methyl-1,2-dihydro-2-pyridylideneacetanilide (10)——This product was prepared according to the method reported previously[16] and was recrystallized from acetone to give yellow prisms, mp 163 °C, in 1.5% yield. IR cm^{-1}: 1645 (C=O). NMR (in DMSO-d_6): 12.33 (1H, s, N-H), 8.66 (1H, slightly split doublet, pyridine C_6-H), 6.67—7.83 (7H, m, aromatic C–H and pyridine C_3-H, C_4-H), 6.10 (1H, ddd, $J_{5,6}=9$ Hz, $J_{5,4}=5$ Hz, $J_{5,3}=2$ Hz, pyridine C_5-H), 3.97 (1H, s, =CH–), 2.85 (3H, s, $-CH_3$).

1-Benzyl-1,2-dihydro-2-pyridylideneacetanilide (11)——Prepared according to the method reported previously.[16]

Kinetics——Solutions of 2-anilino-3-picoline (2.33×10^{-4} M) and phenyl isocyanate (11.6 M) in xylene were prepared. Two ml of each solution was pipetted into a 10 × 10 nm quartz cell. The cell was sealed with a ground glass stopper and thermostated with flowing water at constant temperature (50 ± 0.05 °C). The reaction rate was followed by measuring the change of the absorption at 309 nm. Pseudo-first-order rate constants were determined by using infinity values obtained after 10 half-lives.

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References and Notes

1) Part VII: T. Matsuoka, M. Shinada, F. Suematsu, K. Harano, and T. Hisano, *Chem. Pharm. Bull.*, **32**, 2077

(1984).
2) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles, Advances in Heterocyclic Chemistry Supplement 1," ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1976 and references cited therein.
3) *a*) T. Hisano, S. Yoshikawa, and K. Muraoka, *Chem. Pharm. Bull.*, **22**, 1611 (1974); *b*) T. Hisano, T. Matsuoka, and M. Ichikawa, *ibid.*, **24**, 533 (1976); *c*) T. Hisano, M. Ichikawa, T. Matsuoka, H. Hagiwara, K. Muraoka, T. Komori, K. Harano, Y. Ida, and A. T. Christensen, *ibid.*, **27**, 2261 (1979); *d*) T. Hisano, T. Matsuoka, M. Ichikawa, and M. Hamana, *Heterocycles*, **14**, 19 (1980); *e*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Org. Prep. Proced. Int.*, **6**, 243 (1982).
4) *a*) T. Hisano, T. Matsuoka, K. Tsutsumi, K. Muraoka, and M. Ichikawa, *Chem. Pharm. Bull.*, **29**, 3706 (1981); *b*) T. Hisano, T. Matsuoka, K. Fukunaga, and M. Ichikawa, *ibid.*, **30**, 3776 (1982).
5) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, **1961**, 859; S. Inagaki and Y. Hirabayashi, *J. Am. Chem. Soc.*, **99**, 7418 (1977).
6) G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968); L. Salem, *ibid.*, **90**, 543 and 553 (1968).
7) K. Harano, F. Suematsu, T. Matsuoka, and T. Hisano, *Chem. Pharm. Bull.*, **32**, 543 (1984).
8) M. J. S. Dewar, MINDO/3 Program 279, "Quantum Chemistry Exchange (QCPE)," Indiana University, 1975; J. A. Pople and D. L. Beveridge," Approximate Molecular Orbital Theory," McGraw-Hill, New York, 1970.
9) S.-O. Chua, M. J. Cook, and A. R. Katrizky, *J. Chem. Soc., Perkin Trans. 2*, **1973**, 2111.
10) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
11) T.-L. Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry," Academic Press, New York, 1977.
12) S. Sivakamasundari and R. Ganesan, *J. Org. Chem.*, **49**, 720 (1984): During the course of our studies, a mechanistic investigation on the reaction of some alcohols and phenyl isocyanate has appeared. The authors analyzed the kinetic parameters of the reaction of phenyl isocyanate with alcohols in benzene medium and arrived at the conclusion that the reaction between an alcohol and an isocyanate occurs by a concerted mechanism as shown in Chart 4, wherein the dipole–dipole interaction plays a leading role in the primary interaction; thus, the alcohol behaves as an electron donor with the result that the oxygen atom of the alcohol attacks the carbonyl carbon of the isocyanate. The results seem relevant to the reaction of phenyl isocyanate with amines.

$$\mathrm{Ph-N=C=O+ROH \rightleftharpoons [PhNCO\cdot ROH] \rightleftharpoons PhNH-COOR}$$

$$\mathrm{Ph-N-C=O}$$
$$\vdots\quad\vdots$$
$$\mathrm{H-O-R}$$

$$\mathrm{Ph-N^{-}-C^{+}=O \rightleftharpoons Ph-N=C=O \rightleftharpoons Ph-N=C^{+}-O^{-}}$$

13) Y. Takahashi, S. Otsuka, H. Masuda, M. Hirota, Y. Ito, and Y. Hamada, *Bull. Chem. Soc. Jpn.*, **49**, 2770 (1976).
14) For the crude estimation of the stable conformation of 2-anilino-3-methylpyridine (**1a**), CNDO/2 MO calculation on conformational changes were also carried out which the phenyl group was rotated by 0—135° with respect to the plane of the pyridine ring; considerable energy changes were observed. The highest occupied molecular orbital (HOMO) energy level is stabilized by the change of the conformation of the phenyl ring from planar to perpendicular. The calculation of total energy for conformational isomers of **1a** indicate that the isomer having the torsion angle of 30° is more stable by *ca.* 0.3 eV than the planar conformation, and this can be understood in terms of van der Waals interactions.
15) F. M. Menger and L. Mandell, "Electronic Interpretation of Organic Chemistry," Plenum Press, New York, 1980.
16) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 118 (1955).