Novel 1,4-Dihydropyridine Calcium Antagonists. I. Synthesis and Hypotensive Activity of 4-(Substituted Pyridyl)-1,4-dihydropyridine Derivatives

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A series of 4-(substituted pyridyl)-1,4-dihydropyridine derivatives were synthesized and their hypotensive effects examined. Several compounds, 2-(*N*-benzyl-*N*-methylamino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitro-2-pyridyl)-3,5-pyridinedicarboxylate (2b), its 4-(4-nitro-2-pyridyl) analogue (2g), 4-(3-trifluoromethyl-2-pyridyl) analogue (2c), 4-(2-trifluoromethyl-3-pyridyl) analogue (3e), 4-(4-cyano-2-pyridyl) analogue (2e), 4-(2-cyano-3-pyridyl) analogue (3d), and 4-(6-bromo-2-pyridyl) analogue (2i), were found to have a hypotensive activity parallel to that of nicardipine; 2c and 3e, in particular, had approximately twice the duration of nicardipine, and 2e had the most potent hypotensive activity of all the derivatives synthesized.

Keywords 4-(substituted pyridyl)-1,4-dihydropyridine; calcium antagonist; substituted pyridinecarboxaldehyde; hypotensive effect; vasodilating activity; Hantzsch reaction

Introduction

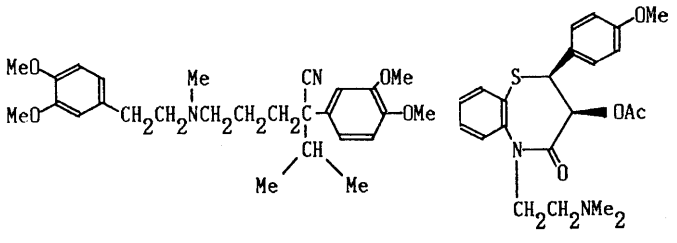
Calcium antagonists are divided into three groups according to their structures: phenylalkylamine type (*e.g.*, verapamil), benzothiazepine type (*e.g.*, diltiazem), and 1,4-dihydropyridine type (*e.g.*, nifedipine and nicardipine) (Fig. 1). Since 1,4-dihydropyridine type calcium antagonists in particular have more vascular selectivity and stronger hypotensive effect than other types of drugs, nifedipine[1] and nicardipine[2] are widely used as therapeutic agents for essential hypertension, angina pectoris, and peripheral and cerebral vascular disorders. These drugs, however, have a clinical drawback in that their action is of rather short duration, so that new drugs having longer duration and potent activity are clinically desired.

The structure–activity relationship of 1,4-dihydropyridine derivatives is partially known[3]; for instance, as the substituents of dihydropyridine ring at 4-position, phenyl groups which possess one or more substituents at *ortho*- or *meta*-position are preferable to other functions such as alkyls, aralkyls, or phenyl groups having a substituent at *para*-position and so on. However, the hypotensive effect of 4-pyridyl-1,4-dihydropyridine derivatives, especially 4-(substituted pyridyl) ones has never been reported at all, and we are interested in how the hypotensive effect is affected by the introduction of substituted pyridyl function to the 4-position of 1,4-dihydropyridine ring.

We, therefore, prepared novel 1,4-dihydropyridine derivatives to which substituted pyridyl groups were introduced instead of phenyl moiety and tested them for their hypotensive activities (Fig. 2). Since the pyridine ring has more variety of modification than does the phenyl ring, compounds with very interesting biological activities were expected to emerge. In this paper, we report syntheses and hypotensive effects of 4-(substituted pyridyl)-1,4-dihydropyridine derivatives.

Chemistry

Synthesis of 1,4-Dihydropyridine Derivatives from Substituted Pyridinecarboxaldehydes (5) Prepared compounds are listed in Tables I—III, according to the binding position of 4-pyridyl ring to 1,4-dihydropyridine ring. The method used in the synthesis of a 1,4-dihydropyridine skeleton was fundamentally based on the Hantzsch reaction,[4] namely, in method A, condensation of pyridine-



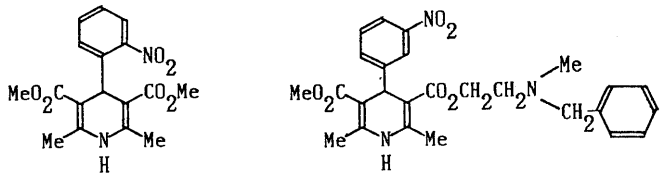


Fig. 1. Specific Calcium Antagonists in Clinical Use

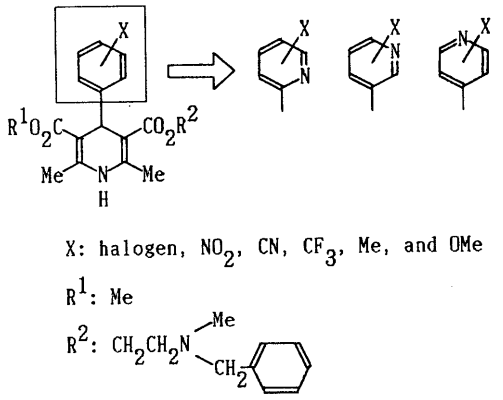


Fig. 2

carboxaldehydes (**5**), 2-chloroethyl acetoacetate (**6**), and methyl 3-aminocrotonate (**7**) was followed by substitution of the chlorine atom with *N*-benzylmethylamine.[2] In method B, condensation of the three components using 2-(*N*-benzyl-*N*-methylamino)ethyl acetoacetate (**8**) instead of **6** was carried out (Chart 1).

Structures of the prepared compounds were confirmed by infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and secondary ion mass spectra (SIMS), and precise mass analyses were performed by high resolution SIMS (HR-SIMS).

Synthesis of the Substituted Pyridinecarboxaldehydes (5) Substituted pyridinecarboxaldehydes (**5**), important intermediates, were prepared by known methods. Substituents were introduced to the pyridyl compounds such as picolines, picoline-*N*-oxides, acetoxymethylpyridines, or acetoxymethylpyridine-*N*-oxides and the intermediates obtained were converted to pyridinemethanols, then oxidized to give pyridinecarboxaldehyde (**5**).

The methods of introduction of substituents to the pyridine ring are shown in Charts 2—5.

Introduction of a NO_2 Group (Chart 2) 2-Picoline-*N*-oxide (**9**) was easily nitrated with fuming HNO_3 and H_2SO_4 to give 4-nitro-2-picoline-*N*-oxide (**10**) in high yield.[5] 3-Nitro group was introduced to **9** and 3-acetoxymethylpyridine-*N*-oxide (**14**) to afford 3-nitro-2-picoline-*N*-oxide (**13**) and 3-acetoxymethyl-5-nitropyridine-*N*-oxide (**15**), respectively, despite low yields by the method reported by Ochiai and Kaneko,[6] *i.e.* *O*-4-nitrobenzoylation and followed by subsequent treatment with $AgNO_3$. 6-Nitro-2-picoline-*N*-oxide (**17**) was obtained by the oxidation of the amino group of 6-acetamido-2-picoline-*N*-oxide (**16**) with Caro's acid.[7] Compound **10**, **13**, and **17** were converted to corresponding acetoxymethylpyridines **11a** (accompanied by **12**), **11b**, and **11d** by treatment with Ac_2O at its refluxing temperature,[8] while compound **15** was treated with PCl_3 to give 3-acetoxymethyl-5-nitropyridine (**11c**).[6]

Introduction of a CN Group (Chart 3) Selective cyanation of 2-picoline-*N*-oxide (**9**) at 6- or 4-positions was carried out by the method of Okamoto and Tani.[9] It was reported that two factors, *O*-alkylating agents and the temperature at which a KCN solution was added, mainly determined the selectivity. Actually, 6-cyano-2-picoline (**18**) was isolated as a sole product when condition A [i, MeI; ii, KCN/EtOH–H_2O (8 : 2), 5 °C—room temperature (r.t.), yield 70%] was used, while utilizing condition B [i, EtI; ii,

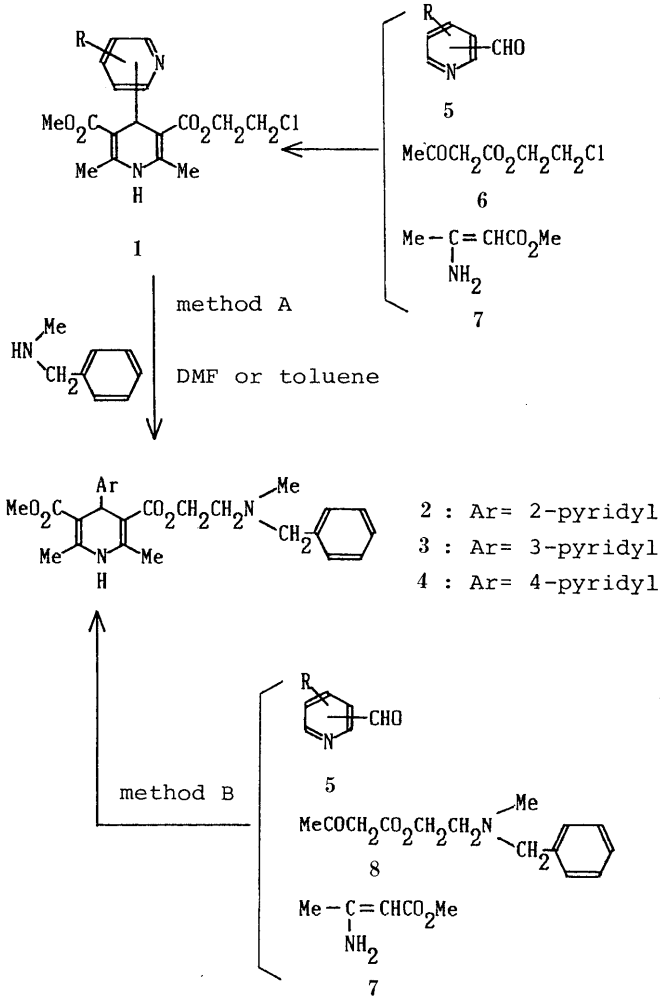
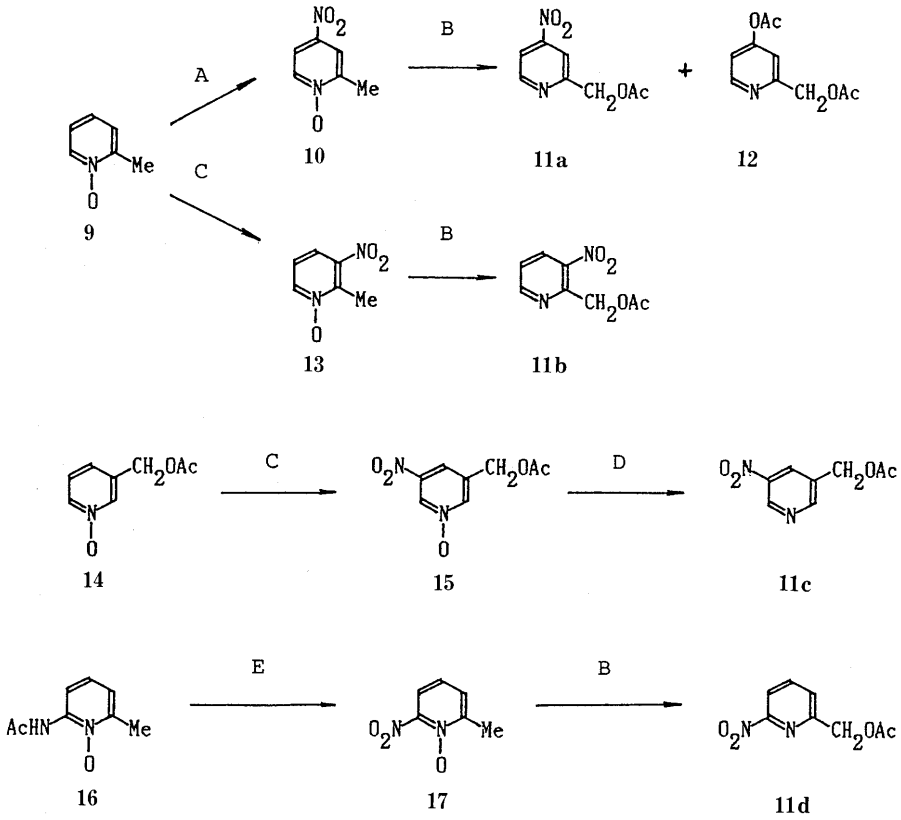


Chart 1

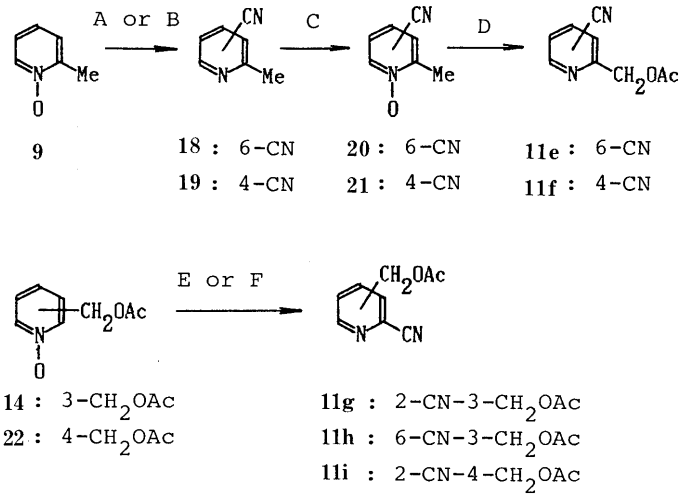
KCN/EtOH–H_2O (7 : 3), 48—50 °C, yield 52%], 4-cyano-2-picoline (**19**) alone was obtained, which is consistent with the reported results. The introduction of a CN group to 3-acetoxymethylpyridine-*N*-oxide (**14**) was a little complicated. By *O*-methylation of **14** with Me_2SO_4, following treatment with aq. KCN solution in 2-propanol–H_2O (8 : 2), 2-cyano-3-acetoxymethylpyridine (**11g**) and 6-cyano-3-acetoxymethylpyridine (**11h**) were obtained in the ratio of 2 : 1 (total yield 42%) (condition E)[10]; in contrast, using benzoyl chloride instead of Me_2SO_4 with aq. KCN solution in $CHCl_3$ (two phase reaction) (condition F),[11] **11g** was more preferentially obtained in the ratio of 87 : 13 (total yield 69%). A cyano group was easily introduced to 4-acetoxymethylpyridine-*N*-oxide (**22**) under condition E to give 4-acetoxymethyl-2-cyanopyridine (**11i**).

