Synthesis and Antihypertensive Activity of 1,4-Dihydropyridine Derivatives with a 4-(Disubstituted Phenyl) Ring and an Aminoalkyl Ester Group: Highly Potent and Long-Lasting Calcium Antagonists[1)]

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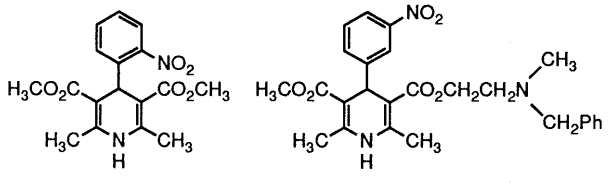
New 1,4-dihydropyridine derivatives bearing a 4-(disubstituted phenyl) ring and an aminoethyl ester or an amino-2,2-dimethylpropyl ester were synthesized and their antihypertensive activities were examined in normotensive rats and spontaneously hypertensive rats. The effects of phenyl substituents and ester groups on the antihypertensive activity are discussed. Several compounds showed a more potent antihypertensive activity than nicardipine and most compounds had a longer duration of action. Among them, 7B·HCl (TC-81) showed highly potent and long-lasting activity and was selected as a candidate for further pharmacological investigations.

Keywords 1,4-dihydropyridine derivative; calcium antagonist; antihypertensive activity; disubstituted phenyl group; spontaneously hypertensive rat

Many compounds which have different structures and pharmaceutical actions have been used in the treatment of hypertension. Calcium channel blockers are one of the most useful groups and 1,4-dihydropyridine derivatives[2)] such as nifedipine[3)] and nicardipine[4)] are typical calcium antagonists (Fig. 1). Dihydropyridine calcium antagonists have been widely used not only for hypertension but also for angina pectoris, and peripheral and cerebral vascular diseases.

Several quantitative structure–activity relationship (QSAR) studies on nifedipine-type dihydropyridines have been reported. For example, Coburn *et al.* evaluated the effects of 46 1,4-dihydropyridine derivatives on the tonic contractile response of longitudinal muscle strips of guinea pig ileum.[5)] These QSAR studies suggested that an electron-withdrawing *meta* substituent in the 4-phenyl ring of 1,4-dihydropyridine enhanced activity but lengthy (not bulky) *meta* substituents and any *para* substituent reduced activity. For a limited series of symmetrical derivatives, which had the same ester groups at the 3,5-positions of the 1,4-dihydropyridine ring, parabolic relationships existed between the hydrophobic character of the esters and calcium antagonist activity.[6)] These phenyl substituent and ester group effects appear to be expressed independently for some 1,4-dihydropyridine compounds,[7)] though this independence of substituent effects may not occur for the entire 1,4-dihydropyridine series.[8)]

In most of these QSAR studies, the structures of 1,4-dihydropyridines are limited to nifedipine-type analogs which are essentially neutral molecules. Nicardipine was developed as a water-soluble calcium antagonist characterized by a basic side chain at the 3-ester group. However, the effects of phenyl substituents on nicardipine-type derivatives are not clear. Moreover, in spite of water solubility and good absorption, nicardipine did not have sufficiently long antihypertensive action by oral administration because of a marked first-pass effect in the liver.[9)] We attempted to synthesize new highly potent 1,4-dihydropyridines by introducing two electron-withdrawing substituents in the 4-phenyl ring. Even more importantly, we had tried earlier to make long-acting derivatives[10)] by introducing a novel branched aminoalkyl ester group that might be expected to delay metabolism of these derivatives.



nifedipine nicardipine

Fig. 1. Typical 1,4-Dihydropyridine Calcium Antagonists

Chemistry

The 1,4-dihydropyridines listed in Table I were synthesized as shown in Chart 1. These compounds can be divided into two groups according to their chemical structure. The compounds in series A have a disubstituted phenyl ring and (*N*-benzyl-*N*-methylamino)ethyl ester group. The compounds in series B have a disubstituted phenyl ring and 3-(*N*-benzyl-*N*-methylamino)-2,2-dimethylpropyl ester which is characterized by a novel branched alkyl moiety.

