A New Route to 2-Amino- or 2-Hydroxy-3-pyridinecarboxylic Acid Derivatives

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Schiff's bases derived from ketones and *t*-butylamine (**1**) reacted with methyl methoxymethylenemalonate to give 2-hydroxy-3-pyridinecarboxylates. Similarly, treatment of **1** with ethoxymethylenemalononitrile gave 2-amino-3-pyridinecarbonitriles. Compounds **1** on reaction with ethyl 2-cyano-3-ethoxypropenoate afforded 2-amino-3-pyridinecarboxylates.

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A number of investigations have been made concerning the preparation of 2-amino- or 2-hydroxy-3-pyridinecarboxylic acid derivatives [1]. Recently, considerable attention has been given to their biological activity [2,3]. In this paper, we report on a new and facile method for the preparation of these compounds.

When Schiff's bases **1** derived from ketones and *t*-butylamine were heated with methyl methoxymethylenemalonate (**2**) in diphenyl ether, condensation of **1** with **2** and subsequent cyclization and a retro-ene reaction took place and 2-hydroxy-3-pyridinecarboxylates **4** were obtained by a one-pot procedure (Scheme 1). The structures of **4** were confirmed on the basis of analytical data and spectral evidence. The results of the reactions and the spectral data of **4** are summarized in Tables 1 and 2, respectively.

1-Alkyl-1,2-dihydro-2-oxo-3-pyridinecarboxylates **5-7**, obtained by reaction of the corresponding Schiff's bases with **2**, showed no sign of a retro-ene reaction when heated at 200° in diphenyl ether. Apparently, the steric strain between the *t*-butyl and R^1 groups at positions 1 and 6 in **3** constitutes an important factor in causing the elimination of 2-methylpropene to take place and leading to **4**.

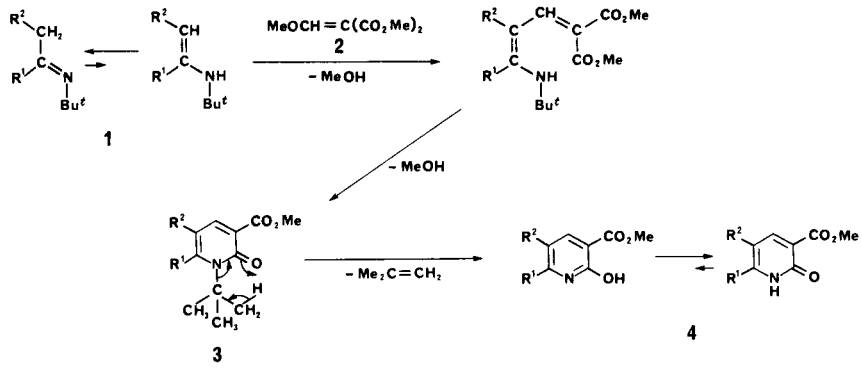
Table 1

Preparation of **4** [a]

Compound	Reaction temperature [b] °C (time, hours)	Yield %
4a	100 (3) and 200 (1)	46
4b	100 (3) and 200 (1)	71
4c	80 (1) and 190 (2)	52
4d	100 (10) and 250 (2)	72
4e	100 (15) and 250 (3)	65
4f	100 (10) and 250 (3)	73
4g	100 (10) and 250 (3)	60
4h	130 (15) and 250 (3)	38

[a] All reactions were carried out in diphenyl ether. **4a,b**: **1**, 100 mmoles; **2**, 100 mmoles; diphenyl ether, 60 ml. **4c**: **1**, 100 mmoles; **2**, 100 mmoles; diphenyl ether, 120 ml. **4d-h**: **1**, 50 mmoles; **2**, 50 mmoles; diphenyl ether, 150 ml. [b] Bath temperature.