Introduction of a Halogen Atom (Br or F) (Chart 4) Substitution of NH_2 of 2-aminopicolines (**23**—**25**) with Br or F atoms were performed by the Sandmeyer[12] and the Schiemann[13] reactions to give 2-bromopicolines (**26**—**28**) and 2-fluoropicolines (**29** and **30**), respectively. 4-Bromo-2-picoline (**34**) was obtained by the reduction of 4-nitro-2-picoline-*N*-oxide (**10**) with PCl_3 and subsequent treatment with acetyl bromide.[14] 6-Chloro-2-picoline (**31**) was commercially available. Halogen-substituted picolines thus obtained were converted to pyridinecarboxylic acids (**32a**—**h**) by the oxidation of the methyl groups with $KMnO_4$



A) fuming HNO_3/H_2SO_4, 100—105 °C (95%); B)Ac_2O, refl. (yields of **11a** and **11d** are shown in Table IV. **12**, 30%); C) i) *p*-NO_2-benzoyl chloride/$CHCl_3$, −7 °C, ii) $AgNO_3$, −10—55 °C (**13**, 10%; **15**, 12%); D) $PCl_3/CHCl_3$, r.t. (96%); E) Caro's acid, r.t. (17%)

Chart 2

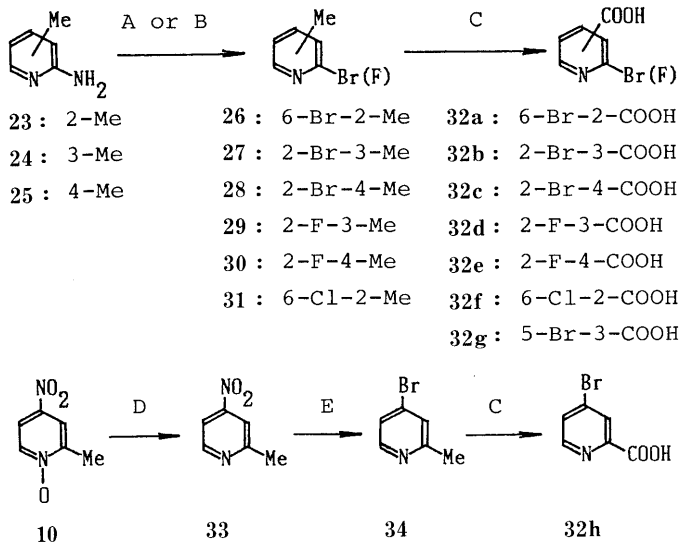


A) i) MeI, r.t., ii) KCN/EtOH–H_2O (8:2), 5 °C—r.t. (**18**, 70%); B) i) EtI, r.t., ii) KCN/EtOH–H_2O (7:3), 48—50 °C (**19**, 52%); C) *m*-chloroperbenzoic acid (MCPBA)/$CHCl_3$, r.t. (**20**, 96%; **21**, 92%); D) Ac_2O, refl. (Yields are shown in Table IV); E) i) Me_2SO_4, 60—70 °C, ii) KCN/iso-PrOH–H_2O (8:2), ice-salt cooling-r.t. (**11g**:**11h**=2:1, total 42%); F) aq. KCN, benzoyl chloride/$CHCl_3$, 4 °C (**11g**:**11h**=87:13, total 69%)

Chart 3

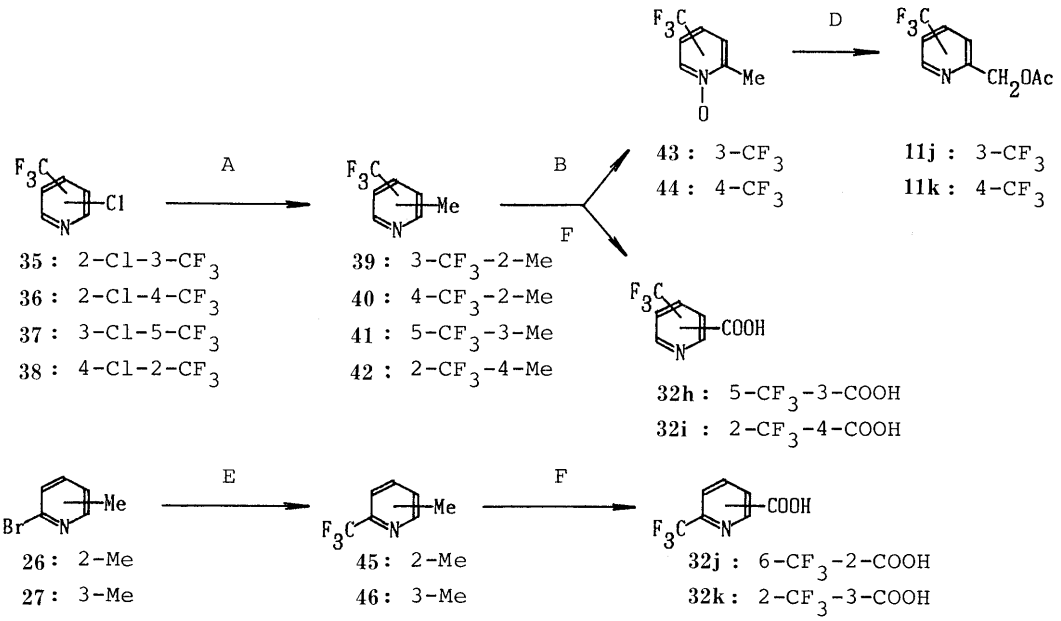
in H_2O.[15] 5-Bromonicotinic acid (**32g**) was also commercially available.

Introduction of a CF_3 Group (Chart 5) Since di-substituted pyridines with Cl and CF_3 (**35**—**38**) were commercially available, substitution of the Cl atom with a methyl group was investigated by Ohta's method.[16] Treatment of **35**—**38** with $AlMe_3$ in the presence of $Pd(PPh_3)_4$ in refluxing dioxane gave corresponding picolines (**39**—**42**) in relatively low yields. Compounds **39** and **40** were converted to corresponding acetoxymethylpyridines (**11j** and **11k**) *via* corresponding *N*-oxides (**43** and **44**). According to Kobayashi *et al.*,[17] 6-trifluoromethyl-2-picoline (**45**) and 2-trifluoromethyl-3-picoline (**46**) were obtained respectively by the treatment of 6-bromo-2-picoline (**26**) and 2-bromo-3-picoline (**27**) with CF_3I in the presence of Cu powder in hexamethylphosphorictriamide



A) $NaNO_2$, Br_2/48%HBr, 5 °C (**26**, 82%; **27**, 88%, **28**, 87%); B) $NaNO_2$/HBF_4, 0 °C—r.t. (**29**, 36%; **30**, 51%); C) $KMnO_4$/H_2O, refl. (Yields are shown in Table V), D) PCl_3/$CHCl_3$, r.t. (85%); E) AcBr, refl. (61%)

Chart 4



A) $AlMe_3$, $Pd(PPh_3)_4$/dioxane, refl.; B) MCPBA/$CHCl_3$, r.t. (**43**, quant.; **44**, 96%); D) Ac_2O, refl. (Yields are shown in Table IV); E) CF_3I, Cu/HMPA, 112—130 °C (**45**, 43%; **46**, 48%); F) $KMnO_4$/H_2O, refl. (yields are shown in Table V)

Chart 5

(HMPA) in moderate yields. Compounds **41**, **42**, **45**, and **46** were converted to corresponding carboxylic acids (**32h—k**) by oxidation with $KMnO_4$.[15]

Methods of Conversion of Acetoxymethylpyridines (11) and Pyridinecarboxylic Acids (32) to Pyridinecarboxaldehydes (5) (Chart 6) Acetoxymethylpyridines (**11**) thus obtained were placed under ester exchange reaction condition or hydrolytic conditions to give pyridinemethanols (**48**) in good yields. Pyridinecarboxylic acids (**32**) were converted to mixed anhydrides (**47**) which were reduced with $LiAlH_4$ to afford **48** also in good yields. The method of synthesis of 4-methoxy-2-pyridinemethanol (**48e**) was as follows: By treatment of 4-acetoxy-2-acetoxymethylpyridine (**12**) with *p*-toluenesulfonic acid monhydrate in MeOH, and following reaction with CH_2N_2, **48e** was obtained directly. The last step was the Moffatt oxidation of **48** to form the important intermediate aldehydes (**5**).[18]

Results and Discussion

The antihypertensive effects of the new 4-(substituted pyridyl)-1,4-dihydropyridine derivatives are shown in Tables I—III.

As to the 2-pyridyl derivatives (**2a—n**), several compounds, such as NO_2-substituted analogues (**2b, g**), and CF_3-substituted (**2c**), Br-substituted (**2i**), and CN-substituted ones (**2e**) indicated hypotensive properties parallel to that of nicardipine. Compound **2c** had approximately twice the duration of nicardipine and **2e** was the most potent

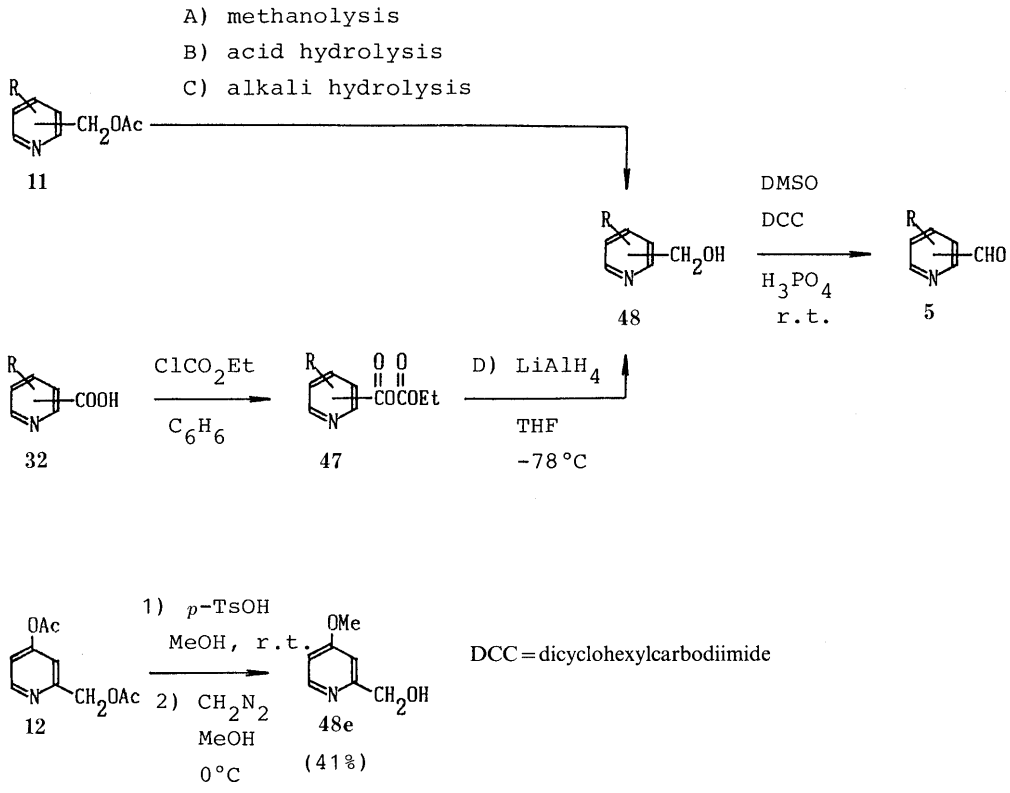
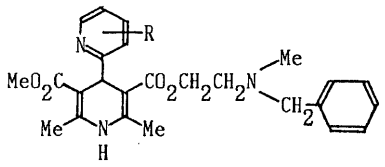


Chart 6

TABLE I. 4-(2-Pyridyl)-1,4-dihydropyridines

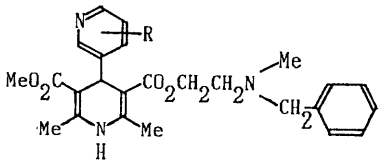


Compd. No.	R	Method	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	HR-SIMS[c] Found (Calcd)	Max. reduction of SBP (%)	Duration (h)
2a	H	A	25	129—131	IPE–M	436.2240 (436.2235)	4	3.3
2b	3-NO_2	A	30	Amorph.	—	481.2159 (481.2086)	35	8.7
2c	3-CF_3	B	55	141—142	E–IPE	504.2030 (504.2108)	33	16.2
2d	4-Br	A	6	Amorph.	—	514.1306 (514.1340)	30	5.8
2e	4-CN	B	36	176—177	IPE–M	461.2177 (461.2187)	39	7.0
2f	4-OMe	A	35	131—133	EA	466.2304 (466.2340)	9	16.5
2g	4-NO_2	A	11	163	M	481.2120 (481.2086)	33	2.3
2h	4-CF_3	B	54	Oil	—	504.2091 (504.2108)	26	5.6
2i	6-Br	A	31	123.5—124.5	IPE–M	514.1340 (514.1340)	37	3.5
2j	6-Cl	A	37	116—118	IPE–M	470.1851 (470.1845)	17	6.0
2k	6-CN	A	16	Amorph.	—	461.2122 (461.2187)	31	4.4
2l	6-NO_2	A	45	Amorph.	—	481.2078 (481.2086)	5	2.4
2m	6-CF_3	A	43	Oil	—	504.2127 (504.2108)	15	4.6
2n	6-CH_3	A	17	Oil	—	450.2345 (450.2391)	21	5.6
Nicardipine·HCl							38	7.0

a) Overall yield of the two steps using method A. *b*) E, ethyl ether: EA, ethyl acetate; IPE, isopropyl ether; M, methanol. *c*) All compounds were converted to corresponding fumarates and analyzed. The method of preparation of fumarates was described in Experimental section.