These new 1,4-dihydropyridines were prepared by three modified Hantzsch reactions. A mixture of disubstituted benzaldehyde, acetoacetate derivative and methyl 3-aminocrotonate was refluxed in 2-propanol to give the 1,4-dihydropyridine I (method A). Disubstituted benzaldehyde and methyl acetoacetate were treated under acidic conditions (HCl gas bubbling)[11)] and reacted with 3-aminocrotonate derivative in 2-propanol to afford the 1,4-dihydropyridine in good yield (method B). Using benzylidene compounds derived from benzaldehyde and methyl acetoacetate, the 1,4-dihydropyridines were also synthesized (method C).

Disubstituted benzaldehydes were prepared using the methods: (a) chromium oxidation of toluene derivatives, (b) replacement of chlorine atom by fluorine atom and/or (c) the Schiemann reaction.[12)] Typical procedures are described in the experimental section.

3-(*N*-Benzyl-*N*-methylamino)-2,2-dimethylpropyl derivatives (**16**, **17**) were prepared as shown in Chart 2. Treatment of *N*-benzyl-*N*-methylamine hydrochloride with isobutylaldehyde and paraformaldehyde was followed by reduction with $NaBH_4$ to give alcohol **15**.[13)] Reaction of **15** with diketene in benzene provided acetoacetate ester **16**. Aminocrotonate **17** was derived from **16** with ethanolic ammonia.

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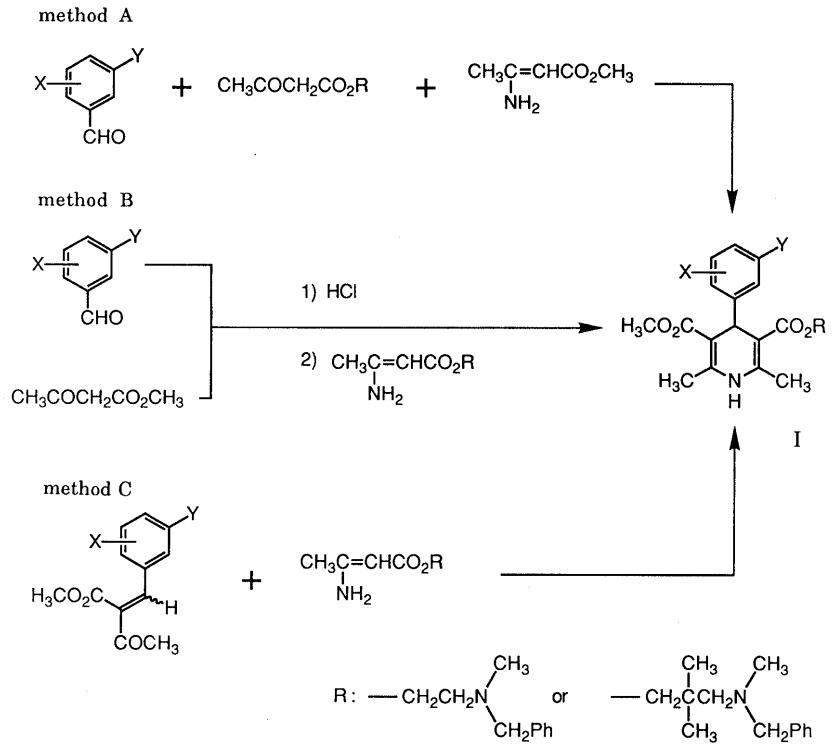
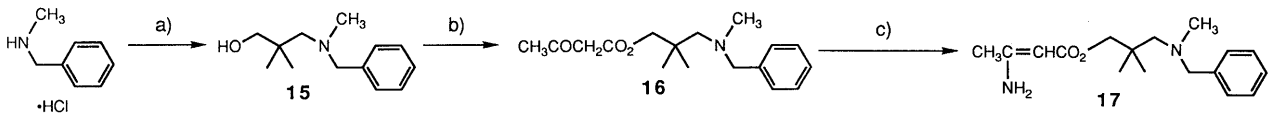


Chart 1



a) (i) isobutylaldehyde, paraformaldehyde / 2-PrOH, reflux; (ii) $NaBH_4$ / MeOH, r.t. (75 %).
b) diketene / benzene, 70 °C (96 %). c) NH_3 / EtOH, 0 °C → r.t. (93 %).