Scheme 1



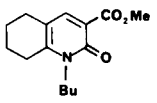
	R^1	R^2		R^1	R^2
a	Et	Me	e	Ph	Me
b	$-(CH_2)_4-$		f	p-Me-C_6H_4	H
c	$-(CH_2)_3-$		g	p-MeO-C_6H_4	H
d	Ph	H	h	p-NO_2-C_6H_4	H

Table 2

Spectral Data of **4**

Compound	IR [a] cm^{-1}	^1H NMR [b] δ	M^+ m/z
4a	1732, 1647	1.30 (3H, t, J = 7.7 Hz, CH_2CH_3), 2.14 (3H, s, CH_3), 2.73 (2H, q, J = 7.7 Hz, CH_2CH_3), 3.89 (3H, s, CO_2CH_3), 8.09 (1H, s, CH), 13.1 (1H, br s, NH)	243
4b	1738, 1647	1.6-2.9 (8H, m, $4CH_2$), 3.89 (3H, s, CO_2CH_3), 8.03 (1H, s, CH), 13.3 (1H, br s, NH)	207
4c	1688, 1655	1.9-3.2 (6H, m, $3CH_2$), 3.90 (3H, s, CO_2CH_3), 8.13 (1H, s, CH), 13.2 (1H, br s, NH)	193
4d	1692, 1647	3.94 (3H, s, CO_2CH_3), 6.94 and 8.29 (each 1H, d, J = 7.8 Hz, CH), 7.4-8.1 (5H, m, C_6H_5), 12.2 (1H, br s, NH)	229
4e	1695, 1642	2.18 (3H, s, CH_3), 3.88 (3H, s, CO_2CH_3), 7.4-7.6 (5H, m, C_6H_5), 8.12 (1H, s, CH), 11.8 (1H, br s, NH)	243
4f	1691, 1649	2.42 (3H, s, CH_3), 3.94 (3H, s, CO_2CH_3), 6.88 and 8.27 (each 1H, d, J = 7.9 Hz, CH), 7.2-8.0 (4H, m, C_6H_4), 12.1 (1H, br s, NH)	243
4g	1690, 1637	3.88 (3H, s, OCH_3), 3.95 (3H, s, CO_2CH_3), 6.90 and 8.25 (each 1H, d, J = 7.9 Hz, CH), 6.9-8.1 (4H, m, C_6H_4), 11.9 (1H, br s, NH)	259
4h	1697, 1663	3.96 (3H, s, CO_2CH_3), 7.60 and 8.32 (each 1H, d, J = 8.0 Hz, CH), 8.2-8.5 (4H, m, C_6H_4), 11.2 (1H, br s, NH) [c]	274

[a] Measured in potassium bromide. [b] Measured in deuteriochloroform unless otherwise noted. [c] Measured in THF-d_8.



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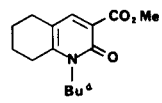

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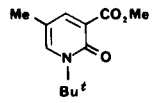

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Similarly, Schiff's bases **1** on reaction with ethoxymethylenemalononitrile (**8**, R^3 = CN) gave 2-amino-3-pyridinecarbonitriles **10** (Scheme 2). With ethyl 2-cyano-3-ethoxypropenoate (**8**, R^3 = CO_2Et), only the compounds resulting from participation of the cyano group in cyclization, 2-amino-3-pyridinecarboxylates **11**, were isolated. The observed vicinal coupling $^3J_{CN,H}$ of 11.6 Hz in the nmr spectrum of **9c** (R^3 = CO_2Et) indicates the *trans* configuration of the cyano group with respect to the olefinic proton; the observed $^3J_{CN,H}$ values for **9c** (R^3 = CN) are 12.2 and 6.7 Hz and it is well established that a *trans* $^3J_{C,H}$ value

Scheme 2

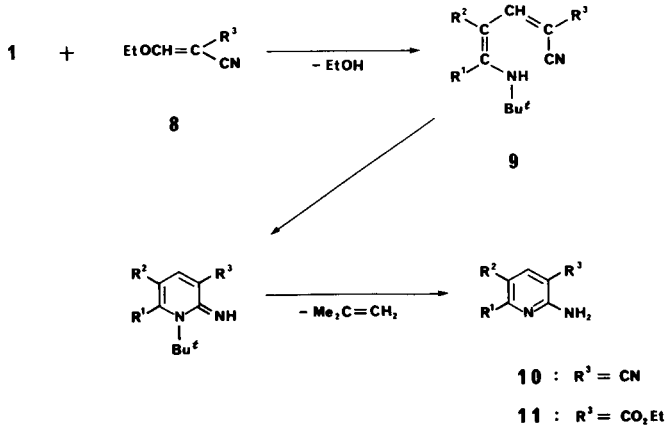

Table 3

Preparation of **10** and **11** [a]

