[Chem. Pharm. Bull. 32(8)2942—2946(1984)]

Ring Transformation Reactions of 1-Substituted 2(1*H*)-Pyrimidinones and Related Compounds with Active Methylene Compounds

AKIRA KATOH,* YOSHIMORI OMOTE, and CHOJI KASHIMA

Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki 305, Japan

(Received October 31, 1983)

1-Substituted 2(1*H*)-pyrimidinones (I) underwent ring transformation with malononitrile and ethyl acetoacetate in the presence of sodium ethoxide to give 2-amino-3-pyridinecarbonitriles (II—VII) and *N*-(substituted)amino-3-pyridinecarboxylic acids (XIV and XV), respectively. Further, I reacted with ethyl cyanoacetate, dialkyl malonate, or ethyl benzoylacetate to give pyridine derivatives (VIII—XIII) bearing various functional groups at the C-3 position. The reaction of 1-substituted 2(1*H*)-pyrimidinethiones and 4,6-dimethyl-1-phenyl-2-phenylimino-1,2-dihydropyrimidine with active methylene compounds is also discussed.

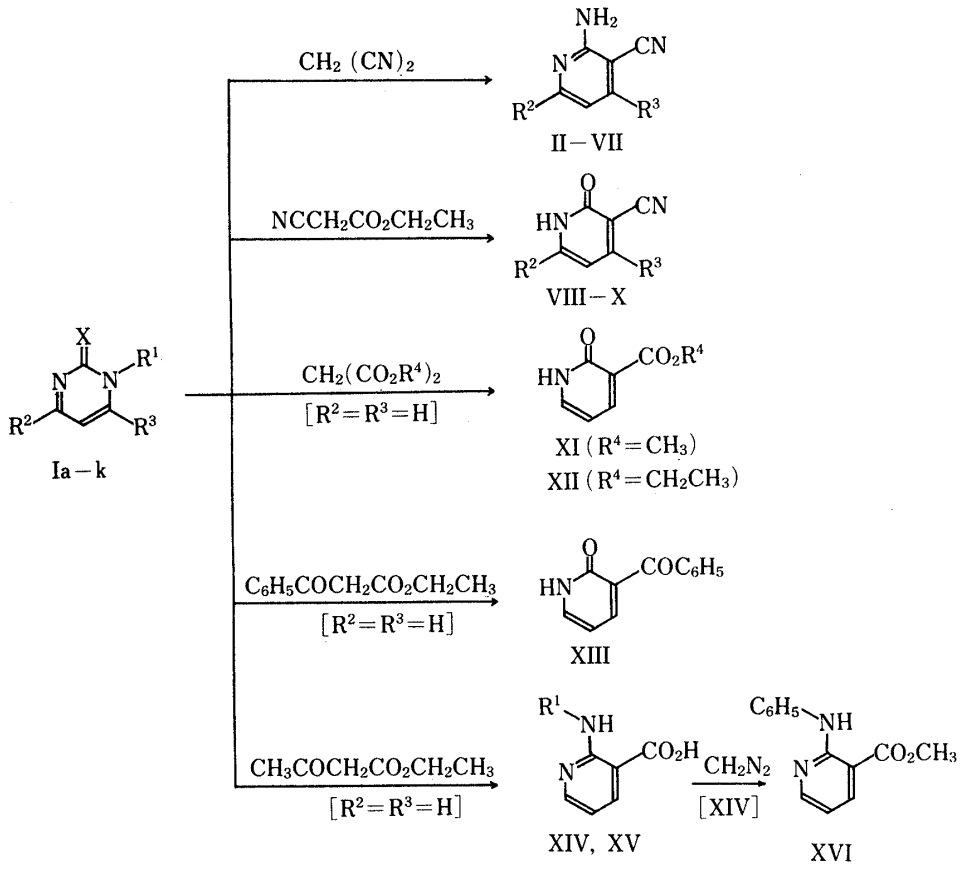
Keywords——ring transformation; 1-substituted 2(1*H*)-pyrimidinone; 1-substituted 2(1*H*)-pyrimidinethione; active methylene compound; sodium alkoxide; pyridine derivative

The synthesis of a new heterocyclic ring by transformation of some other heterocyclic system is of considerable interest, and a number of papers[1] have appeared in the literature. It has been reported that 1-substituted 2(1*H*)-pyrimidinones can be easily converted into isoxazoles,[2] pyrimidines,[2,3] pyrazoles,[4] and *p*-nitrophenols[5] by reaction with various nucleophiles. However, the conversion of 2(1*H*)-pyrimidinones to pyridines has not been reported.