Chart 2

Structure–Activity Relationships and Discussion

We synthesized new 1,4-dihydropyridines and examined their antihypertensive activities in normotensive rats when administered intravenously (Table I). Figure 2 shows the correlations between the antihypertensive activity and the duration of action of these compounds.

First of all, in order to increase antihypertensive activity, we introduced two electron-withdrawing substituents[5] in the 4-phenyl ring of 1,4-dihydropyridine. Since several previous studies suggested that hydrogen atom was preferable at the *para* position of the 4-phenyl ring, we chose 2,3- or 2,5-disubstituted phenyl rings. Substituents were selected from NO_2, Cl or F. As Fig. 2 shows, each compound in series A was a little more active or had a longer duration of action than nicardipine. The most active compound, **2A**, displayed about two times more activity than nicardipine.

Second, we introduced the 2,2-dimethylaminopropyl ester group into the side chain of 1,4-dihydropyridine. Because of the bulkiness and hydrophobicity of this branched ester group, these compounds were expected to resist hydrolysis to give carboxylic acids that had no antihypertensive activity. In fact, each compound in series B had a much longer-lasting antihypertensive action than nicardipine and also than the series A compounds which had the same

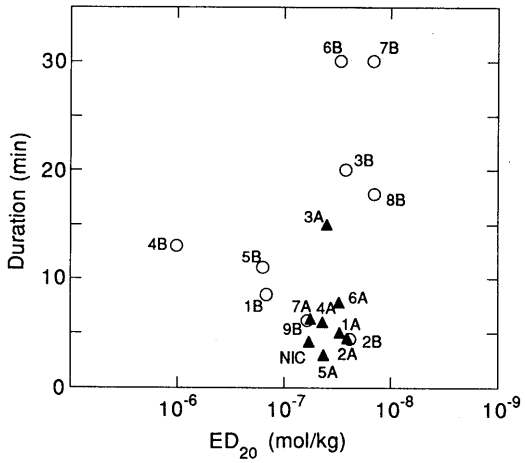


Fig. 2. Correlation between Antihypertensive Activity and Duration of 1,4-Dihydropyridines (I)

▲, series A compounds; ○, series B compounds. Biological data taken from Table I were used. Experimental conditions are described in Experimental.

disubstituted phenyl ring. The values of 50% recovery time of compounds **6B** and **7B** were more than 30 min for the ED_{20} does, but those of compounds **6A** and **7A** were 7.8 and 6.3 min, respectively.

Surprisingly, compounds **3B** and **7B** showed much higher

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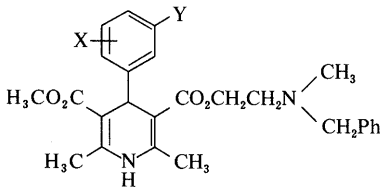
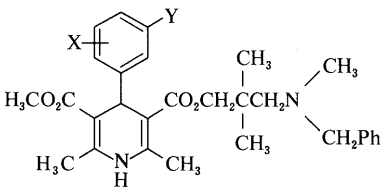
TABLE I. Physical Data and Antihypertensive Activities of 1,4-Dihydropyridines (I)