hypotensive of all the derivatives synthesized. Incidentally, information on hypotensive effects obtained from the relationship between the kinds of substituents and the positions at which they exist was as follows: Concerning NO_2-, CN-, and CF_3-substituted derivatives (**2b**, **2c**, **2e**, **2g**, **2h**, **2k**, **2l**, and **2m**), the hypotensive properties were reduced as the position of the substituent changed from 3 or 4 to 6, while Br-substituted ones (**2d** and **2i**) showed the opposite tendency. It is particularly noteworthy that 6-NO_2 derivative (**2l**) had almost no hypotensive effect despite the others (**2b** and **2g**) having potent activities; this was an interesting result that had never been seen in the case of 4-(substituted phenyl) derivatives. Conformational and electronic change caused by the substitution at different

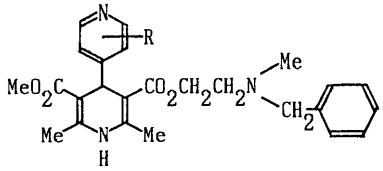
TABLE II. 4-(3-Pyridyl)-1,4-dihydropyridines



Compd. No.	R	Method	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	HR-SIMS[c] Found (Calcd)	Max. reduction of SBP (%)	Duration (h)
3a	H	A	23	144—145	IPE–M	436.2250 (436.2235)	11	1.6
3b	2-Br	A	40	149—151	IPE–M	514.1335 (514.1340)	18	6.7
3c	2-F	A	26	Amorph.	—	454.2090 (454.2140)	16	3.6
3d	2-CN	A	55[d]	169—170.5	IPE–M	461.2211 (461.2187)	34	5.6
3e	2-CF_3	A	65	100.5—103.5	IPE	504.2169 (504.2108)	33	16.2
3f	5-Br	A	43	Amorph.	—	514.1377 (514.1340)	17	9.3
3g	5-NO_2	A	68	Amorph.	—	481.2101 (481.2086)	14	3.7
3h	5-CF_3	A	68	Oil	—	504.2105 (504.2108)	9	4.2
3i	6-CN	A	44	Amorph.	—	461.2235 (461.2187)	17	15.1
Nicardipine·HCl							38	7.0

a) Overall yield of the two steps using method A. *b*) IPE, isopropyl ether; M, methanol. *c*) All compounds were converted to corresponding fumarates and analyzed. The method of preparation of fumarates was described in Experimental section. *d*) Yield of the last step.

TABLE III. 4-(4-Pyridyl)-1,4-dihydropyridines



Compd. No.	R	Method	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	HR-SIMS[c] Found (Calcd)	Max. reduction of SBP (%)	Duration (h)
4a	H	A	11	109—111	E	436.2280 (436.2235)	11	3.4
4b	2-Br	A	47	Amorph.	—	514.1351 (514.1340)	20	3.1
4c	2-F	A	57	Amorph.	—	454.2154 (454.2140)	8	5.5
4d	2-CN	A	23	Amorph.	—	461.2118 (461.2187)	25	1.7
4e	2-CF_3	A	55	Amorph.	—	504.2101 (504.2108)	13	12.5
Nicardipine·HCl							38	7.0

a) Overall yield of the two steps using method A. *b*) E, ethyl ether. *c*) All compounds were converted to corresponding fumarates and analyzed. The method of preparation of fumarates was described in Experimental section.

sites of the pyridine ring might affect interactions of the concerned molecules with drug receptors and thereby influence their potencies. Further investigation will be necessary to make the mode of action clearer.

The 3-pyridyl derivatives (**3a**—**i**) showed a similar tendency to the 2-pyridyl ones, particularly 2-CF_3 analogue (**3e**) which has a hypotensive property identical with that of nicardipine and longer duration decreased its activity when substituted at 5-position (**3h**).

In 4-pyridyl derivatives (**4a**—**e**), analogues having such potent hypotensive activities were not found. The electrons on the nitrogen atom of the pyridine ring at 4-position might play a similar role to functional substituents in these cases.

Other information obtained was as follows: Electron donating substituents decreased the hypotensive activity (**2f** and **2n**). Size of substituents appeared to relate little to the potency of effects (*e.g.*, **2e** > **2d**; **2g** > **2h**). However, more examples will be necessary to explain the detailed structure–activity relationship.

Several compounds, **2b** (3-NO_2-2-pyridyl), **2g** (4-NO_2-2-pyridyl), **2c** (3-CF_3-2-pyridyl), **3e** (2-CF_3-3-pyridyl), **2e** (4-CN-2-pyridyl), **3d** (2-CN-3-pyridyl), and **2i** (6-Br-2-pyridyl) were found to have a hypotensive activity parallel to that of nicardipine; **2c** and **3e** had a duration approximately twice that of nicardipine, and **2e** had the most potent activity of all the derivatives synthesized. Thus, we selected **2c**, **3e**, and **2e** as candidates for further structural modifications in our search for more superior compounds, and the results will be reported before long.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer. ^{1}H-NMR spectra were determined on a Hitachi R-24 (60 Mc) or a BRUKER AC-200 spectometer with tetramethylsilane (TMS) as an internal standard. SIMS were measured on a Hitachi M-2000 instrument. Extraction solvents were dried over anhydrous $MgSO_4$. Silica gel 60, 230—400 mesh (Nacalai Tesque) was used for flash column chromatography and Kieselgel 60, F_{254} (Merck) TLC plates were used for thin layer chromatography (TLC).

4-Nitro-2-picoline-*N*-oxide (10) To a mixture of 2-picoline-*N*-oxide (**9**, 50.0 g; 0.46 mol) and H_2SO_4 (175 ml), fuming HNO_3 (138 ml) was added portionwise at below 10 °C. After the addition was completed, the mixture was heated to 100—105 °C and stirred for 2 h. After cooling to room

temperature, the resulting mixture was poured into crushed ice, neutralized with Na_2CO_3, and extracted with $CHCl_3$. The extract was washed with brine, dried, and the solvent was evaporated to dryness to give the product (**10**) as a pale yellow solid (67.31 g, 95%). IR (KBr): 3050, 1615, 1510, 1460, 1340, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 8.00 (1H, dd, J=7, 3.5 Hz), 8.22 (1H, d, J=3.5 Hz), 8.34 (1H, d, J=7 Hz).

3-Nitro-2-picoline-*N*-oxide (13) To a solution of **9** (12.51 g; 0.12 mol) in $CHCl_3$ (300 ml) was added dropwise $CHCl_3$ solution (200 ml) of *p*-nitrobenzoyl chloride (21.49 g; 0.12 mol) at −7—−5 °C, followed by addition of finely powdered $AgNO_3$ (24.34 g; 0.14 mol. The reaction mixture was stirred for 1 h at −10—−8 °C, 2 h at 20—21 °C, 2.5 h at 40—50 °C, 2 h at 55 °C, and overnight at room temperature. After a precipitated solid was filtered off, the filtrate was washed with 10% K_2CO_3 and brine, dried, and concentrated. The residue was chromatographed on silica gel with AcOEt–MeOH (91 : 9, v/v) to give the product (**13**) as a yellow oil (1.84 g, 10%). IR (film): 3050, 1615, 1530, 1440, 1355, 1265 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, s), 7.15—7.45 (1H, m), 7.6—7.8 (1H, m), 8.35—8.55 (1H, m).

3-Acetoxymethyl-5-nitropyridine-*N*-oxide (**15**) was similarly obtained as a yellow oil (yield 12%). IR (film): 3050, 1735, 1565, 1535, 1430, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 5.16 (2H, s), 7.99 (1H, s), 8.45 (1H, s), 8.93 (1H, t, J=1.5 Hz).

6-Nitro-2-picoline-*N*-oxide (17) 6-Acetamido-2-picoline-*N*-oxide (**16**, 22.52 g; 0.14 mol) and H_2SO_4 (120 ml) were heated at 80 °C for 2 h. After cooling in an ice-water bath, the solution was poured into Caro's acid, prepared by adding powdered $K_2(SO_4)_2$ (221.74 g; 0.82 mol) to H_2SO_4 (155 ml) in an ice-water bath. The paste was stirred at room temperature for 3.5 d before being poured into crushed ice and neutralized with aq. ammonia. The resulting solution was extracted with $CHCl_3$, and the extract was washed with brine, dried, and the solvent was removed. The product (**17**) was isolated by column chromatograhy on silica gel with AcOEt–*n*-hexane (4 : 1, v/v) to yield a yellow solid (3.63 g, 17%). IR (KBr): 3050, 1615, 1560, 1485, 1450, 1375, 1255 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s), 7.1—7.65 (3H, m).

6-Cyano-2-picoline (18) (Condition A) After MeI (93.48 g, 41 ml; 0.66 mol) was added dropwise to **9** (20.17 g; 0.19 mol) at room temperature, the mixture was allowed to stand for 24 h at room temperature. The resulting *N*-methoxy-2-picolinium iodide was collected by filtration and washed with AcOEt and Et_2O. To the solution of this salt (42.79 g; 0.17 mol) in EtOH–H_2O (8 : 2) (190 ml), aq. KCN solution (22.19 g; 0.34 mol of KCN in 56 ml of H_2O) was added dropwise over 80 min at 5 °C. The solution was stirred at room temperature for another 2.5 h, and extracted with $CHCl_3$. The extract was washed with brine, dried, and the solvent was evaporated off. The residue was chromatographed on silica gel with AcOEt–*n*-hexane (1 : 3, v/v) to give the product (**18**) as a pale brown solid (14.00 g, 70%). IR (KBr): 3050, 2900, 2200, 1590, 1460, 1445 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.59 (3H, s), 7.25—7.85 (3H, m).

4-Cyano-2-picoline (19) (Condition B) After EtI (89.70 g, 46 ml; 0.58 mol) was added dropwise to **9** (17.93 g; 0.16 mol) at room temperature, the mixture was allowed to stand for 18 h at room temperature. The resulting *N*-ethoxy-2-picolinium iodide was collected by filtration and washed with Et_2O. To the solution of this salt (40.01 g; 0.15 mol) in EtOH–H_2O (7 : 3) (180 ml), aq. KCN solution (20.16 g; 0.30 mol of KCN in 54 ml of H_2O) was added dropwise over 100 min at 48—50 °C. The solution was stirred at the same temperature for another 30 min and extracted with $CHCl_3$. The extract was washed with brine, dried, and the solvent was removed. The product (**19**) was purified by column chromatography on silica gel with AcOEt–*n*-hexane (2 : 3, v/v) to give a pale brown solid (9.35 g, 52%). IR (KBr): 3050, 2900, 2225, 1600, 1545, 1470 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 7.34 (1H, ddd, J=5, 1.5, 1.5 Hz), 7.40 (1H, d, J=0.5 Hz), 8.68 (1H, dd, J=5, 0.5 Hz).

Method of Introduction of a CN Group to 3-Acetoxymethylpyridine-*N*-oxide (14) Condition E: A mixture of 3-acetoxymethylpyridine-*N*-oxide (**14**, 1.03 g; 6.2 mmol) and Me_2SO_4 (824 mg; 6.5 mmol) was heated at 60—70 °C for 2 h under N_2 atmosphere. The resulting quarternary salt (a pale yellow oil) was washed with Et_2O and immediately used in the next reaction. To the solution of this salt (1.53 g; 5.2 mmol) in 2-propanol–H_2O (8 : 2) (10 ml), aq. KCN solution (704 mg; 10.5 mmol of KCN in 3 ml of H_2O) was added dropwise with an ice-salt bath cooling over 17 min After the addition was completed, the reaction mixture was stirred at the same temperature for 30 min and at room temperature for 1 h, and extracted with $CHCl_3$. The extract was washed with brine, and the solvent was evaporated off. The residue was chromatographed on silica gel with AcOEt–*n*-hexane (5 : 6, v/v) to give 3-acetoxymethyl-6-cyanopyridine (**11h**) as a pale brown oil (53 mg) in the less polar fraction and 3-acetoxymethyl-2-cyanopyridine (**11g**) as a pale brown oil (61 mg) in the more polar fraction, accompanied by a mixture of **11g** and **11h** in the ratio of 5 : 2 (341 mg)[19] (total yield 42%). The spectral data are shown in Table IV.

Condition F: After addition of aq. KCN solution (12.98 g; 0.19 mol of KCN in 100 ml of H_2O) to a solution of **14** (12.99 g; 78 mmol) in $CHCl_3$ (250 ml), a solution of benzoyl chloride (15.29 g; 0.11 mol) in $CHCl_3$ (250 ml) was added dropwise to the mixture with vigorous stirring at 5—6 °C. The reaction mixture was stirred at 4 °C for 7 h. After the $CHCl_3$ layer was separated, the aq. layer was extracted with $CHCl_3$. The combined extract was washed with brine, dried, and concentrated to give a crude mixture (18.18 g). The same treatment was performed with another **14** (12.72 g; 76 mmol) to yield a mixture (17.64 g) in a similar manner. The combined mixture was chromatographed on silica gel with AcOEt–*n*-hexane (5 : 6, v/v) to give **11g** (8.96 g) and a mixture of **11g** and **11h** in the ratio of 3 : 1 (9.74 g)[19] (total yield 69%).