Compound	Solvent [b]	Reaction temperature [c] °C (time, hours)			Yield %
10a	A	Room [d]	and	200 (2)	44
10b	A	Room [d]	and	200 (1)	53
10c	A	Room [d]	and	200 (2)	69
10d	B	80 (2)	and	275 (12)	46
10e	B	80 (2)	and	275 (12)	46
10f	B	80 (2)	and	275 (12)	43
11a	C	50 [d]	and	200 (3)	26
11b	C	50 [d]	and	200 (1)	43
11c	C	50 [d]	and	200 (1)	66
11d	B	100 (2)	and	275 (8)	44
11e	B	100 (3)	and	275 (7)	49
11f	B	100 (2)	and	275 (10)	45

[a] **1**, 10 mmoles; **8**, 10 mmoles; solvent, 30 ml. [b] A: triglyme. B: tetraglyme. C: diphenyl ether. [c] Bath temperature. [d] See Experimental.

Table 4

Spectral Data of **10** and **11**

Compound	IR [a] cm^{-1}	^1H NMR [b] δ	MH^+ [c] m/z
10a	3415, 3325, 2215	1.21 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.18 (3H, s, CH_3), 2.66 (2H, q, J = 7.5 Hz, CH_2CH_3), 5.2 (2H, br s, NH_2), 7.40 (1H, s, CH)	162
10b	3430, 3315, 2210	1.6-2.9 (8H, m, $4CH_2$), 5.4 (2H, br s, NH_2), 7.37 (1H, s, CH)	174
10c	3405, 3320, 2210	1.7-2.9 (6H, m, $3CH_2$), 6.6 (2H, br s, NH_2), 7.63 (1H, s, CH) [d]	160
10d	3465, 3295, 2200	5.4 (2H, br s, NH_2), 7.09 and 7.70 (each 1H, d, J = 8.1 Hz, CH), 7.3-8.1 (5H, m, C_6H_5)	196
10e	3480, 3310, 2210	2.21 (3H, s, CH_3), 5.2 (2H, br s, NH_2), 7.3-7.6 (5H, m, C_6H_5), 7.59 (1H, s, CH)	210
10f	3485, 3360, 2215	2.41 (3H, s, CH_3), 5.2 (2H, br s, NH_2), 7.13 and 7.73 (each 1H, d, J = 8.1 Hz, CH), 7.2-8.0 (4H, m, C_6H_4)	210
11a	3430, 3275, 1688	1.21 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.37 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.18 (3H, s, CH_3), 2.65 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.32 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.3 (2H, br s, NH_2), 7.83 (1H, s, CH)	209
11b	3430, 3270, 1688	1.37 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.6-2.9 (8H, m, $4CH_2$), 4.32 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.3 (2H, br s, NH_2), 7.82 (1H, s, CH)	221
11c	3435, 3260, 1677	1.37 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.8-3.0 (6H, m, $3CH_2$), 4.32 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.5 (2H, br s, NH_2), 7.94 (1H, s, CH)	207
11d	3425, 3280, 1700	1.38 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.35 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.5 (2H, br s, NH_2), 7.06 and 8.18 (each 1H, d, J = 8.1 Hz, CH), 7.3-8.1 (5H, m, C_6H_5)	243
11e	3440, 3290, 1695	1.39 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.20 (3H, s, CH_3), 4.35 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.4 (2H, br s, NH_2), 7.3-7.6 (5H, m, C_6H_5), 8.03 (1H, s, CH)	257
11f	3440, 3270, 1684	1.35 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.37 (3H, s, CH_3), 4.31 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.5 (2H, br s, NH_2), 7.00 and 8.13 (each 1H, d, J = 8.1 Hz, CH), 7.1-8.0 (4H, m, C_6H_4)	257

[a] Measured in potassium bromide. [b] Measured in deuteriochloroform unless otherwise noted. [c] Measured by the CI method with isobutane. [d] Measured in DMSO-d_6.

is greater than a *cis* one in the system H-C=C-C [4]. The results of the reactions and the spectral data of **10** and **11** are given in Tables 3 and 4, respectively.

The present method is useful in regard to the ready availability of the starting materials, experimental simplicity, and satisfactory yield.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Hitachi 260-50 spectrometer. The ^1H- and ^{13}C-nmr data were obtained with a JEOL JNM-FX90Q spectrometer by using tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000 spectrometer at 70 eV of ionization energy by use of a direct-inlet system. Microanalyses were performed at the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, the University of Tokyo.