1A—7A, NIC



1B—9B

Compound No.	Formula[a]	X	Y	Method	Yield (%)	mp (°C)	ED_{20}[b] (nmol/kg)	Duration[c] (min)
1A·HCl	$C_{26}H_{28}Cl_2N_2O_4 \cdot HCl$	2-Cl	3-Cl	A	58	173—177	30.0	5.0 (30 μg/kg)
1B·HCl	$C_{29}H_{34}Cl_2N_2O_4 \cdot HCl$	2-Cl	3-Cl	A	48	184—188	145	8.5 (30 μg/kg)
2A·HCl	$C_{26}H_{28}ClFN_2O_4 \cdot HCl$	2-Cl	3-F	A	59	177—182	25.4	4.5 (30 μg/kg)
2B·HCl	$C_{29}H_{34}ClFN_2O_4 \cdot HCl$	2-Cl	3-F	A	32	172—174	23.9	4.4 (30 μg/kg)
3A·HCl	$C_{26}H_{28}ClFN_2O_4 \cdot HCl$	2-F	3-Cl	A	50	170—175	39.6	15 (30 μg/kg)
3B·HCl	$C_{29}H_{34}ClFN_2O_4 \cdot HCl$	2-F	3-Cl	B	47	195—198	26.3	20 (10 μg/kg)
4A·HCl	$C_{26}H_{28}ClN_3O_6 \cdot HCl$	2-NO_2	3-Cl	A	55	179—184	43.3	6.0 (30 μg/kg)
4B·HCl	$C_{29}H_{34}ClN_3O_6 \cdot HCl$	2-NO_2	3-Cl	B	33	182—187	1010	13 (1000 μg/kg)
5A·HCl	$C_{26}H_{28}ClN_3O_6 \cdot HCl$	2-Cl	3-NO_2	A	49	150—154	42.5	3.0 (30 μg/kg)
5B·HCl	$C_{29}H_{34}ClN_3O_6 \cdot HCl$	2-Cl	3-NO_2	B	56	197—201	157	11 (100 μg/kg)
6A·HCl	$C_{26}H_{28}FN_3O_6 \cdot HCl$	2-F	3-NO_2	A	55	192—196	30.5	7.8 (30 μg/kg)
6B·HCl	$C_{29}H_{34}FN_3O_6 \cdot HCl$	2-F	3-NO_2	A, B, C	43[d]	147—152	29.3	>30 (10 μg/kg)
7A·HCl	$C_{26}H_{28}FN_3O_6 \cdot HCl$	2-F	5-NO_2	A	57	168—173	56.2	6.3 (30 μg/kg)
7B·HCl (TC-81)	$C_{29}H_{34}FN_3O_6 \cdot HCl$	2-F	5-NO_2	A, B, C	47[d]	204—210	14.4	>30 (10 μg/kg)
8B·HCl	$C_{29}H_{34}ClN_3O_6 \cdot HCl$[e]	2-Cl	5-NO_2	A	33	Amorphous	14.2	17.8 (10 μg/kg)
9B·HCl	$C_{29}H_{34}ClFN_2O_4 \cdot HCl$	2-F	5-Cl	A	36	178—183	60.1	6.1 (30 μg/kg)
NIC[f]		—	3-NO_2				58.1	4.2 (30 μg/kg)

a) All compounds were analyzed for C, H and N; the analytical results were within ±0.4% of the calculated values. *b*) 20% effective dose for reducing blood pressure in anesthesized normotensive rats after i.v. administration. *c*) Half-life of the action when test compound of the amount in parentheses was administered. *d*) The yield by method B. *e*) This compound was not analyzed. *f*) Nicardipine hydrochloride.

activity than compounds **3A**, **7A** and nicardipine, whereas each set of compounds **2A** and **2B**, and compounds **6A** and **6B** had a similar antihypertensive activity, respectively. The activity of compound **7B** was about four times more than **7A** and nicardipine. Compound **8B** also had high activity. In contrast to these active compounds, the activities of compounds **1B**, **4B** and **5B** were drastically lowered. These less active compounds have a 2,3-disubstituted phenyl ring and their substituents are Cl or NO_2, which are rather bulky. In the high-potent and long-lasting active compounds (**3B**, **6B**—**8B**), the substituents are at the 2,3-positions or 2,5-positions and a fluorine atom is at the *ortho* position except for compound **8B**. Our results where the 2,5-disubstituted derivative, **8B**, was more active than the 2,3-disubstituted derivative, **5B**, showed a different manner relative to the nifedipine analogs.[14] The most active compounds, **7B** and **8B**, had a *meta* nitro substituent and an *ortho* fluorine or chlorine atom. In the longest lasting active compounds, **6B** and **7B**, and *ortho* fluorine atom and a *meta* nitro substituent existed.

