Notes

Chem. Pharm. Bull. 29(12)3706—3712(1981)

Reaction of Aromatic N-Oxides with Dipolarophiles. IV.[1] Factors affecting the 1,3-Cycloaddition of Pyridine 1-Oxide with Phenyl Isocyanates

Takuzo Hisano,* Toshikazu Matsuoka, Kazuhiro Tsutsumi, Keiji Muraoka and Masataka Ichikawa

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

(Received June 1, 1981)

Pyridine 1-oxide was subjected to 1,3-dipolar cycloaddition with phenyl isocyanates having an *ortho*, *meta* or *para* substituent group. The reaction conducted at 90°C in dimethylformamide gave the 2,3-dihydropyridine-form cycloadduct, although the reaction of pyridine 1-oxide with phenyl isocyanate directly affords 2-anilinopyridine. An increase of the reaction time led to increases in the yields of 2-anilinopyridine and 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridine, while the yield of the cycloadduct tended to decrease. The reaction at 150°C resulted in an increased yield of 2-anilinopyridine. The reactions of 2-anilinopyridine and 5-methyl-2-anilinopyridine with phenyl isocyanate at room temperature afforded the corresponding 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridines, whereas the reactions of 3-methyl- and 3,5-dimethyl-2-anilinopyridines with phenyl isocyanate at 90°C afforded 2-(N-phenylcarbamoylanilino)pyridine derivatives.

Keywords——1,3-dipolar cycloaddition; 2,3-dihydropyridine-form cycloadducts; 2-anilinopyridines; 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridines; 2-(N-phenylcarbamoylanilino)pyridines

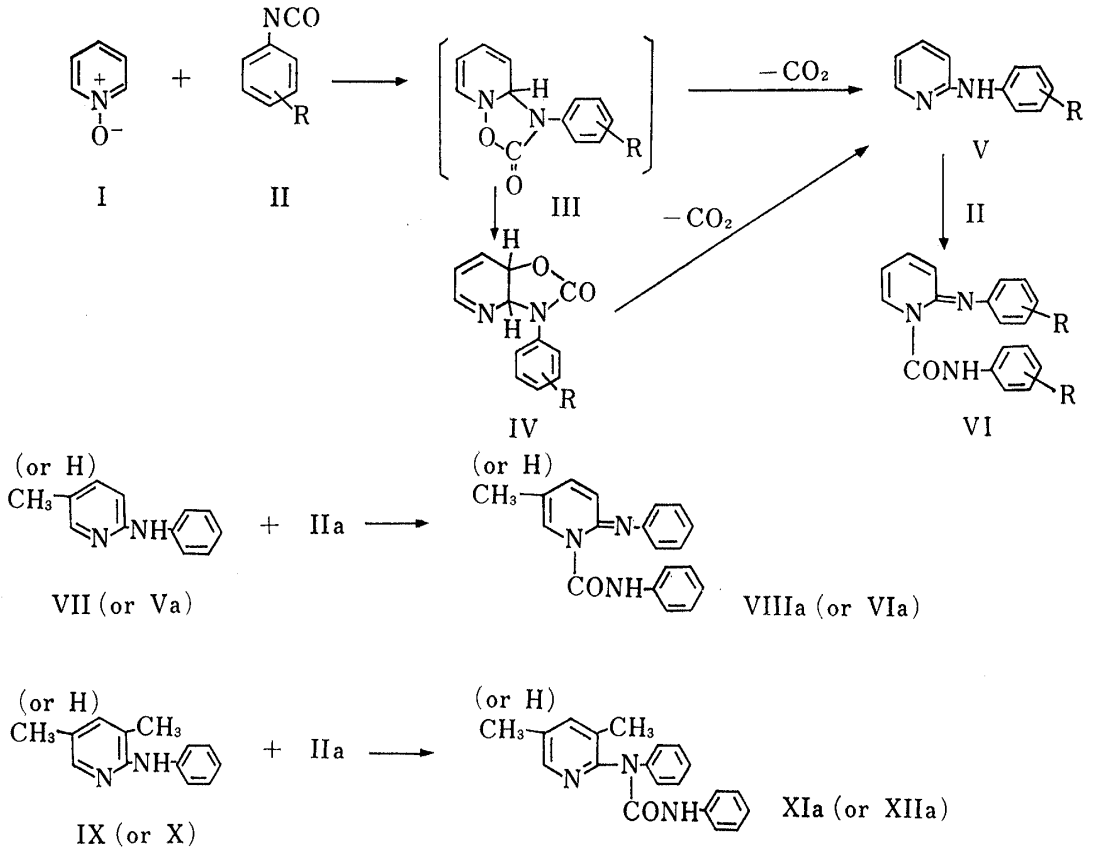
The general character of 1,3-cycloaddition reactions of 3-alkylpyridine 1-oxides with phenyl isocyanates has been well studied[1,2] and the route *via* the 2,3-dihydropyridine-form cycloadduct has been extended to 3-bromopyridine 1-oxide derivatives, which afford the oxazolo[4,5-*b*]pyridine structure.[3] It was reported that the reaction of pyridine 1-oxide (I) with phenyl isocyanate (IIa) directly affords 2-anilinopyridine (Va),[4] but in this work we carried out 1,3-dipolar cycloaddition of IIa to I and succeeded in isolating the 2,3-dihydropyridine-form cycloadduct.