Schiff's bases **1a, d-h** were prepared by the procedure of Weingarten *et al* [5]. Schiff's bases **1b,c** were prepared according to the method of Lai [6]. Compound **2** was obtained by the method of Crombie *et al* [7]. Compounds **8** (R^3 = CN and CO_2Et) were obtained from a commercial source.

Preparation of **4**.

Reaction of **1** with **2** was carried out in a distillation flask under the conditions described in Table 1. Removal of the solvent by distillation *in vacuo* and recrystallization of the residual solid afforded **4**.

Methyl 6-Ethyl-1,2-dihydro-5-methyl-2-oxo-3-pyridinecarboxylate (**4a**).

This compound was obtained as colorless needles, mp 136-137° (from ethyl acetate).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.47; H, 6.79; N, 7.14.

Methyl 1,2,5,6,7,8-Hexahydro-2-oxo-3-quinolinecarboxylate (**4b**).

This compound was obtained as pale yellow needles, mp 193-194° (from ethanol).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63 57; H, 6.35; N, 6.55.

Methyl 2,5,6,7-Tetrahydro-2-oxo-1*H*-1-pyrindine-3-carboxylate (**4c**).

This compound was obtained as colorless needles, mp 174-175° (from ethanol).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.88; H, 5.63; N, 7.17.

Methyl 1,2-Dihydro-2-oxo-6-phenyl-3-pyridinecarboxylate (**4d**).

This compound was obtained as colorless needles, mp 172-173° (from ethyl acetate).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.36; H, 4.89; N, 6.08.

Methyl 1,2-Dihydro-5-methyl-2-oxo-6-phenyl-3-pyridinecarboxylate (**4e**).

This compound was obtained as colorless plates, mp 176-177° (from ethyl acetate).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.91; H, 5.54; N, 5.69.

Methyl 1,2-Dihydro-2-oxo-6-(*p*-tolyl)-3-pyridinecarboxylate (**4f**).

This compound was obtained as light brown plates, mp 200-201° (from ethyl acetate).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.16; H, 5.12; N, 5.61.

Methyl 1,2-Dihydro-6-(*p*-methoxyphenyl)-2-oxo-3-pyridinecarboxylate (**4g**).

This compound was obtained as yellow ocher plates, mp 211-212° (from ethanol-chloroform).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.71; H, 4.98; N, 5.35.

Methyl 1,2-Dihydro-6-(*p*-nitrophenyl)-2-oxo-3-pyridinecarboxylate (**4h**).

This compound was obtained as a yellow powder, mp 271-272° (from *N*,*N*-dimethylformamide).

Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22. Found: C, 56.84; H, 3.55; N, 9.99.

Methyl 1-Butyl-1,2,5,6,7,8-hexahydro-2-oxo-3-quinolinecarboxylate (**5**).

To a stirred solution of *N*-cyclohexylidenebutylamine [8] (4.61 g, 30.1 mmoles) in diglyme (45 ml) heated at a bath temperature of 120° was added a solution of **2** (5.23 g, 30.0 mmoles) in diglyme (45 ml) over a period of 1 hour. Stirring and heating were continued for an additional 3 hours. Distillation gave a fraction, bp 163-190°/0.16 mm Hg, which on standing solidified. Recrystallization from hexane-ethyl acetate afforded 3.60 g (46%) of **5** as pale yellow prisms, mp 67-68°; ir (potassium bromide): 1697, 1661 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.8-4.2 (17H, m, $(CH_2)_3CH_3$ and $4CH_2$), 3.89 (3H, s, CO_2CH_3), 7.91 (1H, s, CH); ms: (CI) m/z 264 (MH^+).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.38; H, 7.97; N, 5.25.

A solution of **5** (1.32 g) in diphenyl ether (3 ml) was heated at 200° for 1 hour. After removal of the solvent by distillation *in vacuo*, **5** (1.28 g, 97%) was recovered by recrystallization of the residual solid.

Methyl 1-(*s*-Butyl)-1,2,5,6,7,8-hexahydro-2-oxo-3-quinolinecarboxylate (**6**).

N-Cyclohexylidene-*s*-butylamine [8] was allowed to react with **2** in the same manner as described above. Distillation gave a fraction, bp 160-178°/0.25 mm Hg, which on standing solidified. Recrystallization from hexane-ethyl acetate provided 3.64 g (46%) of **6** as yellow prisms, mp 104-105°; ir (potassium bromide): 1730, 1640 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.7-4.5 (17H, m, $CH(CH_3)CH_2CH_3$ and $4CH_2$), 3.88 (3H, s, CO_2CH_3), 7.88 (1H, s, CH); ms: (CI) m/z 264 (MH^+).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.23; H, 8.14; N, 5.19.