The results of series A compounds suggested that antihypertensive activity was moderately increased by the introduction of two electron-withdrawing substituents onto the 4-phenyl ring. From the results of series B compounds, we concluded that the duration of action was prolonged by changing from the aminoethyl ester group to the branched dimethylaminopropyl ester. However, with combinations of these variations, the effects of phenyl substituents and the ester group did not seem to be independent. Compounds in series B were separated into two groups. One of them contained highly potent and long-lasting active compounds and the other included milder but long-lasting active compounds. From these results, we considered that introduction of the disubstituted phenyl ring and dimethylaminopropyl moiety was quite effective for antihypertensive activity. However, two bulky substituents at the 2,3-positions of the phenyl ring weakened the activity and a fluorine atom at the *ortho* position was preferable. The 2-fluoro-5-nitrophenyl ring and 2,2-dimethylaminopropyl ester group in compound **7B** then seemed to be the best combination for highly potent and long-lasting antihypertensive activity.

Some of the 1,4-dihydropyridines in Table I were selected in consideration of their high activity and long duration of action and their antihypertensive activities were examined in spontaneously hypertensive rats (SHR) using oral administration (Table II). Compounds **3B**, **6B** and **7B** showed high activity and longer-lasting actions under these experimental conditions. The most active compound, **7B**, had approximately ten times more potent and two times longer-lasting antihypertensive activity than nicardipine. The lipophilicities of these series B compounds are higher than that of nicardipine and this may make these compounds more easily partitioned into the cell membrane of vascular smooth muscle where the binding events occur. In a pharmacokinetics study in rats,[15] levels of **7B** in the aorta were found to be about ten times higher than those of nicardipine, though plasma levels of **7B** were two or three times higher and half-lives in plasma were similar for the two compounds. This suggests that the high potency and

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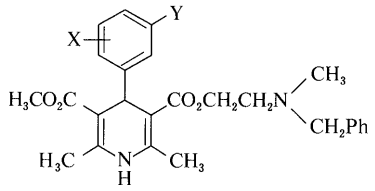
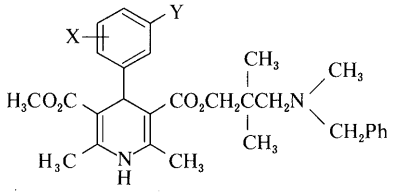
TABLE II. Antihypertensive Activities of 1,4-Dihydropyridines (I) in SHR



3A, NIC



3B, 6B, 7B

Compound No.	X	Y	*n*	ED_{20} (mg/kg)[a]	Duration (h)[b]
3A·HCl	2-F	3-Cl	3	4.6	3.3
3B·HCl	2-F	3-Cl	3	1.1	3.0
6B·HCl	2-F	3-NO_2	4	1.2	3.0
7B·HCl (TC-81)	2-F	5-NO_2	4	0.4	3.9
NIC[c]	—	3-NO_2	4	5.2	2.0

a) 20% effective dose for reducing blood pressure after p.o. administration. *b*) 50% recovery time from maximal hypotension for the ED_{20} dose. *c*) Nicardipine hydrochloride.

long-lasting antihypertensive effect of **7B** may be due to pharmacokinetics in the aorta.

From these profiles, we hope **7B**·HCl (TC-81) will prove to be a useful drug for hypertension. It is now under clinical investigation.

Experimental

All melting points were determined with Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Jasco A-102 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-90H spectrometer with Me_4Si as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were taken on a Hitachi M-80B instrument. Column chromatography was performed on 200—300 silica gel from Wako.