This paper presents a study of the factors affecting the reaction of I with *o*, *m* and *p*-substituted phenyl isocyanates (II) as a typical 1,3-cycloaddition. The results confirm an earlier assumption that the reaction course involves the initial formation of the primary 1,2-dihydropyridine-form intermediate (III), in accord with Huisgen's original proposal.[5]

In the previous report,[3b] a time course study was carried out of the reaction of I with IIa in dimethylformamide (DMF) by determining the product composition by means of quantitative thin-layer chromatography; it was demonstrated that the initially formed 1,2-dihydropyridine-form intermediate (IIIa) immediately rearranged to the 2,3-dihydropyridine-form cycloadduct, namely 2-oxo-3-phenyl-3a,7a-dihydrooxazolo[4,5-*b*]pyridine (IVa), and Va was successively formed from IVa. Since then, we have extended this reaction to dipolarophiles of II having a methyl or chloro substituent group at the *ortho*, *meta* or *para* position, and the effects of reaction time, temperature and solvent on the cycloaddition were investigated.

With double the molar quantity of IIa in DMF, the yield of IVa reached a maximum after heating at 90°C for seven hours. Increase of the reaction time led to increased yields of Va and 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridine (VIa), but the yield of IVa decreased, while elevation of the reaction temperature to 110°C also resulted in increased yields of Va and VIa. However, at 150°C only Va was obtained. In the previous studies,

3-picoline 1-oxide was reacted with IIa at 110°C in DMF to afford two isomeric cycloadducts, 6-methyl- and 7a-methyl-2-oxo-3-phenyl-3a,7a-dihydrooxazolo[4,5-*b*]pyridine, in 24% and 34% yields, respectively,[2b] and the reaction of 3,5-dimethylpyridine 1-oxide with IIa under these conditions also afforded the corresponding 6,7a-dimethyl derivative in 68% yield.[3c] These 2,3-dihydropyridine-form cycloadducts having a methyl group are rather stable even



a: R=H, b: *o*-CH_3, c: *m*-CH_3, d: *p*-CH_3, e: *o*-Cl, f: *m*-Cl, g: *p*-Cl

Chart 1

TABLE I. Effects of Reaction Temperature, Duration and Solvent on the Reaction of Pyridine 1-Oxide with Phenyl Isocyanate

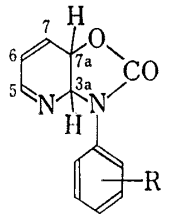
Solvent	Conditions Temperature (°C)	Duration (h)	Product yields (%)[a] IVa	Va	VIa
DMF	70	6	11.7	—	1.7
DMF	90	3	12.3	—	2.2
DMF	90	7	41.0	—	trace
DMF	90	12	25.7	1.5	2.6
DMF	140	7	—	60.0	—
DMF	150	3	—	35.3	—
DMF	150	7	—	38.2	—
DMF	150	12	—	47·1	—
DMSO	90	7	21.0	5.1	0.9
DMSO	150	3	—	43.2	1.9
DMSO	150	7	—	47.2	—
DMSO	150	12		79.4	—
Dioxane	90	7	4.1	—	—
Toluene	90	7	3.5	—	0.4
$CHCl_3$	Reflux	12	—	1.2	—

a) Calcd on the basis of I.

at 150°C. The reaction of I with IIa at 90°C in DMF affords IVa in 41% yield at the most. Thus, it appears that a methyl group at the 3-position has a marked effect on the cycloadduct formation and the driving force for rearomatization is not very strong. In the cycloaddition of II having a methyl or chloro substituent group at the *ortho*, *meta* or *para* position with I, *m*- and *p*-substituted phenyl isocyanates barely afforded the corresponding 2,3-dihydropyridine-form cycloadducts (IV) and there was no formation of 2-anilinopyridines (V) or 1-phenylcarbamoyl-2-phenylimino-1,2-dihydropyridines (VI).