A solution of **6** (1.32 g) in diphenyl ether (3 ml) was heated at 200° for 1 hour. Compound **6** (1.21 g, 92%) was recovered from the solution.

Methyl 1-(*t*-Butyl)-1,2-dihydro-5-methyl-2-oxo-3-pyridinecarboxylate (**7**).

To a stirred solution of **2** (8.71 g, 50.0 mmoles) in decahydronaphthalene (25 ml) heated at a bath temperature of 150° was added a solution of *N*-propylidene-*t*-butylamine [9] (7.41 g, 65.5 mmoles) in decahydronaphthalene (25 ml) during 1 hour. The temperature was maintained at 150° for an additional hour and then raised to 170° and kept for 1.5 hours. On cooling in a refrigerator, crystals separated out. Recrystallization from 1,2-dimethoxyethane gave 5.93 g (53%) of **7** as colorless prisms, mp 133-134°; ir (potassium bromide): 1693, 1660 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.70 (9H, s, $C(CH_3)_3$), 2.12 (3H, d, J = 0.7 Hz, CH_3), 3.89 (3H, s, CO_2CH_3), 7.5-7.6 (1H, m, =CH-N), 7.95 (1H, d, J = 2.6 Hz, CH=C); ms: (CI) m/z 224 (MH^+).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.56; H, 7.71; N, 5.98.

A solution of **7** (2.24 g) in diphenyl ether (6 ml) was heated at 200° for 1 hour. Compound **7** (2.16 g, 97%) was recovered from the solution.

Ethyl (*E*)-3-[2-(*t*-Butylamino)-1-cyclopentenyl]-2-cyanopropenoate (**9c**, $R^3 = CO_2Et$).

To a stirred solution of **1c** (4.18 g, 30.0 mmoles) in tetrahydrofuran (30 ml) heated at a bath temperature of 50° was added a solution of **8** ($R^3 = CO_2Et$) (5.08 g, 30.0 mmoles) in tetrahydrofuran (30 ml) during 0.5 hour. Stirring and heating were continued for an additional hour. The solution was evaporated *in vacuo*, leaving a residue which was recrystallized from ethyl acetate to give 4.63 g (59%) of **9c** ($R^3 = CO_2Et$) as orange prisms, mp 118-119°; ir (potassium bromide): 3360, 2203, 1683 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.32 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.41 (9H, s, $C(CH_3)_3$), 1.7-3.0 (6H, m, $3CH_2$), 4.24 (2H, q, J = 7.0 Hz, CH_2CH_3), 5.87 (1H, br s, NH), 7.78 (1H, t, J = 1.2 Hz, CH); ^{13}C-nmr (deuteriochloroform): δ 119.49 (d, $^3J_{C,H}$ = 11.6 Hz, CN); ms: (CI) m/z 263 (MH^+).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.63; H, 8.53; N, 10.59.

[2-(*t*-Butylamino)-1-cyclopentenyl]methylenemalononitrile (**9c**, R^3 = CN).

To a stirred solution of **1c** (4.18 g, 30.0 mmoles) in tetrahydrofuran (30 ml) was added a solution of **8** (R^3 = CN) (3.66 g, 30.0 mmoles) in tetrahydrofuran (30 ml) during 0.5 hour. Stirring was continued for an additional hour. The solution was evaporated *in vacuo*, leaving a residue which was recrystallized from ethyl acetate to give 4.71 g (73%) of **9c** (R^3 = CN) as yellow needles, mp 198-199°; ir (potassium bromide): 3320, 2205, 2190 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.41 (9H, s, $C(CH_3)_3$), 1.7-3.0 (6H,

m, $3CH_2$), 6.96 (1H, br s, NH), 7.59 (1H, t, J = 1.2 Hz, CH); ^{13}C-nmr (deuteriochloroform): δ 118.06 (d, $^3J_{C,H}$ = 12.2 Hz, CN), 120.49 (d, $^3J_{C,H}$ = 6.7 Hz, CN); ms: (CI) m/z 216 (MH^+).

Anal. Calcd. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.45; H, 7.85; N, 19.47.

Preparation of **10a-c**.