In this paper, we describe a novel ring transformation of 1-substituted 2(1*H*)-pyrimidinones and related compounds by reaction with active methylene compounds as nucleophiles.

Results and Discussion

4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone (Ia) was treated with malononitrile in the presence of sodium ethoxide in absolute ethanol at room temperature to give 2-amino-4,6-dimethyl-3-pyridinecarbonitrile (II) in 93% yield and ethyl phenylcarbamate. The latter compound was identified by gas-liquid chromatographic (GLC) comparison with an authentic sample.[6] A possible mechanism for the ring transformation is illustrated in Chart 2. A carbanion of malononitrile selectively attacks the C-6 position of 2(1*H*)-pyrimidinone (Ia), and the resulting XVII undergoes ring-opening to form the intermediate XVIII and phenyl isocyanate. By the further attack of an anion at the nitrile carbon, the product II can be obtained. Phenyl isocyanate also reacted with ethanol to yield ethyl phenylcarbamate. Similarly, 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione (Ib) and 4,6-dimethyl-1-phenyl-2-phenylimino-1,2-dihydropyrimidine (Id) reacted with malononitrile to give the same product II in 95 and 65% yields, respectively (see the table). When compound Ia was treated with ethyl cyanoacetate instead of malononitrile, 4,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (VIII)[7] was obtained. Compound Ia was also reacted with diethyl malonate, but the starting material Ia was recovered unchanged. However, 1-phenyl-2(1*H*)-pyrimidinone (Ie) which has no substituent at the C-4 and C-6 position of the pyrimidine ring, underwent ring



	X	R^1	R^2	R^3
a	O	C_6H_5–	CH_3–	CH_3–
b	S	C_6H_5–	CH_3–	CH_3–
c	S	CH_3–	CH_3–	CH_3–
d	N–C_6H_5	C_6H_5–	CH_3–	CH_3–
e	O	C_6H_5–	H–	H–
f	O	*p*-$CH_3C_6H_4$–	H–	H–
g	S	C_6H_5–	CH_3–	CH_3CH_2–
h	O	C_6H_5–	C_6H_5–	CH_3–
i	S	C_6H_5–	CH_3–	C_6H_5–
j	S	CH_3–	CH_3–	C_6H_5–
k	S	C_6H_5–	CH_3–	*p*-ClC_6H_4–

Chart 1

transformation to give ethyl 2-oxo-1,2-dihydro-3-pyridinecarboxylate (XII). The difference of reactivity between compounds Ia and Ie might be due to steric effects. Further, the reaction of compound Ie with ethyl benzoylacetate gave 3-benzoyl-2(1*H*)-pyridone (XIII). In these reactions, the N_1–C_2 fragment of the pyrimidine ring was replaced by the C–C portion of carbon nucleophiles such as malononitrile, ethyl cyanoacetate, dialkyl malonates, or ethyl benzoylacetate, and thus the substituents at the N_1-position of the starting materials were removed.

In contrast, 1-phenyl-2(1*H*)-pyrimidinone (Ie) reacted with ethyl acetoacetate to give a product, mp 257—258 °C, with the formula $C_{12}H_{10}N_2O_2$. The signals due to acetyl and ethoxycarbonyl moieties of ethyl acetoacetate were not observed in the proton magnetic resonance (^{1}H-NMR) spectrum of the product. Further, the signals due to protons of the phenyl group at the N_1-position still remained in the ^{1}H-NMR spectrum. From these data and the infrared (IR), ^{13}C-nuclear magnetic resonance (^{13}C-NMR), and mass spectra (MS),

TABLE I. Ring Transformation of 1-Substituted 2(1*H*)-Pyrimidinones and Related Compounds into Various Pyridine Derivatives (II—XV)