The cycloadducts (IV) thus obtained gave elemental analysis data corresponding to 1:1 adducts of the reactants and their ultraviolet (UV), infrared (IR) and nuclear magnetic resonance (NMR) spectra were similar to those of cycloadducts formed from 3-picoline 1-oxide and IIa.[1)]

Table II. Analytical and Spectral Data for 2,3-Dihydropyridines (IV)



Compd. No.	R	mp (°C)	Appearance ( ): recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Yield (%)
IVa	H	160—161	Colorless prisms (CH_3CN)	$C_{12}H_{10}N_2O_2$	67.28 (67.25	4.71 4.85	13.08 13.21)	41.0
IVc	*m*-CH_3	184	Colorless prisms acetone–*n*-hexane)	$C_{13}H_{12}N_2O_2$	68.41 (68.38	5.30 5.21	12.27 12.20)	1.8
IVd	*p*-CH_3	159—160	Colorless prisms (benzene)	$C_{13}H_{12}N_2O_2$	68.41 (68.46	5.30 5.32	12.27 12.41)	2.2
IVf	*m*-Cl	121—122	Colorless prisms (acetone–*n*-hexane)	$C_{12}H_9ClN_2O_2$	57.96 (58.01	3.65 3.49	11.27 11.18)	5.2
IVg	*p*-Cl	170	Colorless prisms (benzene)	$C_{12}H_9ClN_2O_2$	57.96 (57.92	3.65 3.61	11.27 11.28)	10.1

Compd. No.	IR ν_{max}^{KBr}: cm^{-1} (C=O)	NMR (in $CDCl_3$, 60 MHz): τ C_{7a}–H(d-d, $J_{7a-3a}=9$, $J_{7a-7}=5$)	C_{3a}–H(d-d, $J_{3a-7a}=9$, $J_{3a-7}=2$)	C_6 and C_7–H (2H, m)	C_5 and phenyl C–H (5H, m)	MS (*m/e*) M^+	M^+-CO_2
IVa	1735	4.80		3.26—4.00 (3H, m)	2.00—3.00 (6H, m)	214	170
IVc	1739	4.98	4.05	3.20—3.85	2.00—2.70	228	184
IVd	1755	4.98	4.15	3.40—4.00	2.15—2.83	228	184
IVf	1743	4.80		3.40—4.00 (3H, m)	2.00—3.00	248, 250[a)]	204, 206[a)]
IVg	1752	4.80		3.25—4.00 (3H, m)	2.00—2.70	248, 250[a)]	204, 206[a)]

a) Relative intensity 3:1, due to chlorine atom.

In order to gain some insight into the interaction between V and II, the effects on the carbamation of V with IIa of reaction time, temperature and solvent were investigated, and the results were applied to the synthesis of analogous compounds (VII, IX and X).

The starting material (V) were prepared from the reaction of 2-bromopyridine with anilines having a methyl or chloro substituent group at the *ortho*, *meta* or *para* position according to

Table III. Analytical Data for 2-Anilinopyridines (V)

Compd. No.	mp (°C) (lit.)	IR ν_{max}^{KBr}: cm^{-1} (NH)	Appearance ( ): recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Yield[a] (%)
Va	109—110 (106—107)[5b]	3180	Colorless plates (ether)	$C_{11}H_{10}N_2$	77.62 (77.57	5.92 5.92	16.46 16.47)	69.1
Vb	88—90	3150	Colorless prisms (*n*-hexane)	$C_{12}H_{12}N_2$	78.23 (78.48	6.57 6.56	15.21 15.10)	56.1
Vc	67—69	3170	Colorless prisms (*n*-hexane)	$C_{12}H_{12}N_2$	78.23 (78.38	6.57 6.67	15.21 15.47)	67.3
Vd	110—111 (105—106)[7]	3160	Colorless prisms (EtOH–H_2O)	$C_{12}H_{12}N_2$	78.23 (78.52	6.57 6.53	15.21 15.10)	51.9
Ve	85—87	3160	Colorless prisms (*n*-hexane)	$C_{11}H_9ClN_2$	64.54 (64.65	4.44 4.48	13.69 13.67)	74.2
Vf	79—81	3170	Colorless needles (*n*-hexane)	$C_{11}H_9ClN_2$	64.54 (64.68	4.44 4.44	13.69 13.84)	50.0
Vg	116—118 (116)[8]	3180	Colorless prisms (*n*-hexane)	$C_{11}H_9ClN_2$	64.54 (64.82	4.44 4.55	13.69 13.92)	63.6