Disubstituted Benzaldehydes 2,3-Dichlorobenzaldehyde and 2-chloro-5-nitrobenzaldehyde were purchased from Aldrich. 3-Chloro-2-fluorotoluene was converted to 3-chloro-2-fluorobenzaldehyde in the same manner as described for the preparation of 2-chloro-3-nitrobenzaldehyde (**11**). 3-Chloro-2-nitrobenzaldehyde was synthesized from 3-chloro-2-nitrobenzyl alcohol by the Swern oxidation.[16] 2-Fluoro-5-nitrobenzaldehyde[17] was prepared from 2-fluorobenzaldehyde. Other disubstituted benzaldehydes were synthesized as follows.

2-Chloro-3-nitrobenzaldehyde (11) To a solution of 2-chloro-3-nitrotoluene (3.02 g, 17.7 mmol) in acetic anhydride (20 ml) was added dropwise concentrated H_2SO_4 (20 ml) with ice-cooling. Then, chromium trioxide (5.0 g, 47.5 mmol) in acetic anhydride (20 ml) was added dropwise over the period of 1 h maintaining a constant temperature of $<10\,°C$. After being stirred for another 2 h, the reaction mixture was poured into ice water (150 ml) and extracted with CH_2Cl_2. The organic phase was washed with 2% $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed to give a solid which was added to the mixture of dioxane (10 ml), water (4 ml) and concentrated H_2SO_4 (4 ml). The mixture was refluxed for 30 min and extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent afforded **11** (1.88 g, 58%) as a pale yellow solid. Recrystallization from CCl_4 gave analytically pure **11**, mp 98 °C (lit.[18] 95—96 °C). IR (KBr): 1692, 1590, 1540, 1348 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.48—7.77 (1H, m), 8.03—8.29 (2H, m), 10.64 (1H, s).

5-Chloro-2-fluorobenzaldehyde (12) Under the same conditions as described for the preparation of **11**, 5-chloro-2-fluorotoluene was converted to **12**, mp 32—33 °C. IR (KBr): 1688, 1604, 1476, 826 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.14 (1H, dd, J=9 Hz), 7.56 (1H, ddd, J=3, 5, 9 Hz), 8.30 (1H, dd, J=3, 6 Hz), 10.31 (1H, s). MS *m/z*: 158 (M^+), 157 (M^+-H), 129 (M^+-CHO). HRMS *m/z*: Calcd for C_7H_4ClF–H: 156.9856. Found: 156.9872.

2-Fluoro-3-nitrobenzaldehyde (13) To a solution of **11** (15.1 g, 81.4 mmol) in anhydrous dimethylformamide (75 ml) was added spray-dried KF[19] (10.2 g, 174 mmol) and the mixture was heated at 150 °C for 4 h. Under reduced pressure dimethylformamide was removed to leave a residue and CH_2Cl_2 was added to the residue. The solution was washed with water and dried over Na_2SO_4. Short column chromatography on aluminum oxide (Merck 1077, 25 g) eluting with CH_2Cl_2 followed by distillation (105 °C/50 mmHg) gave **13** (11.4 g, 82%) as a pale yellow crystalline solid, mp 46—47 °C. IR (KBr): 1698, 1610, 1534, 1348 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.69 (1H, m), 8.14—8.56 (2H, m), 10.54 (1H, s). MS *m/z*: 169 (M^+), 168 (M^+-H).

2-Chloro-3-fluorobenzaldehyde (14) i) 2-Chloro-3methylaniline was converted to 2-chloro-3-methylbenzenediazonium tetrafluoroborate using the method of Doyle and Bryker.[20] One of several portions of 2-chloro-3-methylbenzenediazonium tetrafluoroborate (24.9 g, 104 mmol) was added to a 500 ml round-bottled flask and heated to 160 °C. The decomposition reaction of diazonium tetrafluoroborate proceeded smoothly, and another portion of diazonium salts was subsequently added. After all the diazonium salts had reacted, CH_2Cl_2 was added to the reaction mixture and the organic phase was washed with $NaHCO_3$ aq. and dried over $MgSO_4$. Removal of the solvent gave an orange oil which was purified by short column chromatography on silica gel eluting with hexane followed by distillation (81 °C/50 mmHg) to provide 2-chloro-3-fluorotoluene (8.14 g, 54%) as a colorless oil. IR (neat): 1606, 1460, 1266, 786 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 6.9—7.1 (3H, m). MS *m/z*: 144 (M^+). HRMS *m/z*: Calcd for C_7H_6ClF: 144.0142. Found: 144.0136.