Starting material	Reaction conditions	Product	Yield (%)	mp (°C)	Lit. mp (°C)
Ia	r.t. 7 h	II	93	213[a]	249—251[6]
Ib	r.t. 7 h	II	95		
Ic	r.t. 7 h	II	98		
Id	r.t. 12 h	II	65		
Ie	r.t. 6 h	III	21	132—133[b]	131—133[11]
Ig	r.t. 7 h	IV	83	183.5—185[a]	
Ih	r.t. 7 h	V	92	146—147[b]	
Ii	r.t. 9 h	VI	89	233—235[a]	235—236[12]
Ij	r.t. 9 h	VI	83		
Ik	r.t. 7 h	VII	90	255—256[a]	
Ia	Reflux 7 h	VIII	48	>280[a]	293[7]
Ib	Reflux 7 h	VIII	41		
Ic	Reflux 24 h	VIII	39		
Ih	Reflux 7 h	IX	100	>280[a]	310[13]
Ii	r.t. 12 h	X	86	270—272[a]	274—275[14]
Ie	r.t. 2 h	XI	33	145—148[c]	142—143[15]
If	r.t. 1 h	XI	10		
Ie	r.t. 4 h	XII	27	137—139[c]	139[8]
If	r.t. 1 h	XII	42		
Ie	r.t. 6 h	XIII	17	150—150.5[b]	
If	r.t. 6 h	XIII	18		
Ie	r.t. 6 h	XIV	25	257—258[d]	263[9]
If	r.t. 2 h	XV	21	239—241[d]	

r.t. = room temperature.
a) Recrystallized from ethanol.
b) Recrystallized from benzene–hexane.
c) Recrystallized from benzene.
d) Recrystallized from ethyl acetate.

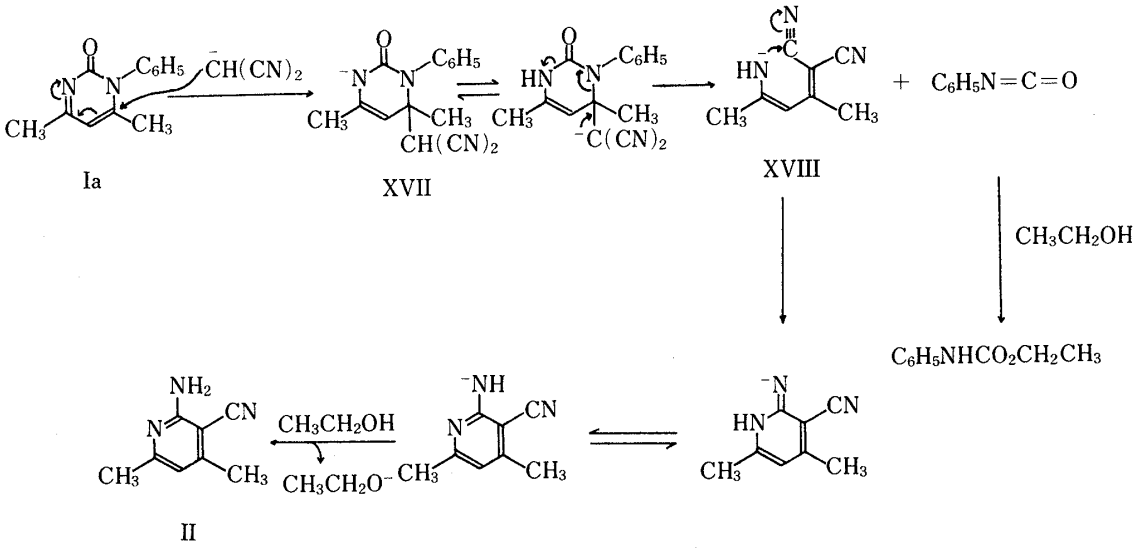


Chart 2

the product was assigned as 2-anilino-3-pyridinecarboxylic acid (XIV). In this reaction, the N_1 unit of the pyrimidine ring was replaced by the C unit of ethyl acetoacetate. Although the mechanism of deacetylation[10] is obscure, a possible mechanism is shown in Chart 3.