a) Calcd on the basis of 2-bromopyridine as described in "Experimental."

Huisgen *et al.*[5b] (Table III), and 2-anilino-3-methylpyridines (VII, IX and X) were prepared from the corresponding 2,3-dihydro-methylpyridine-form cycloadducts by elimination of carbon dioxide as described in the previous reports.[1,2b]

It has become apparent that the product of this carbamation procedure with IIa depends on the reaction temperature and the presence of a methyl group in the pyridine ring of 2-anilinopyridines (Va, VII, IX and X) markedly influences the structure of the reaction product.

1-Phenylcarbamoyl-2-phenylimino-1,2-dihydropyridines (VIa and VIIIa) are obtained almost quantitatively when the reactions of Va and VII with IIa are run at room temperature for three hours, but the reaction of Va with IIa in chloroform under reflux for three hours resulted in a lower yield.

On the other hand, IX and X hardly reacted with IIa on heating to 90°C and the products isolated were not the imino-form compounds (VIa and VIIIa) but the carbamation products (XIa and XIIa) as shown in Chart 1. The imino-form compounds (VIa and VIIIa) possess intense bands at longer wavelengths. They are located in the range of 290 to 300 nm and assigned to the π–π^* electronic transitions of the iminodiene chromphores,[6] while XIa and XIIa give a UV spectrum with a maximum at 250 nm as shown in Fig. 1.

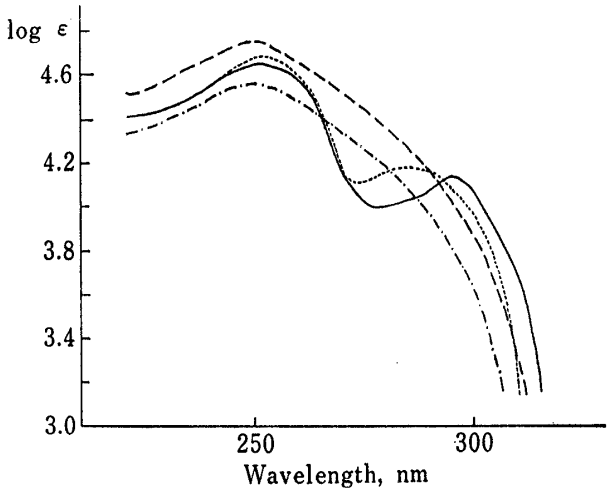


Fig. 1. UV Spectra of Imino (VIa and VIIIa) and Anilino (XIa and XIIa) Compounds
·····: VIa, ——: VIIIa, ----: XIa, —·—·: XIIa.

The NMR spectra of the imino-form compounds (VI) in deuterated chloroform exhibit one proton signal due to the olefinic hydrogen on the beta carbon as a doublet (J_{3-4}=8.3 Hz) at τ 3.66—3.88. Their mass spectra (MS) and elemental analyses are consistent with the empirical formulae for the carbamation products of 2-anilinopyridines (V).

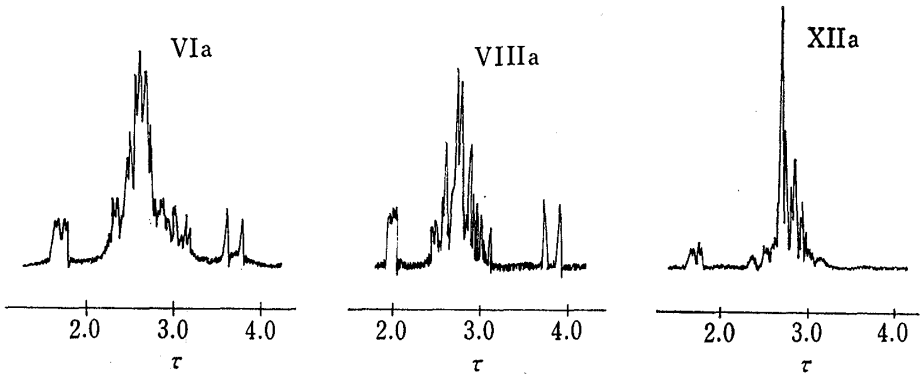
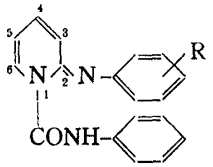