4-Acetoxymethyl-2-cyanopyridine (11i) Compound **11i** was obtained as a pale brown oil from 4-acetoxymethylpyridine-*N*-oxide (**22**) using condition E (yield 47%). The spectral data are shown in Table IV.

4-Bromo-2-picoline (34) A mixture of 4-nitro-2-picoline (**33**, 12.87 g; 93 mmol) and acetyl bromide (32.68 g, 21.5 ml; 0.27 mol) was refluxed for 6 h and the resulting mixture was poured into crushed ice. After neutralization with Na_2CO_3, the mixture was extracted with Et_2O. The extract was washed with brine, dried, and the solvent was evaporated off. The product (**34**) was isolated by chromatography on silica gel with AcOEt–*n*-hexane (1 : 2, v/v) to give a pale orange oil (9.70 g, 61%). IR (film): 3050, 2925, 1575, 1555, 1470, 1445 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 7.1—7.3 (2H, m), 8.23 (1H, d, J=5 Hz).

4-Cyano-2-picoline-*N*-oxide (21) To a solution of **19** (1.03 g; 8.7 mmol) in $CHCl_3$ (7 ml) a solution of *m*-chloroperbenzoic acid (1.98 g; 9.2 mmol) in $CHCl_3$ (23 ml) was added dropwise at room temperature. After the addition was completed, the reaction mixture was stirred at the same temperature for 4 h before Na_2SO_3 (750 mg) was added and stirred for 1 h. The resulting mixture was washed with aq. saturated $NaHCO_3$, and the aq. layer was further extracted with $CHCl_3$. The organic extracts were combined, washed with brine, dried, and the solvent was evaporated to dryness to give the product (**21**) as a pale yellow solid (1.12 g, 96%). IR (KBr): 3050, 2900, 2225, 1620, 1535, 1470, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 7.43 (1H, dd, J=6.5, 2 Hz), 7.50 (1H, br s), 8.23 (1H, d, J=6.5 Hz).

Other *N*-oxides (**20**, **43**, and **44**) were similarly obtained.

6-Cyano-2-picoline-*N*-oxide (**20**): A pale yellow solid, yield 92%. IR (KBr): 3075, 2225, 1605, 1485, 1440, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 7.15—7.95 (3H, m).

3-Trifluoromethyl-2-picoline-*N*-oxide (**43**): A colorless solid, yield quant. IR (KBr): 3075, 1605, 1570, 1490, 1450, 1220, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s), 7.0—7.6 (2H, m), 8.39 (1H, d, J=5.5 Hz).

4-Trifluoromethyl-2-picoline-*N*-oxide (**44**): A colorless solid, yield 96%. IR (KBr): 3075, 1635, 1560, 1480, 1465, 1265, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 7.2—7.6 (1H, m), 8.29 (1H, d, J=6.5 Hz).

4-Nitro-2-picoline (33) To a solution of 4-nitro-2-picoline-*N*-oxide (**10**, 18.91 g; 0.12 mol) in $CHCl_3$ (260 ml) a solution of PCl_3 (47.6 ml; 0.55 mol) in $CHCl_3$ (260 ml) was added dropwise with ice-water cooling under N_2 atmosphere. After the addition was completed, the solution was stirred at room temperature for 3 h, poured into crushed ice, and neutralized with aq. ammonia. The organic layer was separated and the aq. layer was further extracted with $CHCl_3$. The combined extract was washed with brine, dried, and the solvent was evaporated to dryness to give the product (**33**) as a yellow solid (13.92 g, 85%). IR (KBr): 3050, 1575, 1525, 1470, 1435, 1355 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.69 (3H, s), 7.65—7.9 (2H, m), 8.72 (1H, dd, J=5, 1.5 Hz).

3-Acetoxymethyl-5-nitropyridine (**11c**) was similarly obtained as a yellow oil. The spectral data are shown in Table IV.

Methods for Synthesis of Halogen-Substituted Picolines (26—30) Bromine substituted picolines (**26**—**28**) were synthesized by the method reported by Adams and Miyano.[12]

6-Bromo-2-picoline (**26**): A colorless liquid, yield 82%, bp 102—103 °C (20 mmHg). IR (film): 3075, 2950, 2925, 1585, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 7.0—7.55 (3H, m).

2-Bromo-3-picoline (**27**): A colorless liquid, yield 88%, bp 104—106 °C (35 mmHg). IR (film): 3075, 2950, 1580, 1555, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 7.12 (1H, dd, J=8, 4.5 Hz), 7.48 (1H, dd, J=8, 2 Hz), 8.16 (1H, dd, J=4.5, 2 Hz).

2-Bromo-4-picoline (**28**): A colorless liquid, yield 87%, bp 95—100 °C (15 mmHg). IR (film): 3075, 2925, 1595, 1560, 1540, 1465 cm^{-1}. ^{1}H-NMR

($CDCl_3$) δ: 2.31 (3H, s), 7.04 (1H, ddd, J=5, 1.5, 1.5 Hz), 7.27 (1H, dd, J=1.5, 1.5 Hz), 8.16 (1H, d, J=5 Hz).

Fluorine substituted picolines (**29** and **30**) were synthesized by the same method reported by Roe.[13]

2-Fluoro-3-picoline (**29**): A colorless liquid, yield 36%. IR (film): 3075, 2925, 1610, 1580, 1450, 1420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s), 6.9—7.2 (1H, m), 7.4—7.8 (1H, m), 7.99 (1H, d, J=4.5 Hz).

2-Fluoro-4-picoline (**30**): A colorless liquid, yield 51%. IR (film): 3075, 2925, 1600, 1585, 1455 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s), 6.7—6.9 (1H, m), 7.0—7.2 (1H, m), 7.83 (1H, d, J=5 Hz).

Typical Method for the Synthesis of CF_3-Substituted Picolines (39—42) 5-Trifluoromethyl-3-picoline (**41**): To a suspension of $Pd(PPh_3)_4$ (polymer supported, 4.0 g) in dioxane (40 ml), 3-chloro-5-trifluoromethylpyridine (**37**, 14.68 g; 81 mmol) and a solution of $AlMe_3$ in *n*-hexane (19% (w/v), 20 ml) were successively added at room temperature under N_2 atmosphere. The reaction mixture was refluxed for 21 h, and the resulting mixture was poured into H_2O. After the catalyst was filtered off, the filtrate was extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. The residue was distilled *in vacuo* to yield a mixture of the product (**41**) and the starting material (**37**) (4.60 g), which was used in the next reaction without further purification.

Other CF_3-substituted picolines (**39**, **40**, and **42**) were similarly obtained as a mixture of the corresponding starting materials (**35**, **36**, and **38**).

Typical Method for the Synthesis of CF_3-Substituted Picolines (45 and 46) 2-Trifluoromethyl-3-picoline (**46**): A 1000 ml stainless steel autoclave (NAC-5, Nitto Autoclave Co., Ltd.) equipped with a magnetic stirrer was charged with **27** (33.50 g; 0.20 mol), Cu powder (63 g; 0.99 mol), and HMPA (140 ml) and sealed. The autoclave was cooled in dry ice–acetone and CF_3I (76.40 g; 0.39 mol), prepared by the method of Tiers,[20] was introduced. The autoclave was heated at 112—130 °C with vigorous stirring for 4 h. After cooling to room temperature and venting gases, the content of the autoclave was poured into H_2O. The precipitated solid was filtered off and the filtrate was extracted with Et_2O. The extract was washed with brine, dried, and the solvent was evaporated off. The residue was distilled *in vacuo* to give the product (**46**) as a colorless liquid (15.10 g, 48%), bp 86 °C (60 mmHg). IR (film): 3075, 2950, 1580, 1455, 1430, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 7.25 (1H, dd, J=7.5, 4 Hz), 7.55 (1H, d, J=7.5 Hz), 8.38 (1H, d, J=4 Hz).

6-Trifluoromethyl-2-picoline (**45**) was similarly obtained as a colorless liquid (yield 43%), bp 56—66 °C (33 mmHg). IR (film): 3075, 2850, 1610, 1470, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s), 7.28 (1H, d, J=7 Hz), 7.52 (1H, d, J=7 Hz), 7.70 (1H, dd, J=7, 7 Hz).

General Method for the Synthesis of Substituted Acetoxymethylpyridines (11a, 11b, 11d—f, 11j, and 11k) from Substituted Picoline-*N*-oxides (10, 13, 17, 20, 21, 43, and 44) To Ac_2O (30 ml) preheated at 110—120 °C a substituted picoline-*N*-oxide (58 mmol) was added. After stirring at the same temperature for 5 min, the reaction mixture was refluxed for 45—90 min. EtOH (30 ml) was added cautiously to the mixture, which was refluxed for 10 min. After cooling in ice-water, the mixture was poured into H_2O, and neutralized with $NaHCO_3$. The resulting mixture was extracted with Et_2O and the extract was washed with brine, dried, and the solvent was evaporated off. The residue was chromatographed on silica gel to afford the product, of which yields and spectral data are shown in Table IV.

General Method for the Synthesis of Substituted Pyridinecarboxylic Acids (32) from Substituted Picolines (26—31, 34, 41, and 42) To a mixture of a substituted picoline (0.118 mol) and H_2O (530 ml) was added $KMnO_4$ (0.121 mol) at room temperature. After the mixture was refluxed for 1.5 h, another $KMnO_4$ (0.121 mol) was added and the mixture was refluxed for an additional 20 h. After filtration of precipitated MnO_2, the filtrate was concentrated to about 300 ml. The resulting clear solution was acidified to about pH 3 with 35% HCl to give the product (**32**) as a precipitate, which was collected by filtration, dried *in vacuo*. Yields and spectral data are shown in Table V.

General Method for the Synthesis of Substituted Pyridinemethanols (48) from Substituted Acetoxymethylpyridines (11) A) Methanolysis: To a solution of substituted acetoxymethylpyridine (**11**, 20 mmol) in MeOH (20 ml) a catalytic amount of K_2CO_3 (about 3 mol%) was added and

TABLE IV. Yields and Spectral Data of Substituted Acetoxymethylpyridines (**11**)

Compd. No.	Yield (%)	IR (film) ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
11a	18	3050, 1745, 1590, 1440	2.17 (3H, s), 5.20 (3H, s), 7.3—7.6 (2H, m), 8.6—8.8 (1H, m)
11b	43	3100, 1745, 1605, 1530, 1440, 1350	2.17 (3H, s), 5.58 (2H, s), 7.47 (1H, dd, J=8.5 Hz), 8.38 (1H, dd, J=8, 1.5 Hz), 8.82 (1H, dd, J=5, 1.5 Hz)
11c	30	3050, 1745, 1585, 1450	2.16 (3H, s), 5.18 (2H, s), 8.47 (1H, t, J=2 Hz), 8.83 (1H, s), 9.26 (1H, d, J=2 Hz)
11d	—	1740, 1615, 1550, 1355	2.19 (3H, s), 5.29 (2H, s), 7.6—8.2 (3H, m)
11e	50	3100, 2225, 1745, 1590, 1450	2.16 (3H, s), 5.19 (2H, s), 7.45—8.0 (3H, m)
11f	63	3050, 2225, 1740, 1595, 1470, 1430	2.17 (3H, s), 5.18 (2H, s), 7.25—7.55 (2H, m), 8.55—8.75 (1H, m)
11g	—	3050, 2225, 1740, 1585, 1570, 1430	2.16 (3H, s), 5.29 (2H, s), 7.53 (1H, dd, J=8, 4.5 Hz), 7.92 (1H, dd, J=8, 1.5 Hz), 8.14 (1H, dd, J=5, 1.5 Hz)
11h	—	3050, 2225, 1740, 1570, 1470	2.13 (3H, s), 5.19 (2H, s), 7.6—8.0 (2H, m), 8.70 (1H, br s)
11i	—	3050, 2250, 1745, 1605, 1565, 1440, 1420	2.18 (3H, s), 5.17 (2H, s), 7.4—7.6 (1H, m), 7.67 (1H, s), 8.68 (1H, d, J=6 Hz)
11j	54	3075, 1750, 1595, 1580, 1450, 1430, 1120	2.13 (3H, s), 5.28 (2H, s), 7.23 (1H, dd, J=8, 4.5 Hz), 7.83 (1H, d, J=8 Hz), 8.58 (1H, d, J=4.5 Hz)
11k	59	3050, 1740, 1590, 1440, 1120	2.15 (3H, s), 5.27 (2H, s), 7.42 (1H, d, J=5 Hz), 7.53 (1H, s), 8.75 (1H, d, J=5 Hz)

TABLE V. Yields and Spectral Data of Substituted Pyridinecarboxylic Acids (**32**)

Compd. No.	Yield (%)	IR (KBr) ν_{max} (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (ppm)
32a	53	3050, 1690, 1560, 1450, 1420	7.75—8.15 (3H, m), 9.25 (1H, br s)
32b	70	3100, 2750, 2450, 1720, 1575	7.55 (1H, dd, J=8, 4.5 Hz), 8.10 (1H, dd, J=8, 2 Hz), 8.45 (1H, dd, J=4.5, 2 Hz), 9.88 (1H, br s)
32c	48	3100, 2775, 2450, 1710, 1600, 1545, 1450	7.81 (1H, dd, J=5, 1.5 Hz), 7.92 (1H, d, J=1.5 Hz), 8.02 (1H, d, J=5 Hz)
32d	30	2800, 2450, 1730, 1610, 1460, 1430	7.3—7.6 (1H, m), 8.2—8.6 (2H, m), 8.6—10.0 (1H, br)
32e	26	3100, 1730, 1620	7.50 (1H, s), 7.75 (1H, d, J=5 Hz), 8.40 (1H, d, J=5 Hz)
32f	51	3075, 1700, 1670, 1455, 1425	7.55—7.85 (1H, m), 7.9—8.1 (2H, m), 7.0—9.5 (1H br)
32h	22	2500, 1700, 1610, 1485, 1430, 1140	8.3—8.5 (1H, m), 9.0—9.3 (2H, m)
32i	25	2800, 2450, 1715, 1620, 1475, 1155	8.00 (1H, d, J=5 Hz), 8.05 (1H, s), 8.83 (1H, d, J=5 Hz)
32j	21	2900, 2600, 1730, 1595, 1140	7.79 (1H, dd, J=7.5, 4.5 Hz), 8.28 (1H, d, J=7.5 Hz), 8.83 (1H, d, J=4.5 Hz)
32k	34	3100, 2900, 1705, 1590, 1475, 1450, 1150	6.5—7.5 (1H, br), 7.85—8.35 (3H, m)

stirred for 2—2.5 h under N_2 atmosphere. After addition of H_2O to the mixture and neutralization with 5% CH_3COOH, the solution was extracted with $CHCl_3$, and the extract was washed with brine, dried, and the solvent was removed. The residue was purified by column chromatography on silica gel to give the product (**48**).