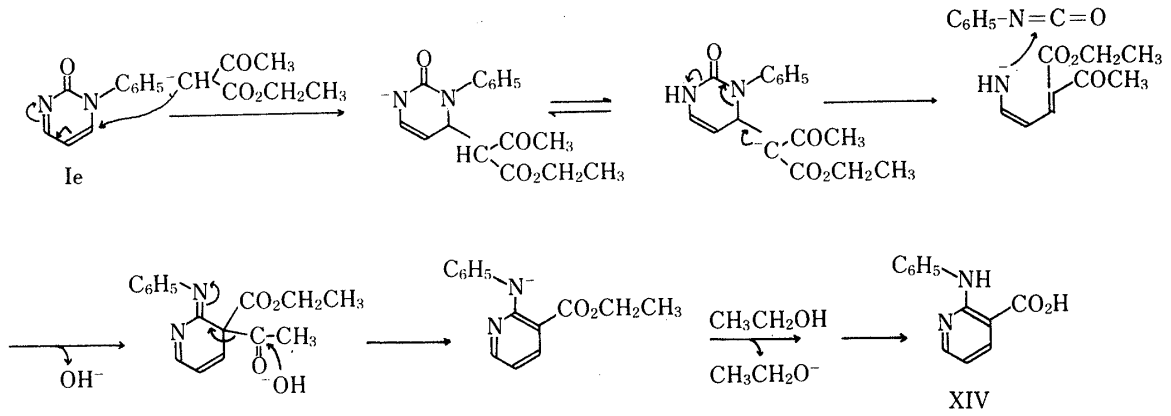


Chart 3

In conclusion, 1-substituted 2(1*H*)-pyrimidinones undergo ring transformation with active methylene compounds to give various pyridine derivatives. The reaction with malononitrile is especially useful for the selective synthesis of 2-amino-3-cyanopyridines having different substituents at the C-4 and C-6 positions, offering mild conditions and high yield.

Experimental

All melting points are uncorrected. IR spectra were obtained on a Jasco IRA-1 infrared spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Hitachi R-24 and JEOL-100 NMR spectrometers, respectively, using tetramethylsilane as an internal standard. GLC was carried out by using a Shimadzu GC-4CM gas chromatograph equipped with a flame thermionic detector (FTD) and a Silicon OV-1 (80—100 mesh) column run at a temperature of 80 °C, with a detector temperature of 260 °C. MS were determined on a Hitachi M80 spectrometer.

General Procedure for Preparation of 4,6-Disubstituted 2-Amino-3-pyridinecarbonitriles (II—VII). A Typical Example——2-Amino-4,6-dimethyl-3-pyridinecarbonitrile (II): 4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone (Ia, 3 mmol) and malononitrile (12 mmol) were added to an ethanolic sodium ethoxide solution (prepared by dissolving 12 mmol of sodium in 20 ml of absolute ethanol). The mixture was stirred for 7 h at room temperature. The resulting precipitate II was filtered off and recrystallized from ethanol. IR (KBr): 3380, 3220, 3140, 2220 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.28 (3H, s), 2.30 (3H, s), 6.45 (1H, s); ^{13}C-NMR (DMSO-d_6+$CDCl_3$) δ: 19.7 (q), 23.9 (q), 113.0 (d), 116.2 (s), 152.5 (s), 159.7 (s), 161.0 (s), 170.7 (s); *Anal.* Calcd for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.13; H, 6.14; N, 28.52.

2-Amino-3-pyridinecarbonitrile (III): IR (KBr): 3410, 3320, 3200, 2220 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 5.5—6.1 (2H, br s), 6.72 (1H, dd, J=5 and 7.8 Hz), 7.77 (1H, dd, J=2 and 7.8 Hz), 8.30 (1H, dd, J=2 and 5 Hz).

2-Amino-4-ethyl-6-methyl-3-pyridinecarbonitrile (IV): IR (KBr): 3400, 3320, 3160, 2220 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 2.30 (3H, s), 2.61 (2H, q, J=7 Hz), 6.42 (1H, s), 6.5 (2H, br s); *Anal.* Calcd for $C_9H_{11}N_3$: C, 67.05; H, 6.87; N, 26.06. Found: C, 67.05; H, 6.90; N, 26.12.