Fig. 2. NMR Spectra of VIa, VIIIa and XIIa in Deuterated Chloroform

The use of DMF, dimethylsulfoxide (DMSO) and dioxane as solvents unexpectedly resulted in lower yields of VI, and elevation of the reaction temperature to 90°C also resulted in a decreased yield. With regard to the influence of substituent groups in the anilino site among 2-(*o*-, *m* or *p*-substituted anilino)pyridines, a methyl substituent group has more effect on the carbamation than a chloro substituent group, probably because of its electron-donating power.

On the other hand, the carbamation products (XIa and XIIa) of 3-methyl- and 3,5-dimethyl-2-anilinopyridines were confirmed to possess an aromatic pyridine nucleus by UV and NMR spectroscopy (Figs. 1 and 2). In this case, the substitution by IIa is considered to occur on the anilino nitrogen site to give 2-(N-phenylcarbamoylanilino)pyridines; it is evident that the presence of the methyl group adjacent to the anilino group has a pronounced effect, leading to predominant carbamation on the anilino nitrogen.

TABLE IV. Analytical and Spectral Data for 1-Phenylcarbamoyl-2-(substituted phenyl-imino)-1,2-dihydropyridines



Compd. No.	mp (°C)	Appearance ( ): recryst. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Yield (%)
VIa	119—120	Colorless prisms (ether–acetone)	$C_{18}H_{15}N_3O \cdot 1/2H_2O$	72.46 (72.61	5.41 5.36	14.08 14.15)	98.8
VIb	127—128.5	Colorless prisms (ether–acetone)	$C_{19}H_{17}N_3O$	75.22 (75.46	5.65 5.73	13.85 13.97)	80.1
VIc	87—89	Colorless needles (ether–acetone)	$C_{19}H_{17}N_3O$	75.22 (75.27	5.65 5.67	13.85 14.01)	84.1
VId	135—137	Colorless prisms (ether–acetone)	$C_{19}H_{17}N_3O$	75.22 (75.02	5.65 5.67	13.85 13.83)	86.5
VIe	109—110.5	Colorless prisms (ether–acetone)	$C_{18}H_{14}ClN_3O$	66.76 (66.56	4.37 4.32	12.98 13.10)	67.2
VIf	122—123	Colorless needles (ether–acetone)	$C_{18}H_{14}ClN_3O$	66.76 (66.86	4.37 4.27	12.98 13.16)	75.9
VIg	160—162	Colorless prisms (ether–acetone)	$C_{18}H_{14}ClN_3O$	66.76 (66.51	4.37 4.25	12.98 12.76)	89.9
VIIIa	130—131	Colorless prisms (ether–acetone)	$C_{19}H_{17}N_3O$	75.23 (75.46	5.65 5.68	13.85 13.66)	95.0

Compd. No.	NMR (in $CDCl_3$, 60 MHz): τ				MS (*m/e*)	
	C_3–H (d, $J_{3-4}=8.3$)	C_6–H (d-d, $J_{6-5}=5.0$, $J_{6-4}=1.8$)	N–H[a] (br. s)	Others (C_4–H, C_5–H, 2 phenyl C–H)	M^+	$M^+-CONHC_6H_5$
VIa	3.66	1.70	−2.72	2.60—3.37 (12H, m)	289	169
VIb	3.73	1.65	−2.93	7.80 (3H, s, CH_3); 2.10—3.33 (11H, m)	303	183
VIc	3.66	1.70	−2.73	7.53 (3H, s, CH_3); 2.20—3.30 (11H, m)	303	183
VId	3.66	1.70	−2.72	7.53 (3H, s, CH_3); 2.20—3.30 (11H, m)	303	183
VIe	3.73	1.66	−2.93	2.06—3.22 (11H, m)	323, 325[b]	203, 205[b]
VIf	3.66	1.70	−2.57	2.10—3.30 (11H, m)	323, 325[b]	203, 205[b]
VIg	3.66	1.70	−2.72	2.07—3.60 (11H, m)	323, 325[b]	203, 205[b]
VIIIa	3.88	1.85 (d, $J_{6-4}=2.0$)	−2.60	2.20—3.20 (11H, m, C_4–H, 2 phenyl C–H)	303	183