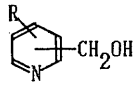
B) Acid Hydrolysis: To a solution of substituted acetoxymethylpyridine (**11**, 36 mmol) in tetrahydrofuran (THF) (45 ml) was added 1 N H_2SO_4 (30 ml) and allowed to reflux for 20 h. The resulting solution was poured into H_2O, and the mixture was neutralized with $NaHCO_3$ before extraction with $CHCl_3$. The extract was washed with brine, dried, and the solvent was evaporated off. The residue was chromatographed on silica gel to give the product (**48**).

C) Alkali Hydrolysis: A mixture of substituted acetoxymethyl pyridine (**11**, 34 mmol), 1 N NaOH (45 ml), and MeOH (90 ml) was stirred at room temperature for 1.5 h. The reaction mixture was poured into H_2O, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried, and the solvent was removed. The product (**48**) was isolated by column chromatography on silica gel.

Yields and spectral data are shown in Table VI. 2-Cyano-3-pyridinemethanol (**48o**) was not isolated because of its lability to chromatography on silica gel.

General Method for the Synthesis of Substituted Pyridinemethanols (48) from Substituted Pyridinecarboxylic Acids (32) Reduction of **32**: To a suspension of a carboxylic acid (**32**, 15 mmol) in C_6H_6 (80 ml) NEt_3 (15.8 mmol) was added at room temperature. After the carboxylic acid was dissolved, ethyl chloroformate (15.8 mmol) was added to the solution, and the mixture was stirred for 1 h at room temperature. Precipitated $Et_3N \cdot HCl$ was filtered off, and the filtrate was evaporated to dryness to give a mixed anhydride (**47**), which was immediately used in the next reaction. A solution of the mixed anhydride (**47**) in THF (50 ml) was added

TABLE VI. Yields and Spectral Data of Substituted Pyridinemethanols (**48**)



Compd. No.	R	Position of CH_2OH	Method (Yield %)	IR ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
48a	3-NO_2	2	A (72)	3450, 3100, 1610, 1535, 1435, 1350 (KBr)	4.73 (1H, br s), 5.14 (2H, s), 7.56 (1H, dd, J=8.5, 5 Hz), 8.55 (1H, dd, J=8.5, 1.5 Hz), 8.93 (1H, dd, J=5, 1.5 Hz)
48b	3-CF_3	2	C (76)	3250, 2925, 1625, 1575, 1430, 1130 (film)	4.24 (1H, br s), 4.83 (2H, s), 7.25 (1H, dd, J=7.5, 4.5 Hz), 7.83 (1H, d, J=7.5 Hz), 8.59 (1H, d, J=4.5 Hz)
48c	4-Br	2	D (60)	3275, 2900, 1635, 1575, 1555, 1440 (film)	4.25 (1H, br s), 4.69 (2H, s), 7.28 (1H, dd, J=5, 1.5 Hz), 7.46 (1H, d, J=1.5 Hz), 8.25 (1H, d, J=5 Hz)
48d	4-CN	2	B (68)	3400, 3100, 2900, 2250, 1605, 1555, 1460 (KBr)	3.84 (1H, br s), 4.80 (2H, s), 7.3—7.5 (1H, m), 7.58 (1H, s), 8.62 (1H, d, J=5 Hz)
48e	4-OMe	2	— (41)	3250, 2900, 1640, 1565, 1470 (KBr)	3.72 (1H, br s), 4.66 (2H, s), 6.82 (2H, dd, J=6, 2.5 Hz), 7.00 (1H, d, J=2.5 Hz), 8.40 (1H, d, J=5 Hz)
48f	4-NO_2	2	C (74)	3350, 3075, 2925, 1605, 1580, 1535, 1420, 1340 (KBr)	3.23 (1H, br s), 4.94 (2H, s), 7.95 (1H, dd, J=5.5, 2 Hz), 8.09 (1H, dd, J=1.5, 0.5 Hz), 8.87 (1H, d, J=5.5 Hz)
48g	4-CF_3	2	C (70)	3300, 2925, 1620, 1575, 1485, 1420, 1130 (film)	3.78 (1H, br s), 4.83 (2H, s), 7.40 (1H, d, J=5.5 Hz), 7.53 (1H, s), 8.70 (1H, d, J=5.5 Hz)
48h	6-Br	2	D (54)	3400, 2900, 1585, 1555 ($CHCl_3$)	3.55 (1H, t, J=5 Hz), 4.72 (2H, d, J=5 Hz), 7.15—7.7 (3H, m)
48i	6-Cl	2	D (61)	3400, 2900, 1580, 1555 ($CHCl_3$)	3.73 (1H, br s), 4.70 (2H, s), 7.7—7.55 (3H, m)
48j	6-CN	2	A (75)	3250, 2850, 2225, 1590, 1460, 1440 (KBr)	3.63 (1H, t, J=4 Hz), 4.80 (2H, d, J=4 Hz), 7.5—7.9 (3H, m)
48k	6-NO_2	2	A (64)	3350, 2900, 1620, 1545, 1420, 1355 (KBr)	3.80 (1H, br s), 4.89 (3H, s), 7.7—8.25 (3H, m)
48l	6-CF_3	2	D (66)	3375, 2900, 1605, 1580, 1470, 1445, 1140 (film)	3.62 (1H, s), 4.76 (2H, s), 7.44 (1H, d, J=7 Hz), 7.60 (1H, d, J=7 Hz), 7.82 (1H, dd, J=7, 7 Hz)
48m	2-Br	3	D (81)	3250, 2900, 1585, 1565, 1440 (KBr)	3.90 (1H, br s), 4.71 (2H, s), 7.25 (1H, dd, J=7.5, 4.5 Hz), 7.75—8.0 (1H, m), 8.18 (1H, dd, J=4.5, 2 Hz)
48n	2-F	3	D (74)	3350, 2875, 1615, 1580, 1435 (film)	3.66 (1H, br s), 4.70 (2H, s), 7.0—7.3 (1H, m), 7.7—8.1 (2H, m)
48o[a]	2-CN	3	B	—	—
48p	2-CF_3	3	D (85)	3300, 2900, 1590, 1575, 1455, 1435, 1120 (film)	3.25 (1H, br s), 4.89 (2H, s), 7.43 (1H, dd, J=7.5, 4.5 Hz), 8.12 (1H, d, J=7.5 Hz), 8.47 (1H, d, J=4.5 Hz)
48q	5-Br	3	D (48)	3350, 2950, 1600, 1580, 1560 ($CHCl_3$)	4.37 (1H, br s), 4.66 (2H, s), 7.85 (1H, t, J=2.5 Hz), 8.38 (1H, d, J=2.5 Hz), 8.47 (1H, d, J=2.5 Hz)
48r	5-NO_2	3	D (60)	3350, 2900, 1610, 1545, 1420, 1350 (KBr)	2.33 (1H, br s), 4.92 (2H, s), 8.55 (1H, t, J=2 Hz), 8.90 (1H, d, J=1.5 Hz), 9.36 (1H, d, J=2 Hz)
48s	5-CF_3	3	D (63)	3300, 2875, 1610, 1595, 1460, 1440, 1130 (film)	3.85 (1H, br s), 4.77 (2H, s), 7.95 (1H, s), 8.65 (2H, s)
48t	6-CN	3	A (53)	3200, 2850, 2225, 1590, 1570, 1475 (KBr)	3.36 (1H, br s), 4.83 (2H, s), 7.55—8.0 (2H, m), 8.65 (1H, s)
48u	2-Br	4	D (67)	3225, 2800, 1595, 1550, 1530, 1465, 1450 (KBr)	3.80 (1H, t, J=5 Hz), 4.73 (2H, d, J=5 Hz), 7.22 (1H, dd, J=5, 1 Hz), 7.50 (1H, dd, J=2, 1 Hz), 8.20 (1H, d, J=5 Hz)
48v	2-F	4	D (73)	3250, 1620, 1420 (KBr)	3.50 (1H, br s), 4.73 (2H, s), 6.92 (1H, s), 7.10 (1H, d, J=5 Hz), 8.03 (1H, d, J=5 Hz)
48w	2-CN	4	A (89)	3300, 2825, 2225, 1605, 1580, 1470, 1445 (KBr)	4.64 (2H, d, J=6 Hz), 5.58 (1H, d, J=6 Hz), 7.65 (1H, dd, J=6, 1 Hz), 7.86 (1H, s), 8.66 (1H, d, J=6 Hz)
48x	2-CF_3	4	D (25)	3350, 2900, 1620, 1435, 1140 (film)	3.95 (1H, br s), 4.76 (2H, s), 7.41 (1H, d, J=5 Hz), 7.68 (1H, s), 8.47 (1H, d, J=5 Hz)

a) **48o** was not isolated.

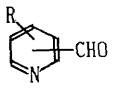
dropwise to a suspension of $LiAlH_4$ (15.8 mmol) in THF (20 ml) at −78 °C, and the mixture was stirred for 30 min at the same temperature. The mixture was worked up as usual to give the substituted pyridinemethanol (**48**). Yields and spectral data are shown in Table VI.

4-Methoxy-2-pyridinemethanol (48e) To a solution of 4-acetoxy-2-acetoxymethylpyridine (**12**, 4.01 g; 19 mmol) in MeOH (50 ml), *p*-toluenesulfonic acid monohydrate (20 mg; 0.10 mmol) was added and the mixture was refluxed for 4 h. After evaporating the solvent, H_2O was added to the residue, and the resulting mixture was washed with CH_2Cl_2. After the aq. layer was neutralized with $NaHCO_3$ and removed, MeOH was added to the residue and insoluble salt was filtered off. After the filtrate was concentrated to about 50 ml, Et_2O (150 ml) solution of CH_2N_2 (*ca.* 1.5 g) was added to the solution and stirred for 1 h with ice-water cooling. After the insolubles were removed by filtration, the filtrate was evaporated off. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (5 : 1, v/v) to give the product (**48e**) as a pale yellow solid (1.08 g, 48%). The spectral data are shown in Table VI.

General Method for the Synthesis of Substituted Pyridinecarboxyaldehydes (5) After dissolving a substituted pyridinemethanol (**48**, 10 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (30 mmol) in dimethyl sulfoxide (DMSO) (22 ml), 1.0 M anhydrous H_3PO_4 in DMSO (5 ml) was added to the mixture, and the reaction mixture was stirred for 1.5 h at room temperature. Precipitated dicyclohexylurea was filtered off, which on the filter was rinsed with Et_2O and H_2O. The aq. layer was extracted with Et_2O and the organic layers were combined, washed with brine, dried, and evaporated to dryness. The residue was chromatographed on silica gel to give the substituted pyridinecarboxaldehyde (**5**). Since **5** was easily air-oxidized, it was used in the next reaction as soon as possible. Yields and spectral data are shown in Table VII. 2-Cyano-3-pyridinecarboxaldehyde (**5o**) was not isolated because of its lability to chromatography on silica gel.