2-Amino-4-methyl-6-phenyl-3-pyridinecarbonitrile (V): IR (KBr): 3470, 3300, 3160, 2215 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 5.4 (2H, br s), 7.02 (1H, s), 7.3—7.6 (3H, m), 7.9—8.1 (2H, m); *Anal.* Calcd for $C_{13}H_{11}N_3$: C, 74.61; H, 5.29; N, 20.08. Found: C, 74.44; H, 5.31; N, 20.02.

2-Amino-6-methyl-4-phenyl-3-pyridinecarbonitrile (VI): IR (KBr): 3390, 3310, 3180, 2220 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.38 (3H, s), 6.6—6.9 (2H, br s), 6.65 (1H, s), 7.5—7.7 (5H, m).

2-Amino-4-(*p*-chlorophenyl)-6-methyl-3-pyridinecarbonitrile (VII): IR (KBr): 3390, 3310, 3170, 2220 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.37 (3H, s), 6.56 (1H, s), 6.8 (2H, br s), 7.4—7.6 (4H, m); *Anal.* Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.13; N, 17.24. Found: C, 64.16; H, 4.11; N, 17.43.

General Procedure for Preparation of 4,6-Disubstituted 2-Oxo-1,2-dihydro-3-pyridinecarbonitriles (VIII—X). A Typical Example——4,6-Dimethyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (VIII): A solution of compound Ia (3 mmol), ethyl cyanoacetate (12 mmol) and sodium ethoxide (12 mmol) in absolute ethanol (20 ml) was heated at reflux for 7 h. The resulting precipitate was filtered off and dissolved in water. The aqueous solution was acidified with hydrochloric acid and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate. The product VIII was recrystallized from ethanol. IR (KBr): 3200—2600 (br), 2220, 1650 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.25 (3H, s), 2.33 (3H, s), 6.12 (1H, s).

4-Methyl-6-phenyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (IX): IR (KBr): 3200—2600 (br); 2240, 1630 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.47 (3H, s), 6.62 (1H, s), 7.3—7.8 (5H, m).

6-Methyl-4-phenyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (X): IR (KBr): 3200—2600 (br), 2225, 1660 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.33 (3H, s), 6.25 (1H, s), 7.4—7.7 (5H, m).

General Procedure for Preparation of Alkyl 2-Oxo-1,2-dihydro-3-pyridinecarboxylates (XI and XII). A Typical Example——Methyl 2-Oxo-1,2-dihydro-3-pyridinecarboxylate (XI): A solution of compound Ie (2 mmol), dimethyl malonate (8 mmol) and sodium methoxide (8 mmol) in absolute methanol (15 ml) was stirred for 2 h at room temperature. The resulting precipitate was worked up as described in the case of reaction with ethyl cyanoacetate. The product XI was recrystallized from benzene. IR (KBr): 3500—3100 (br) 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 6.43 (1H, t, J=8 Hz), 7.83 (1H, dd, J=2 and 8 Hz), 8.33 (1H, dd, J=2 and 8 Hz).

In the case of diethyl malonate, the reaction was carried out by using sodium ethoxide–absolute ethanol.

Ethyl 2-Oxo-1,2-dihydro-3-pyridinecarboxylate (XII): IR (KBr): 3200 (br), 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7 Hz), 4.37 (2H, q, J=7 Hz), 6.31 (1H, t, J=8 Hz), 7.88 (1H, dd, J=2 and 8 Hz), 8.30 (1H, dd, J=2 and 8 Hz).

Reaction of 4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone (Ia) with Diethyl Malonate——A solution of compound Ia (3 mmol), diethyl malonate (12 mmol) and sodium ethoxide (12 mmol) in absolute ethanol (20 ml) was stirred overnight, but the starting material was recovered unchanged.

Reaction of 1-Aryl-2(1*H*)-pyrimidinones (Ie and If) with Ethyl Benzoylacetate——A solution of compound Ie or If (2 mmol), ethyl benzoylacetate (8 mmol) and sodium ethoxide (8 mmol) in absolute ethanol (15 ml) was stirred for 6 h at room temperature. The solvent was evaporated off, and the residue was dissolved in water. The aqueous solution was acidified with hydrochloric acid and extracted with dichloromethane. Compounds Ie and If gave the same product, XIII.