a) Disappeared upon the addition of D_2O.
b) Relative intensity 4: 1, due to chlorine atom.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Nippon Bunko DS-301 infrared spectrometer. ^1H-NMR spectra were taken with a JNM-C-60 H spectrometer in *ca.* 5% (w/v) solution with tetramethylsilane as an internal standard; the chemical shifts are expressed as τ values. MS were taken with a JEOL JMS-01SG spectrometer.

Reaction of Pyridine 1-Oxide (I) with Phenyl Isocyanates (II)——Compound II (0.08 mol) was added dropwise to a solution of 3.8 g (0.04 mol) of I in 30 ml of DMF with stirring at room temperature, and the mixture was heated under the conditions indicated in Table I.

a) Separation of IV: When the reaction was over, the reaction mixture was concentrated *in vacuo* below 60°C and the residue was dissolved in a small amount of benzene. Next, 20 ml of ether was added with shaking. The mixture was allowed to stand overnight below 10°C and the resulting colorless crystals were collected by suction then washed with a small amount of cold ether. The crystalline mass was recrystallized to give an analytical sample of IV (Table II).

b) Separations of V and VI: The above ethereal solution was washed with H_2O and dried over Na_2SO_4, then the solvent was removed. The residue was dissolved in a small amount of $CHCl_3$ for chromatography on 30 g of Silica gel (200 mesh), using $CHCl_3$ as an eluent. The first effluent fraction yielded VI, which was purified by recrystallization. The product showed melting point and spectral absorption properties identical with those of the product from the reaction of V and IIa (Table IV). Subsequently, V was obtained from the second effluent fraction and purified by recrystallization; the product showed melting point and spectral absorption properties identical with those of the material prepared from the reaction of 2-bromopyridine with II (see below).

2-(*o*-, *m*-, or *p*-Substituted-anilino)pyridines (Va—g)——A mixture of 2-bromopyridine (0.01 mol) and an aniline (0.02 mol) was heated at 175°C for 1 h. After cooling, the reaction mixture was treated with 5% NaOH aq. soln. and extracted with CH_2Cl_2. The organic layer was dried over K_2CO_3 and then concentrated *in vacuo*. The residue was recrystallized to give an analytical sample (Table III).

1-Phenylcarbamoyl-2-(*o*-, *m*-, or *p*-substituted-phenyl)imino-1,2-dihydropyridines (VIa—g and VIIIa)——Phenyl isocyanate (0.71 g, 0.006 mol) was added to V (0.003 mol) at room temperature and the mixture was stirred for 3 h. When the reaction was over, the reaction mixture was treated with a small amount of ether and the resulting crystalline mass was collected by suction. The colorless crystals were recrystallized to give an analytical sample (Table IV). 5-Methyl-2-anilinopyridine (VII) was reacted with IIa at room temperature for 3 h and then treated in the manner described for V to give VIIIa (Table IV).

2-(N-Phenylcarbamoylanilino)-3,5-dimethylpyridine (XIa)——A mixture of IX (500 mg, 0.0025 mol) and IIa (600 mg, 0.005 mol) was heated at 90°C for 3 h with stirring. After cooling, the reaction mixture was dissolved in 50 ml of benzene and then 20 ml of H_2O was added with shaking to decompose excess IIa. The separated diphenylurea was filtered off and the organic layer was extracted with 20 ml of 5% HCl. The aqueous layer was neutralized with anhyd. powdered Na_2CO_3 and then extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo*, then the residue was recrystallized form ether to give XIa, mp 94—95°C, as colorless prisms in 95% yield. UV λ_{max}^{EtOH} nm (log ε): 249 (4.74). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1680 (C=O). NMR (in $CDCl_3$, 60 MHz) τ: 1.75 (1H, d, $J=2.0$ Hz, pyridine C_6–H), 2.30—3.20 (12H, m, pyridine C_4–H, 2 phenyl C–H, N–H) in which range one proton signal due to the N–H disappeared upon the addition of D_2O, 7.70 and 7.80 (3H, s, CH_3). MS *m/e*: 317 (M^+), 225 ($M^+-C_6H_5NH$), 197 ($M^+-C_6H_5$-

NHCO). *Anal.* Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.77; H, 6.07; N, 12.96.