To a stirred solution of **1a-c** (10.0 mmoles) in triglyme (15 ml) was added a solution of **8** (R^3 = CN) (10.0 mmoles) in triglyme (15 ml) during 0.5 hour. The mixture was stirred for an additional hour at room temperature and then heated at the temperature indicated in Table 3. After removal of the solvent by distillation *in vacuo*, the residue was chromatographed on an alumina column using hexane-ethyl acetate (1:1) as an eluent to give **10a-c**.

2-Amino-6-ethyl-5-methyl-3-pyridinecarbonitrile (**10a**).

This compound was obtained as colorless plates, mp 152-153° (from ethyl acetate) (reference [10], mp 153-155°).

2-Amino-5,6,7,8-tetrahydro-3-quinolinecarbonitrile (**10b**).

This compound was obtained as colorless prisms, mp 194-195° (from ethyl acetate) (reference [11], mp 195°).

2-Amino-6,7-dihydro-5*H*-1-pyrindine-3-carbonitrile (**10c**).

This compound was obtained as colorless prisms, mp 217-218° (from ethyl acetate) (reference [10], mp 219°).

Preparation of **10d-f**.

Reaction of **1d-f** with **8** (R^3 = CN) was carried out under the conditions described in Table 3. After removal of the solvent by distillation *in vacuo*, the residue was chromatographed on an alumina column using hexane-ethyl acetate (1:1) as an eluent to give **10d-f**.

2-Amino-6-phenyl-3-pyridinecarbonitrile (**10d**).

This compound was obtained as colorless plates, mp 145-146° (from ethyl acetate) (reference [12], mp 145°).

2-Amino-5-methyl-6-phenyl-3-pyridinecarbonitrile (**10e**).

This compound was obtained as orange plates, mp 152-153° (from ethyl acetate).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.37; H, 5.17; N, 19.84.

2-Amino-6-(*p*-tolyl)-3-pyridinecarbonitrile (**10f**).

This compound was obtained as yellow plates, mp 179-180° (from ethyl acetate) (reference [12], mp 174°).

Preparation of **11a-c**.

To a stirred solution of **1a-c** (10.0 mmoles) in diphenyl ether (15 ml) heated at a bath temperature of 50° was added a solution of **8** (R^3 = CO_2Et) (10.0 mmoles) in diphenyl ether (15 ml) during 0.5 hour. The temperature was maintained at 50° for an additional hour and then raised and kept as described in Table 3. After removal of the solvent by distillation *in vacuo*, the residue was chromatographed on an alumina column using hexane-ethyl acetate (10:1) as an eluent to give **11a-c**.

Ethyl 2-Amino-6-ethyl-5-methyl-3-pyridinecarboxylate (**11a**).

This compound was obtained as colorless prisms, mp 103-104° (from ethyl acetate).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.33; H, 7.60; N, 13.24.

Ethyl 2-Amino-5,6,7,8-tetrahydro-3-quinolinecarboxylate (**11b**).

This compound was obtained as colorless needles, mp 128-129° (from hexane-ethyl acetate) (reference [13], mp 126-128°).

Ethyl 2-Amino-6,7-dihydro-5*H*-1-pyrindine-3-carboxylate (**11c**).

This compound was obtained as colorless needles, mp 121-122° (from hexane-ethyl acetate) (reference [1b], mp 121-122°).

Preparation of **11d-f**.

Reaction of **11d-f** with **8** (R^3 = CO_2Et) was carried out under the conditions described in Table 3. After removal of the solvent by distillation *in vacuo*, the residue was chromatographed on an alumina column using hexane-ethyl acetate (4:1) as an eluent to give **11d-f**.

Ethyl 2-Amino-6-phenyl-3-pyridinecarboxylate (**11d**).

This compound was obtained as colorless plates, mp 108-109° (from hexane-ethyl acetate) (reference [14], mp 107-108°).

Ethyl 2-Amino-5-methyl-6-phenyl-3-pyridinecarboxylate (**11e**).

This compound was obtained as colorless prisms, mp 130-131° (from hexane-ethyl acetate).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.50; H, 6.43; N, 10.86.

Ethyl 2-Amino-6-(*p*-tolyl)-3-pyridinecarboxylate (**11f**).

This compound was obtained as pale yellow prisms, mp 134-135° (from hexane-ethyl acetate).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.16; H, 6.22; N, 10.91.

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