3-Benzoyl-2(1*H*)-pyridone (XIII)——IR (KBr): 3200—2600 (br), 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 6.30 (1H, t, J=7 Hz), 7.2—8.0 (7H, m); *Anal.* Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.33; H, 4.51; N, 7.03.

Reaction of 1-Aryl-2(1*H*)-pyrimidinones (Ie and If) with Ethyl Acetoacetate——A solution of compound Ie or If (2 mmol), ethyl acetoacetate (8 mmol) and sodium ethoxide (8 mmol) in absolute ethanol (15 ml) was stirred for 6 h (2 h in the case of compound If) at room temperature. The solvent was evaporated off, and the residue was worked up in the same manner as described for the reaction with ethyl benzoylacetate. Compounds Ie and If gave the products XIV and XV, respectively.

2-Anilino-3-pyridinecarboxylic Acid (XIV)——IR (KBr): 3600—2600 (br), 1675 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 6.56 (1H, t, J=7 Hz), 7.1—7.8 (6H, m), 8.49 (1H, dd, J=2 and 7 Hz), 12.2 (1H, br s), 12.7 (1H, br s); MS *m/e*: 214 (M^+), 122, 93, 44; *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.96; H, 4.65; N, 12.96.

2-(*p*-Toluidino)-3-pyridinecarboxylic Acid (XV)——IR (KBr): 3600—2600 (br), 1670 cm^{-1}; ^{1}H-NMR (DMSO-d_6+$CDCl_3$) δ: 2.28 (3H, s), 6.50 (1H, t, J=7 Hz), 7.1—7.3 (2H, m), 7.5—7.8 (3H, m), 8.47 (1H, dd, J=2 and 7 Hz); *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.22; H, 5.26; N, 12.16.

Methylation of Compound XIV with Diazomethane——A solution of compound XIV (1 mmol) and an excess of diazomethane [prepared from *N*-nitrosomethylurea (1.05 g) and 40% aqueous potassium hydroxide (3.2 g)] in ether (15 ml) was stirred overnight at room temperature. The ether layer was evaporated to dryness, and the residue was chromatographed on silica gel with chloroform–acetone–ethanol (50 : 5 : 1) to give the product XVI.

Methyl 2-Anilino-3-pyridinecarboxylate (XVI)——IR (KBr): 3200—2800 (br), 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s), 6.30 (1H, t, J=7 Hz), 7.0—7.8 (6H, m), 8.48 (1H, dd, J=2 and 7 Hz), 12.0 (1H, br s); *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.48; H, 5.33; N, 12.19.

References and Notes

1) For a comprehensive review of ring transformations, see "Ring Transformation of Heterocycles," Vol. 1 and 2, ed. by H. C. van der Plas, Academic Press, New York, 1973.
2) C. Kashima, A. Katoh, Y. Yokota, and Y. Omote, *Chem. Pharm. Bull.*, **29**, 2516 (1981).
3) C. Kashima, A. Katoh, Y. Yokota, and Y. Omote, *Chem. Pharm. Bull.*, **30**, 1942 (1982).
4) R. G. Dickinson, N. W. Jacobsen, and R. G. Gillis, *Aust. J. Chem.*, **28**, 859 (1975).
5) J. J. Fox, T.-L. Su, L. M. Stempel, and K. A. Watanabe, *J. Org. Chem.*, **47**, 1081 (1982).
6) P. J. Vanderhorst and C. S. Hamilton, *J. Am. Chem. Soc.*, **75**, 656 (1953).
7) H. M. van Wagtendonk and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas*, **61**, 728 (1942).
8) T. B. Windholz, L. H. Peterson, and C. J. Kent, *J. Org. Chem.*, **28**, 1443 (1963).
9) W. O. Kermack and A. P. Weatherhead, *J. Chem. Soc.*, **1942**, 726.
10) The deacetylation of β-diketones under basic conditions has been reported, P. J. Hamrick, Jr., C. F. Hauser, and C. R. Hauser, *J. Org. Chem.*, **24**, 583 (1959).
11) E. C. Taylor, Jr. and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).
12) A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **41**, 430 (1963).
13) J. C. Bardham, *J. Chem. Soc.*, **1929**, 2223.
14) A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **40**, 1680 (1967).
15) L. R. Fibel and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 3908 (1948).