2-(N-Phenylcarbamoylanilino)-3-methylpyridine (XIIa)——A mixture of X (1.80 g, 0.01 mol) and IIa (2.40 g, 0.02 mol) was heated at 90°C for 3 h with stirring. After cooling, the reaction mixture was treated in the same manner as described for XIIa, mp 134—135°C as colorless needles in 93% yield. UV λ_{max}^{EtOH} nm (log ε): 250 (4.56). IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1655 (C=O). NMR (in $CDCl_3$, 60 MHz) τ: 1.70 (1H, d-d, $J_{6-5}=4.8$ Hz, $J_{6-4}=1.8$ Hz, pyridine C_6–H), 2.33—3.27 (13H, m, pyridine C_4 and C_5–H, 2 phenyl C–H, N–H) in which range one proton signal due to the N–H disappeared upon the addition of D_2O, 7.79 (3H, s, CH_3). MS *m/e*: 303 (M^+), 211 ($M^+-C_6H_5NH$), 183 ($M^+-C_6H_5NHCO$). *Anal.* Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.44; H, 5.48; N, 14.05.

Acknowledgement The authors are grateful to the staff of the Analytical Department of this Faculty for the microanalyses and spectral measurements. The authors are also grateful to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co., Inc., for the supply of several chemicals.

References and Notes

1) Part III: T. Hisano, M. Ichikawa, T. Matsuoka, H. Hagiwara, K. Muraoka, T. Komori, K. Harano, Y. Ida, and A.T. Christensen, *Chem. Pharm. Bull.*, **27**, 2261 (1979).
2) *a*) R.A. Abramovitch, I. Shinkai, and R.V. Dahn, *J. Heterocycl. Chem.*, **13**, 171 (1976); *b*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Chem. Pharm. Bull.*, **24**, 533 (1976).
3) *a*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Heterocycles*, **2**, 163 (1974); *b*) T. Hisano, T. Matsuoka, M. Ichikawa, and M. Hamana, *Heterocycles*, **14**, 19 (1980); *c*) T. Hisano, T. Matsuoka, and M. Ichikawa, *Org. Prep. Proced. Int.*, **6**, 243 (1974).
4) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 256; A.R. Katrizky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press Inc., London, 1971, p. 330.
5) *a*) R. Huisgen, *Proc. Chem. Soc.*, **1961**, 357; *b*) H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).
6) Y. Takahashi, S. Otsuka, H. Masuda, M. Hirota, Y. Ito, and Y. Hamada, *Bull. Chem. Soc. Jpn.*, **49**, 2770 (1976).
7) R.A. Abramovitch and G.M. Singer, *J. Org. Chem.*, **39**, 1975 (1974).
8) R.R. Burtner, U.S. Patent 2802008 (1957) [*C.A.*, **52**, 1280*g* (1958)].

[Chem. Pharm. Bull. 29(12)3712—3715(1981)]

Mannich Reaction of 1,4-Dihydroquinoline Derivatives

JIRO ARITOMI,* SHOZO UEDA, and HARUKI NISHIMURA

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., 33-94, Enoki-cho, Suita, Osaka 564, Japan

(Received June 3, 1981)

Two ethyl 1,2-dimethyl-1,4-dihydroquinoline-3-carboxylate derivatives (I, III) were subjected to the Mannich reaction to give 1-methyl-2-(2-disubstituted aminoethyl) derivatives (II, IV). They are additional examples of the Mannich reaction at the γ-carbon atom of enaminoester compounds.

Keywords——1,2-dimethyl-1,4-dihydroquinoline-3-carboxylic acid; Mannich reaction; enaminoester; γ-substitution; 1-methyl-2-(2-disubstituted aminoethyl)-1,4-dihydroquinoline-3-carboxylic acid

In the previous papers,[1] we reported the Mannich reaction of dialkyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives, and found that their 2-(and 6-)methyl carbons react easily. They are the first examples of the Mannich reaction at the γ-carbons of cyclic enaminoester compounds, so it seemed interesting to investigate the generality of γ-substitution