Typical Examples of Method A: 2-(*N*-Benzyl-*N*-methylamino)ethyl Methyl 4-(6-Bromo-2-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (2i) A solution of 6-bromo-2-pyridinecarboxaldehyde (**5h**,

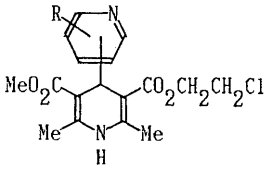
TABLE VII. Yields and Spectral Data of Substituted Pyridinecarboxaldehyde (**5**)



Compd. No.	R	Position of CHO	Yield (%)	IR ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
5a	3-NO_2	2	38	2925, 2825, 1720, 1600, 1530, 1450, 1350 (film)	7.70 (1H, dd, *J*=7.5, 5 Hz), 8.27 (1H, dd, *J*=7.5, 1 Hz), 8.94 (1H, dd, *J*=5, 1 Hz), 10.16 (1H, s)
5b	3-CF_3	2	84	2850, 1735, 1585, 1575, 1460, 1435, 1120 (film)	7.68 (1H, dd, *J*=8, 4.5 Hz), 8.20 (1H, d, *J*=8 Hz), 9.00 (1H, d, *J*=4.5 Hz), 10.21 (1H, s)
5c	4-Br	2	69	2925, 2850, 1705, 1565, 1555, 1460 (KBr)	7.68 (1H, dd, *J*=6, 2 Hz), 8.04 (1H, dd, *J*=2, 1 Hz), 8.52 (1H, dd, *J*=6, 1 Hz), 9.96 (1H, s)
5d	4-CN	2	71	3050, 2925, 2875, 2250, 1710, 1625, 1590, 1470 (KBr)	7.69 (1H, dd, *J*=5.5, 2 Hz), 8.08 (1H, dd, *J*=2, 1 Hz), 8.89 (1H, dd, *J*=5.5, 1 Hz), 9.94 (1H, s)
5e	4-OMe	2	57	2925, 2825, 1700, 1575, 1460 (KBr)	6.95 (1H, dd, *J*=6, 2 Hz), 6.99 (1H, d, *J*=2 Hz), 8.68 (1H, dd, *J*=6, 2 Hz), 9.92 (1H, s)
5f	4-NO_2	2	66	2925, 2800, 1720, 1530, 1460, 1350 (KBr)	8.12 (1H, dd, *J*=6, 2 Hz), 8.50 (1H, d, *J*=2 Hz), 9 01 (1H, dd, *J*=6, 2 Hz), 10.15 (1H, s)
5g	4-CF_3	2	25	2900, 2800, 1720, 1455, 1135 (film)	7.75 (1H, d, *J*=5 Hz), 8.16 (1H, s), 8.98 (1H, d, *J*=5 Hz), 10.13 (1H, s)
5h	6-Br	2	89	3025, 2900, 2850, 1730, 1570, 1550, 1435 (KBr)	7.6—8.0 (3H, m), 9.96 (1H, s)
5i	6-Cl	2	76	3100, 2925, 2875, 1710, 1575, 1555, 1440 (KBr)	7.5—9.75 (3H, m), 9.95 (1H, s)
5j	6-CN	2	81	3100, 2925, 2875, 2250, 1630, 1580, 1450 (KBr)	7.85—8.25 (3H, m), 10.04 (1H, s)
5k	6-NO_2	2	63	3050, 2825, 1705, 1595, 1540, 1440, 1350 (KBr)	8.15—8.55 (3H, m), 10.06 (1H, s)
5l	6-CF_3	2	36	2925, 2875, 1720, 1595, 1440, 1140 (film)	7.75—8.2 (3H, m), 10.05 (1H, s)
5m	2-Br	3	83	3025, 2925, 2875, 1695, 1655, 1575, 1560, 1440 (KBr)	7.40 (1H, ddd, *J*=8, 4.5, 1 Hz), 8.11 (1H, dd, *J*=8, 2 Hz), 8.52 (1H, dd, *J*=4.5, 2 Hz), 10.65 (1H, d, *J*=1 Hz)
5n	2-F	3	67	3075, 2875, 2750, 1700, 1670, 1600, 1575, 1460, 1440 (film)	8.1—8.5 (1H, m), 9.1—9.5 (2H, m), 10.30 (1H, s)
5o[a]	2-CN	3	—	—	—
5p	2-CF_3	3	76	2900, 1700, 1580, 1445, 1130 (film)	7.67 (1H, dd, *J*=8, 5 Hz), 8.43 (1H, d, *J*=8 Hz), 8.90 (1H, d, *J*=5 Hz), 10.50 (1H, s)
5q	5-Br	3	82	3025, 2825, 1690, 1575, 1435, 1420 (KBr)	8.28 (1H, t, *J*=2.5 Hz), 8.89 (1H, d, *J*=2.5 Hz), 8.98 (1H, d, *J*=2.5 Hz), 10.07 (1H, s)
5r	5-NO_2	3	71	3050, 2925, 2850, 1700, 1600, 1570, 1530, 1455, 1360 (KBr)	8.93 (1H, dd, *J*=2.5, 2 Hz), 9.40 (1H, d, *J*=2 Hz), 9.67 (1H, d, *J*=2.5 Hz), 10.26 (1H, s)
5s	5-CF_3	3	52	2925, 1700, 1610, 1590, 1450, 1140 (KBr)	8.40 (1H, br s), 9.08 (1H, br s), 9.24 (1H, br s), 10.20 (1H, s)
5t	6-CN	3	76	3100, 2825, 2225, 1710, 1585, 1565, 1460 (KBr)	7.92 (1H, d, *J*=8 Hz), 8.33 (1H, dd, *J*=8, 2 Hz), 9.17 (1H, d, *J*=2 Hz), 10.54 (1H, s)
5u	2-Br	4	88	2925, 2850, 1700, 1585, 1550, 1460 (KBr)	7.76 (1H, dd, *J*=5, 2 Hz), 7.87 (1H, t, *J*=2 Hz), 8.60 (1H, d, *J*=5 Hz), 9.99 (1H, s)
5v	2-F	4	51	2925, 1710, 1575, 1460 (KBr)	7.30 (1H, s), 7.55 (1H, d, *J*=5 Hz), 8.35 (1H, d, *J*=5 Hz), 9.95 (1H, s)
5w	2-CN	4	59	3100, 2950, 2900, 2275, 1715, 1630, 1565, 1460 (KBr)	7.9—8.2 (2H, m), 9.02 (1H, dd, *J*=5, 1 Hz), 10.47 (1H, s)
5x	2-CF_3	4	69	2925, 1715, 1620, 1570, 1470, 1140 (KBr)	7.89 (1H, d, *J*=5 Hz), 8.06 (1H, s), 8.97 (1H, d, *J*=5 Hz), 10.07 (1H, s)

a) **5o** was not isolated.

TABLE VIII. Spectral Data of 3-(2-Chloroethoxycarbonyl)-4-(substituted pyridyl)-1,4-dihydropyridines (**1**)



Compd. No.	R	Binding position of 4-Py to 1,4-DHP[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR δ (ppm)
1a	H	2	3200, 3050, 1685, 1640, 1590, 1505, 1430 (KBr)	2.22 (6H, s), 3.59 (2H, t, J=6 Hz), 3.59 (3H, s), 4.28 (2H, t, J=6 Hz), 5.20 (1H, s), 7.0—7.8 (3H, m), 8.4—8.6 (1H, m), 9.53 (1H, br s) (DMSO-d_6–$CDCl_3$, 4:3)
1b	3-NO_2	2	3200, 1700, 1680, 1640, 1535, 1430, 1350 (KBr)	2.21, 2.28 (each 3H, s), 3.45 (3H, s), 3.60 (2H, t, J=6 Hz), 4.16 (2H, t, J=6 Hz), 5.76 (1H s), 7.29 (1H, dd, J=8, 5 Hz), 7.95—8.2 (1H, m), 8.6—8.9 (2H, m) (DMSO-d_6–$CDCl_3$, 5:2),
1c	4-Br	2	3050, 1675, 1640, 1570, 1500, 1430 (KBr)	2.26 (6H, s), 3.65 (3H, s), 3.65 (2H, t, J=6 Hz), 4.30 (2H, t, J=6 Hz), 5.14 (1H, s), 7.2—7.65 (2H, m), 8.15—8.35 (2H, m) ($CDCl_3$)
1d	4-OMe	2	3175, 3050, 1690, 1675, 1600, 1565, 1510, 1490, 1430 (KBr)	2.22, 2.24 (each 3H, s), 3.64 (3H, s), 3.64 (2H, t, J=6 Hz), 3.87 (3H, s), 4.29 (2H, t, J=6 Hz), 5.14 (1H, s), 6.68 (1H, dd, J=6, 2.5 Hz), 6.97 (1H, d, J=2.5 Hz), 8.29 (1H, d, J=6 Hz), 9.26 (1H, s) ($CDCl_3$)
1e	4-NO_2	2	3050, 1690, 1640, 1620, 1540, 1500, 1430, 1360 (KBr)	2.35, 2.36 (each 3H, s), 3.65 (3H, s), 3.65 (2H, t, J=6 Hz), 4.2—4.5 (2H, m), 5.31 (1H, s), 6.31 (1H, s), 7.80 (1H, dd, J=5.5, 2 Hz), 8.06 (1H, d, J=2 Hz), 8.77 (1H, d, J=5.5 Hz) ($CDCl_3$)
1f	6-Br	2	3325, 3100, 1705, 1680, 1650, 1585, 1555, 1505, 1435 (KBr)	2.30, 2.32 (each 3H, s), 3.60 (2H, t, J=6 Hz), 3.60 (3H, s), 4.28 ((2H, t, J=6 Hz), 5.25 (1H, s), 7.15—7.5 (3H, m), 7.74 (1H, s) ($CDCl_3$)
1g	6-Cl	2	3300, 3100, 1700, 1645, 1625, 1580, 1560, 1500, 1435 (KBr)	2.28, 2.30 (each, 3H, s), 3.60 (2H, t, J=6 Hz), 3.60 (3H, s), 4.28 (2H, t, J=6 Hz), 5.25 (1H, s), 7.0—7.7 (3H, m), 8.09 (1H, s) ($CDCl_3$)
1h	6-CN	2	3325, 2225, 1695, 1680, 1645, 1480, 1435 (KBr)	2.30 (6H, s), 3.60 (2H, t, J=6 Hz), 3.60 (3H, s), 4.27 (2H, t, J=6 Hz), 5.19 (1H, s), 7.3—7.7 (4H, m) ($CDCl_3$)
1i	6-NO_2	2	3300, 1690, 1675, 1640, 1535, 1355 (KBr)	2.31 (6H, s), 3.61 (2H, t, J=6 Hz), 3.61 (3H, s), 4.26 (2H, t, J=6 Hz), 5.23 (1H, s), 6.56 (1H, s), 7.6—7.95 (3H, m) ($CDCl_3$)
1j	6-CF_3	2	3350, 3100, 1680, 1600, 1485, 1435, 1150 (KBr)	2.28 (6H, s), 3.57 (2H, t, J=6 Hz), 3.60 (3H, s), 4.27 (2H, t, J=6 Hz), 5.17 (1H, s), 6.26 (1H, s), 7.3—7.65 (3H, m) ($CDCl_3$)
1k	6-Me	2	3150, 3025, 1675, 1640, 1590, 1565, 1505, 1440, 1425 (KBr)	2.26, 2.28 (each 3H, s), 2.50 (3H, s), 3.57 (2H, t, J=6 Hz), 3.59 (3H, s), 4.26 (2H, t, J=6 Hz), 5.24 (1H, s), 6.8—7.6 (3H, m), 8.71 (1H, s) ($CDCl_3$)
1l	H	3	3200, 3050, 1690, 1640, 1585, 1510, 1430 (KBr)	2.32 (6H, s), 3.62 (2H, t, J=6 Hz), 3.62 (3H, s), 4.29 (2H, t, J=6 Hz), 5.00 (1H, s), 7.15 (1H, dd, J=7.5, 4.5 Hz), 7.50 (1H, s), 7.64 (1H, dt, J=7.5, 2 Hz), 8.35 (1H, dd, J=4.5, 2 Hz), 8.51 (1H, d, J=2 Hz) ($CDCl_3$)
1m	2-Br	3	3275, 3075, 1695, 1645, 1625, 1560, 1500, 1430 (KBr)	2.23, 2.28 (each 3H, s), 3.51 (3H, s), 3.69 (2H, t, J=7 Hz), 4.21 (2H, t, J=7 Hz), 5.12 (1H, s), 7.20 (1H, dd, J=7, 4.5 Hz), 7.61 (1H, dd, J=7, 2 Hz), 8.01 (1H, dd, J=4.5, 2 Hz), 8.79 (1H, s) (DMSO-d_6–$CDCl_3$, 5:2)
1n	2-F	3	3300, 3100, 1700, 1645, 1600, 1580, 1495, 1440 (KBr)	2.31 (6H, s), 3.52 (3H, s), 3.60 (2H, t, J=6 Hz), 4.21 (2H, t, J=6 Hz), 5.10 (1H, s), 6.9—7.2 (1H, m), 7.5—7.9 (2H, m), 8.49 (1H, s) (DMSO-d_6–$CDCl_3$, 1:1)
1o	2-CN	3	3200, 3100, 2225, 1705, 1650, 1620, 1500, 1435 (KBr)	2.29, 2.33 (each 3H, s), 3.55 (3H, s), 3.68 (2H, t, J=6 Hz), 4.24 (2H, t, J=6 Hz), 5.16 (1H, s), 7.47 (1H, dd, J=7.5, 5 Hz), 7.78 (1H, dd, J=7.5, 1.5 Hz), 8.39 (1H, dd, J=5, 1.5 Hz), 8.85 (1H, s) (DMSO-d_6–$CDCl_3$, 1:1)
1p	2-CF_3	3	3275, 3075, 1695, 1640, 1620, 1500, 1450, 1430, 1120 (KBr)	2.30 (6H, s), 3.50 (2H, t, J=6 Hz), 3.50 (3H, s), 4.0—4.3 (2H, m), 5.47 (1H, s), 7.35 (1H, dd, J=8.5, 4 Hz), 7.87 (1H, d, J=8.5 Hz), 8.37 (1H, d, J=4 Hz), 8.50 (1H, s) (DMSO-d_6–$CDCl_3$, 5:2)
1q	5-Br	3	3275, 3075, 1695, 1645, 1500, 1425 (KBr)	2.30 (6H, s), 3.55 (3H, s), 3.72 (2H, t, J=6 Hz), 4.25 (2H, t, J=6 Hz), 4.86 (1H, s), 7.64 (1H, br s), 8.39 (2H, t, J=1 Hz), 9.01 (1H, s) (DMSO-d_6–$CDCl_3$, 5:2)
1r	5-NO_2	3	3275, 3075, 1700, 1665, 1625, 1530, 1495, 1425, 1355 (KBr)	2.39, 2.41 (each 3H, s), 3.65 (2H, t, J=5.5 Hz), 3.66 (3H, s), 4.2—4.4 (2H, m), 5.15 (1H, s), 5.96 (1H, s), 8.34 (1H, t, J=2 Hz), 8.86 (1H, d, J=2 Hz), 9.22 (1H, d, J=2 Hz) ($CDCl_3$)
1s	5-CF_3	3	3275, 3075, 1700, 1645, 1625, 1500, 1460, 1430, 1120 (KBr)	2.28 (6H, s), 3.50 (3H, s), 3.6—3.9 (2H, br), 4.05—4.35 (2H, br), 4.89 (1H, s), 7.55—7.8 (1H, br), 8.5—8.7 (2H, br), 8.99 (1H, s) (DMSO-d_6)
1t	6-CN	3	3200, 3075, 2225, 1690, 1645, 1490, 1435 (KBr)	2.31 (6H, s), 3.54 (3H, s), 3.71 (3H, t, J=7 Hz), 4.23 (2H, t, J=7 Hz), 4.93 (1H, s), 7.78 (2H, br s), 8.52 (1H, s), 9.00 (1H, s) (DMSO-d_6–$CDCl_3$, 3:1)
1u	H	4	3325, 1670, 1590, 1475, 1435 (KBr)	2.35 (6H, s), 3.61 (2H, t, J=6 Hz), 3.61 (3H, s), 4.30 (2H, t, J=6 Hz), 5.01 (1H, s), 7.21 (1H, s), 7.27 (2H, dd, J=5, 1.5 Hz), 8.40 (2H, dd, J=5, 1.5 Hz) ($CDCl_3$)
1v	2-Br	4	3325, 3100, 1680, 1585, 1540, 1485, 1460, 1435 (KBr)	2.37 (6H, s), 3.66 (2H, t, J=7 Hz), 3.66 (3H, s), 4.33 (2H, t, J=7 Hz), 4.99 (1H, s), 6.68 (1H, s), 7.22 (1H, dd, J=5, 1.5 Hz), 7.38 (1H, s), 8.13 (1H, d, J=5 Hz) ($CDCl_3$)
1w	2-F	4	3325, 3100, 1685, 1580, 1480, 1435 (KBr)	2.34 (6H, s), 3.63 (2H, t, J=6 Hz), 3.63 (3H, s), 4.30 (2H, t, J=6 Hz), 5.05 (1H, s), 6.65 (1H, s), 6.78 (1H, s), 7.10 (1H, d, J=5 Hz), 7.95 (1H, d, J=5 Hz) ($CDCl_3$)
1x	2-CN	4	3375, 2275, 1705, 1655, 1625, 1600, 1480, 1440 (KBr)	2.34 (6H, s), 3.59 (3H, s), 3.71 (2H, t, J=7 Hz), 4.29 (2H, t, J=7 Hz), 4.95 (1H, s), 7.43 (1H, dd, J=5.5, 1 Hz), 7.61 (1H, s), 8.48 (1H, d, J=5.5 Hz), 8.89 (1H, s) (DMSO-d_6–$CDCl_3$, 1:1)
1y	2-CF_3	4	3325, 1690, 1600, 1490, 1140 (KBr)	2.35 (6H, s), 3.64 (2H, t, J=5 Hz), 3.64 (3H, s), 4.32 (2H, t, J=5 Hz), 5.10 (1H, s), 6.47 (1H, s), 7.39 (1H, d, J=5 Hz), 7.56 (1H, s), 8.50 (1H, d, J=5 Hz) ($CDCl_3$)

a) Binding position of 4-(substituted pyridyl) group to 1,4-dihydropyridine.

1.54 g; 8.3 mmol), 2-chloroethyl acetoacetate (**6**, 1.39 g; 8.4 mmol), and methyl 3-aminocrotonate (**7**, 984 mg; 8.3 mmol) in 2-propanol (12 ml) was stirred at 40 °C for 9 h and then at room temperature for 13 h. The reaction solvent was evaporated off and the residue was chromatographed on silica gel with AcOEt–*n*-hexane (2:3, v/v). The product (**1f**) was recrystallized from isopropyl ether–MeOH to yield pale yellow crystals (1.73 g, 49%),

TABLE IX. Spectral Data of 1,4-Dihydropyridines (**2**) Listed in Tables I, II, and III

Compd. No.	IR ν_{max} (cm^{-1})	^{1}H-NMR δ ($CDCl_3$) (ppm)
2a	3200, 3100, 1695, 1640, 1625, 1590, 1500, 1435 (KBr)	2.20 (9H, s), 2.61 (2H, t, J=6.6 Hz), 3.49 (2H, s), 3.59 (3H, s), 4.15 (2H, t, J=6.5 Hz), 5.22 (1H, s), 7.0—7.4 (7H), 7.45 (1H, dd, J=6.5, 1.5 Hz), 8.45 (1H, br d, J=6.5 Hz), 9.22 (1H, s)
2b	3300, 1690, 1650, 1520, 1470, 1355 ($CHCl_3$)	2.13 (2H, s), 2.28 (6H, s), 2.57 (2H, t, J=6 Hz), 3.41 (2H, s), 3.52 (3H, s), 4.14 (2H, t, J=6 Hz), 5.90 (1H, s), 6.32 (1H, s), 7.0—7.3 (6H), 7.92 (1H, dd, J=7.5, 1.5 Hz), 8.60 (1H, dd, J=5.5, 1.5 Hz)
2c	3200, 3100, 1705, 1675, 1630, 1580, 1510, 1460, 1120 (KBr)	2.13 (3H, s), 2.22 (6H, s), 2.53 (2H, t, J=6.5 Hz), 3.42 (2H, s), 3.52 (3H, s), 3.9—4.4 (2H, m), 5.63 (1H, s), 6.78 (1H, s), 7.0—7.3 (6H), 7.75 (1H, dd, J=8, 1.5 Hz), 8.60 (1H, d, J=4.5 Hz)
2d	3200, 3075, 1700, 1675, 1640, 1575, 1505, 1435 (KBr)	2.22 (9H, s), 2.62 (2H, t, J=6 Hz), 3.49 (2H, s), 3.61 (3H, s), 4.14 (2H, t, J=6 Hz), 5.11 (1H, s), 7.1—7.3 (6H), 7.54 (1H, d, J=1.5 Hz), 8.14 (1H, s), 8.19 (1H, d, J=5.5 Hz)
2e	3200, 2250, 1710, 1665, 1600, 1500, 1440 (KBr)	2.23 (3H, s), 2.27 (6H, s), 2.60 (2H, t, J=6 Hz), 3.51 (2H, s), 3.61 (3H, s), 4.14 (2H, t, J=6 Hz), 5.21 (1H, s), 7.00 (1H, s), 7.1—7.35 (6H), 7.59 (1H, s), 8.57 (1H, d, J=5.5 Hz)
2f	3175, 3050, 1690, 1595, 1560, 1505, 1455, 1430 (KBr)	2.20 (3H, s), 2.27 (6H, s), 2.65 (2H, t, J=6 Hz), 3.50 (2H, s), 3.63 (3H, s), 3.78 (3H, s), 4.18 (2H, t, J=6 Hz), 5.13 (1H, s), 6.61 (1H, dd, J=5.5, 2.5 Hz), 6.69 (1H, d, J=2.5 Hz), 7.15—7.35 (5H), 7.64 (1H, s), 8.29 (1H, d, 5.5 Hz)
2g	3175, 3050, 1690, 1640, 1620, 1580, 1540, 1360 (KBr)	2.20 (3H, s), 2.32, 2.33 (each 3H, s), 2.55—2.75 (2H, m), 3.50 (2H, AB-q, J=13 Hz), 3.63 (3H, s), 4.17 (2H, t, J=6 Hz), 5.32 (1H, s), 6.39 (1H, s), 7.2—7.35 (5H), 7.77 (1H, dd, J=5.5, 2 Hz), 8.04 (1H, d, J=2 Hz), 8.75 (1H, d, J=5.5 Hz)
2h	3300, 3100, 1700, 1650, 1620, 1490, 1435, 1140 (KBr)	2.17 (3H, s), 2.25 (6H, s), 2.60 (2H, t, J=6 Hz), 3.48 (2H, s), 3.60 (3H, s), 4.13 (2H, t, J=6 Hz), 5.27 (1H, s), 7.1—7.4 (6H), 7.60 (1H, br s), 8.63 (1H, d, J=5 Hz)
2i	3300, 3100, 1695, 1650, 1625, 1580, 1555, 1500, 1435 (KBr)	2.20 (3H, s), 2.30 (6H, s), 2.61 (2H, t, J=6 Hz), 3.50 (2H, s), 3.60 (3H, s), 4.17 (2H, t, J=6 Hz), 5.26 (1H, s), 7.2—7.45 (8H), 7.66 (1H, s)
2j	3300, 3100, 1700, 1695, 1645, 1625, 1580, 1560, 1500, 1435 (KBr)	2.16 (3H, s), 2.26 (6H, s), 2.59 (2H, t, J=6 Hz), 3.46 (2H, s), 3.56 (2H, s), 4.12 (2H, t, J=6 Hz), 5.24 (1H, s), 6.95—7.6 (8H), 7.95 (1H, s)
2k	3300, 2225, 1685, 1615, 1580, 1460 (KBr)	2.18 (3H, s), 2.29 (6H, s), 2.60 (2H, t, J=6 Hz), 3.49 (2H, s), 3.60 (3H, s), 4.14 (2H, t, J=6 Hz), 5.22 (1H, s), 6.91 (1H, s), 7.25 (5H, s), 7.4—7.65 (3H, m)
2l	3400, 1690, 1615, 1540, 1460, 1355 ($CHCl_3$)	2.18 (3H, s), 2.30 (6H, s), 2.60 (2H, t, J=6 Hz), 3.47 (2H, s), 3.60 (3H, s), 4.14 (2H, t, J=6 Hz), 5.25 (1H, s), 6.33 (1H, s), 7.19 (5H, s), 7.55—7.95 (3H, m)
2m	3300, 3100, 1690, 1500, 1440, 1140 (KBr)	2.17 (3H, s), 2.27 (6H, s), 2.60 (2H t, J=6 Hz), 3.48 (2H, s), 3.59 (3H, s), 4.16 (2H, t, J=6 Hz), 5.20 (1H, s), 5.98 (1H, s), 7.15 (5H, s), 7.25—7.45 (3H, m)
2n	3325, 3200, 3050, 1685, 1590, 1575, 1490, 1445 (film)	2.19 (3H, s), 2.27 (6H, s), 2.49 (3H, s), 2.61 (2H, t, J=6 Hz), 3.50 (2H, s), 3.60 (3H, s), 4.17 (2H, t, J=6 Hz), 5.27 (1H, s), 6.91 (1H, dd, J=7.5, 1.5 Hz), 7.0—7.55 (7H), 8.44 (1H, s)
3a	3200, 3050, 1690, 1630, 1590, 1500, 1435 (KBr)	2.20 (3H, s), 2.30 (6H, s), 2.63 (2H, t, J=6 Hz), 3.50 (2H, s), 3.62 (3H, s), 4.18 (2H, t, J=6 Hz), 5.03 (1H, s), 7.0—7.35 (7H), 7.64 (1H, dt, J=7.5, 1 Hz), 8.34 (1H, dd, J=4.5, 1 Hz), 8.54 (1H, d, J=1 Hz)
3b	3275, 3100, 1695, 1645, 1630, 1560, 1495, 1450, 1425 (KBr)	2.16 (3H, s), 2.27 (6H, s), 2.64 (2H, t, J=7 Hz), 3.45 (2H, s), 3.60 (3H, s), 4.17 (2H, t, J=7 Hz), 5.26 (1H, s), 6.22 (1H, s), 6.95—7.3 (6H), 7.64 (1H, dd, J=7, 1.5 Hz), 8.06 (1H, dd, J=5, 1.5 Hz)
3c	3300, 3100, 1700, 1645, 1630, 1600, 1580, 1495, 1440 (KBr)	2.15 (3H, s), 2.28 (6H, s), 2.59 (2H, t, J=6 Hz), 3.42 (2H, s), 3.53 (3H, s), 4.09 (2H, t, J=6 Hz), 5.10 (1H, s), 6.05 (1H, s), 6.75—7.05 (1H, m), 7.14 (5H, s), 7.4—7.95 (2H, m)
3d	3350, 2225, 1700, 1645, 1620, 1500, 1430 (KBr)	2.09 (3H, s), 2.31 (6H, s), 2.60 (2H, t, J=6 Hz), 3.42 (2H, s), 3.57 (3H, s), 4.13 (2H, t, J=6 Hz), 5.18 (1H, s), 7.18 (5H, s), 7.48 (1H, dd, J=8, 5 Hz), 7.83 (1H, dd, J=8, 1.5 Hz), 8.40 (1H, dd, J=5, 1.5 Hz), 8.87 (1H, s)[a]
3e	3300, 3100, 1700, 1650, 1625, 1495, 1455, 1430, 1120 (KBr)	2.12 (3H, s), 2.24 (6H, s), 2.52 (2H, t, J=6 Hz), 3.38 (2H, s), 3.48 (3H, s), 3.9—4.3 (2H, m), 5.55 (1H, s), 5.92 (1H, s), 7.1—7.45 (6H), 7.83 (1H, dd, J=8, 1.5 Hz), 8.37 (1H, br d, J=4.5 Hz)
3f	3300, 1690, 1620, 1460 ($CHCl_3$)	2.21 (3H, s), 2.32 (6H, s), 2.63 (2H, t, J=6 Hz), 3.50 (2H, s), 3.61 (3H, s), 4.15 (2H, t, J=6 Hz), 5.00 (1H, s), 6.58 (1H, s), 7.25 (2H, s), 7.7—7.85 (1H, m), 8.35—8.5 (1H, m)
3g	3275, 3050, 1695, 1645, 1625, 1525, 1495, 1425, 1360 (KBr)	2.21 (3H, s), 2.37, 2.39 (each, 3H, s), 2.63 (2H, t, J=6 Hz), 3.51 (2H, AB-q, J=13 Hz), 3.64 (3H, s), 4.17 (2H, t, J=6 Hz), 5.16 (1H, s), 7.2—7.4 (5H, m), 8.32 (1H, t, J=2 Hz), 8.86 (1H, d, J=2 Hz), 9.19 (1H, d, J=2 Hz)
3h	3350, 3100, 1680, 1585, 1490, 1440, 1120 (KBr)	2.17 (3H, s), 2.30 (6H, s), 2.59 (2H, t, J=6 Hz), 3.48 (2H, s), 3.60 (3H, s), 4.15 (2H, t, J=6 Hz), 5.07 (1H, s), 6.07 (1H, s), 7.20 (5H, s), 7.7—7.9 (1H, m), 8.55—8.8 (2H, m)
3i	3400, 2225, 1680, 1620, 1460 (KBr)	2.19 (3H, s), 2.34 (6H, s), 2.60 (2H, t, J=7 Hz), 3.48 (2H, s), 3.60 (3H, s), 4.15 (2H, t, J=7 Hz), 5.05 (1H, s), 6.28 (1H, s), 7.21 (5H, s), 7.41 (1H, d, J=8 Hz), 7.68 (1H, dd, J=8, 2 Hz), 8.58 (1H, d, J=2 Hz)
4a	3200, 3050, 1690, 1640, 1600, 1500, 1450, 1430 (KBr)	2.20 (3H, s), 2.32 (6H, s), 2.63 (2H, t, J=6 Hz), 3.50 (2H, s), 3.62 (3H, s), 4.19 (2H, t, J=6 Hz), 5.08 (1H, s), 7.05—7.45 (8H), 8.2—8.5 (2H, m)
4b	3325, 3100, 1685, 1620, 1585, 1545, 1490, 1460, 1435 (KBr)	2.22 (3H, s), 2.34 (6H, s), 2.54 (2H, t, J=7 Hz), 3.51 (2H, s), 3.65 (3H, s), 4.17 (2H, t, J=7 Hz), 5.01 (1H, s), 6.33 (1H, s), 7.1—7.4 (7H), 8.10 (1H, d, J=5 Hz)
4c	3300, 3050, 1690, 1500, 1460 (KBr)	2.19 (3H, s), 2.31 (6H, s), 2.60 (2H, t, J=6 Hz), 3.47 (2H, s), 3.60 (3H, s), 4.15 (2H, t, J=6 Hz), 5.05 (1H, s), 6.40 (1H, s), 6.76 (1H, s), 6.9—7.1 (1H, m), 7.18 (5H, s), 7.18 (5H, s), 7.88 (1H, d, J=5 Hz)
4d	3300, 2250, 1690, 1620, 1595, 1460 ($CHCl_3$)	2.22 (3H, s), 2.34, 2.36 (each 3H, s), 2.62 (2H, t, J=7 Hz), 3.50 (2H, s), 3.64 (3H, s), 4.18 (2H, t, J=7 Hz), 5.08 (1H, s), 6.30 (1H, s), 7.24 (5H, s), 7.47 (1H, dd, J=6, 1.5 Hz), 7.64 (1H, d, J=1.5 Hz), 8.47 (1H, d, J=6 Hz)
4e	3300, 3100, 1690, 1490, 1455, 1140 (KBr)	2.17 (3H, s), 2.31 (6H, s), 2.63 (2H, t, J=6 Hz), 3.47 (2H, s), 3.60 (3H, s), 4.13 (2H, t, J=6 Hz), 5.06 (1H, s), 6.43 (1H, s), 7.14 (5H, s), 7.31 (1H, d, J=5 Hz), 7.47 (1H, s), 8.38 (1H, d, J=5 Hz)

a) ^{1}H-NMR spectrum of **3d** was determined in DMSO-d_6–$CDCl_3$ (4:3).

mp 152—153 °C. The 2-chloroethyl ester (**1f**, 1.51 g; 3.5 mmol) and *N*-benzylmethylamine (894 mg; 7.4 mmol) were dissolved in *N*,*N*-dimethylformamide (DMF) (11 ml) and stirred at 100—110 °C for 15.5 h. The solvent was removed and H_2O was added to the residue, which was extracted with AcOEt. The extract was washed with brine, dried and concentrated. The residue was chromatographed on silica gel with

AcOEt–*n*-hexane (5 : 2, v/v) to give a crude product. The product (**2i**) was recrystallized from isopropyl ether–MeOH to give pale yellow crystals (1.14 g, 63%).

2-(*N*-Benzyl-*N*-methylamino)ethyl Methyl 4-(2-Trifluoromethyl-3-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (3e) A solution of 2-trifluoromethyl-3-pyridinecarboxaldehyde (**5p**, 1.70 g; purity 69% (w/w); 6.7 mmol), 2-chloroethyl acetoacetate (**6**, 1.16 g; 6.7 mmol), and methyl 3-aminocrotonate (**7**, 810 mg; 7.0 mmol) in 2-propanol (12 ml) was stirred at 41—42 °C for 21 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel with AcOEt–$CHCl_3$ (7 : 3, v/v). The product (**1p**) was recrystallized from isopropyl ether to yield a slightly yellow powder (2.20 g, 85%), mp 186.5—187.5 °C. To the solution of 2-chloroethyl ester (**1p**, 3.30 g; 7.91 mmol) in DMF (27 ml) *N*-benzylmethylamine 3.16 g; 26.1 mmol) was added and stirred at 102—107 °C for 45 h. After evaporation of the reaction solvent, H_2O was added to the residue, which was extracted with AcOEt. The extract was washed with brine, dried, and the solvent was evaporated off. The residue was chromatographed on silica gel with AcOEt–$CHCl_3$ (9 : 1, v/v) to give the crude product (**3e**), which was rechromatographed on silica gel with $CHCl_3$–MeOH (95 : 5, v/v), and finally purified by recrystallization from isopropyl ether to yield a slightly yellow powder (3.02 g, 76%).

2-(*N*-Benzyl-*N*-methylamino)ethyl Methyl 4-(2-Cyano-4-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (4d) A solution of 2-cyano-4-pyridinecarboxaldehyde (**5w**, 2.15 g; 16 mmol), 2-chloroethyl acetoacetate (**6**, 2.67 g; 16 mmol), and methyl 3-aminocrotonate (**7**, 1.93 g; 16 mmol) in 2-propanol (20 ml) was stirred at 30—40 °C for 20 h. The solvent was removed and the residue obtained was chromatographed on silica gel with AcOEt–*n*-hexane (15 : 11, v/v). The product (**1x**) was recrystallized from AcOEt to give pale yellow crystals (1.88 g). After the mother liquor was evaporated to dryness, the residue was recrystallized from isopropyl ether–MeOH to give pale yellow crystals (1.68 g) (total yield 3.56 g, 58%), mp 181—183 °C (isopropyl ether–MeOH). *N*-Benzylmethylamine (1.22 g; 10 mmol) was added to the solution of **1x** (1.80 g; 4.8 mmol) in DMF (14 ml) and stirred at 100—105 °C for 15 h. After the reaction solvent was removed, H_2O was added to the residue, which was extracted with $CHCl_3$. The extract was washed with brine, dried, and the solvent was evaporated off. The residue was chromatographed on silica gel with AcOEt–*n*-hexane (6 : 1, v/v) to give the product (**4d**), which was purified by rechromatography on silica gel with $CHCl_3$–MeOH (94 : 6, v/v) to yield a pale yellow oil (873 mg, 40%).

Typical Examples of Method B: 2-(*N*-Benzyl-*N*-methylamino)ethyl Methyl 4-(3-Trifluoromethyl-2-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (2c) A solution of 3-trifluoromethyl-2-pyridinecarboxaldehyde (**5b**, 2.80 g; 16 mmol), 2-(*N*-benzyl-*N*-methylamino)ethyl acetoacetate (**8**, 4.10 g; 17 mmol), and methyl 3-aminocrotonate (**7**, 1.92 g; 17 mmol) in 2-propanol (30 ml) was stirred at 42 °C for 66 h. After the solvent was removed, the residue was chromatographed on silica gel with Et_2O–MeOH (94 : 6, v/v). The product (**2c**) was recrystallized from Et_2O–isopropyl ether to give a slightly yellow powder (2.50 g, 55%).

2-(*N*-Benzyl-*N*-methylamino)ethyl Methyl 4-(4-Cyano-2-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (2e) A solution of 4-cyano-2-pyridinecarboxaldehyde (**5d**, 2.00 g; 15 mmol), **8**, (3.78 g; 15 mmol), and methyl 3-aminocrotonate (**7**, 1.80 g; 15 mmol) in 2-propanol (20 ml) was stirred at 40—45 °C for 22.5 h. After the solvent was removed, the product (**2e**) was isolated by chromatography on silica gel with AcOEt–MeOH (98 : 2, v/v). Recrystallization from isopropyl ether–MeOH gave a slightly yellow powder (2.54 g, 36%).

Spectral data of **1** and **2** are shown in Tables VIII and IX, respectively.

Method for the Preparation of Fumarates of 2 To a solution of a 1,4-dihydropyridine derivative (**2**, 5.00 mmol) in EtOH (160 ml) fumaric acid (5.00 mmol) was added and stirred at room temperature for 2 h. The solvent was evaporated to dryness to give the fumarate of **2**. All of the fumarates were prepared as amorphous solids and subjected to pharmacological testing.

Biological Test[21] The experiments were performed in groups of 3—6 male Wistar rats (10 to 11 weeks old). Systolic blood pressure (SBP) was measured in a conscious state by a tail cuff plethysmographic method with an electrosphygmomanometer (PE-300, Narco Bio-System) at 0, 1, 2, 4, 7, and 24 h after administration. The test compounds (**2a—n**, **3a—i**, and **4a—e**) were converted to the corresponding fumarates and prepared as a solution or a suspension in 0.1% Tween 80 solution and were orally administered at a dose of 25 mg/kg(10 ml/kg). Hypotensive effects are shown as maximum reductions in SBP (%) from the 0 hour values. Duration of hypotensive effect is shown in hours by which SBP recovered to half maximum reductions.

References and Notes

1) W. Vater, G. Kroneberg, F. Hoffmeister, H. Kaller, K. Meng, A. Oberdorf, W. Plus, K. Schlossmann, and K. Stoepel, *Arzneim.-Forsch.*, **22**, 1 (1972).
2) M. Iwanami, T. Shibanuma, M. Fujimoto, R. Kawai, K. Tamazawa, T. Takenaka, and M. Murakami, *Chem. Pharm. Bull.*, **27**, 1426 (1979).
3) D. J. Triggle and V. C. Swamy, *Chest* (Suppl.), **78**, 174 (1980); R. Rodenkirchen, R. Bayer, R. Steiner, F. Bossert, H. Meyer, and E. Moller, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **310**, 69 (1979); R. Mannhold, R. Rodenkirchen, and R. Bayer, *Prog. Pharmacol.*, **5**, 9 (1982); R. Fossheim, K. Svarteng, A. Mostad, C. Romming, E. Shefter, and D. J. Triggle, *J. Med. Chem.*, **25**, 126 (1982).
4) F. Bossert, H. Meyer, and E. Wehinger, *Angew. Chem. Int. Ed. Engl.*, **20**, 762 (1981) and references cited therein.
5) H. J. den Hertog and J. Overhoff, *Rec. Trav. Chim. Pays-Bas*, **69**, 468 (1950).
6) E. Ochiai and C. Kaneko, *Chem. Pharm. Bull.*, **8**, 28 (1960).
7) R. M. Johnson, *J. Chem. Soc.* (*B*), **1966**, 1058.
8) E. J. Blanz, Jr., F. A. French, J. R. DoAmaral, and D. A. French, *J. Med. Chem.*, **13**, 1124 (1970).
9) T. Okamoto and H. Tani, *Chem. Pharm. Bull.*, **7**, 925 (1959); H. Tani, *ibid.*, **7**, 930 (1959).
10) E. Matsumura, M. Ariga, and T. Ohfuji, *Bull. Chem. Soc. Jpn.*, **43**, 3210 (1970).
11) Y. Kobayashi and I. Kumadaki, *Chem. Pharm. Bull.*, **17**, 510 (1969).
12) R. Adams and S. Miyano, *J. Am. Chem. Soc.*, **76**, 3168 (1954).
13) G. Balz and G. Schiemann, *Chem. Ber.*, **60**, 1186 (1927); A. Roe, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, 1960, pp. 193—228.
14) E. Ochiai and I. Suzuki, *Chem. Pharm. Bull.*, **2**, 147 (1954).
15) A. W. Singer and S. M. McElvain, "Organic Syntheses," Col. Vol. III, John Wiley and Sons, Inc., New York, 1955, p. 740.
16) A. Ohta, A. Inoue, and T. Watanabe, *Heterocycles*, **22**, 2317 (1984).
17) Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, and E. Chikami, *Chem. Pharm. Bull.*, **18**, 2334 (1970).
18) K. E. Pfitzner and J. G. Moffat, *J. Am. Chem. Soc.*, **87**, 5661, (1965) and references cited therein.
19) The ratio of **11g** and **11h** was determined by ^{1}H-NMR by the comparison of integrated values of methylene protons at α position of the pyridine ring observed at 5.29 and 5.19 ppm, respectively.
20) G. V. D. Tiers, *J. Am. Chem. Soc.*, **82**, 5513 (1960).
21) D. Pruneau and F. Roy, *Arzneim.-Forsch.*, **37**, 416 (1987).