ii) 2-Chloro-3-fluorotoluene was oxidized under the same conditions as described for the preparation of **11** to give **14** as a pale yellow oil (41—45 °C/1 mmHg). IR (neat): 1692, 1460, 1262, 782 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.3—7.4 (2H, m), 7.7—7.8 (1H, m), 10.46 (1H, s). MS *m/z*: 158 (M^+), 157 (M^+-H), 129 (M^+-CHO). HRMS *m/z*: Calcd for C_7H_4ClFO–H: 156.9856. Found: 156.9876.

3-(*N*-Benzyl-*N*-methylamino)-2,2-dimethylpropanol (15) To a solution of *N*-benzyl-*N*-methylamine hydrochloride (27.2 g, 172 mmol) in 2-propanol (80 ml) were added isobutylaldehyde (12.4 g, 172 mmol) and paraformaldehyde (11.4 g, 380 mmol). The mixture was refluxed for 6 h. The solvent was removed under reduced pressure to leave a residue. The residue was dissolved in MeOH (200 ml) and cooled with ice water. Sodium borohydride (12.0 g, 317 mmol) was added to the mixture in small portions with stirring. Then, the reaction mixture was stirred for 3 h at room temperature. The solvent was removed leaving a residue. To the residue was added 20% NaOH (40 ml) and the mixture was extracted with Et_2O. The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue which was purified by distillation (122—124 °C/2 mmHg) to provide **15** (26.6 g, 75%) as a colorless oil. IR (neat): 2960, 1448, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, s), 2.24 (3H, s), 2.49 (2H, s), 3.46 (2H, s), 3.55 (2H, s), 7.30 (5H, s).

3-(*N*-Benzyl-*N*-methylamino)-2,2-dimethylpropyl Acetoacetate (16) To a solution of **15** (2.07 g, 10.0 mmol) in benzene (1 ml) was added dropwise diketene (1.00 g, 11.9 mmol) with stirring. After stirring for another 1.5 h at 70 °C, the solvent was removed to leave an oily residue which was purified by chromatography on silica gel eluting with hexane–AcOEt (1 : 1, v/v) to afford **16** (2.8 g, 96%) as a colorless oil. IR (neat): 1740, 1716, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, s), 2.20 (3H, s), 2.25 (3H, s), 2.34 (2H, s), 3.41 (2H, s), 3.55 (2H, s), 4.00 (2H, s), 7.29 (5H, s). *Anal.* Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.72; H, 8.53; N, 4.67.

3-(*N*-Benzyl-*N*-methylamino)-2,2-dimethylpropyl 3-Aminocrotonate (17) A solution of **16** (5.07 g, 17.4 mmol) in ethanol (15 ml) was cooled with ice water. Gaseous ammonia was bubbled through the solution for 30 min and the solution was allowed to stand at room temperature overnight. To the solution was added ice water and a precipitated solid was collected by filtration, washed with water and dried under reduced pressure to provide **17** (4.70 g, 93%). Recrystallization from CCl_4 gave analytically pure crystals, mp 68—70 °C. IR (KBr): 1648, 1552, 1292, 1164 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, s), 1.88 (3H, s), 2.18 (3H, s), 2.36 (2H, s), 3.57 (2H,

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TABLE. III. Spectral Data of 1,4-Dihydropyridines (I)

Compound No.	IR ($CHCl_3$) ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
1A	3450, 1690, 1616, 1464, 1296, 1272, 1134, 1114, 1100	2.17 (3H, s), 2.30 (6H, s), 2.60 (2H, t, J=6 Hz), 3.47 (2H, s), 3.60 (3H, s), 4.16 (2H, t, J=6 Hz), 5.46 (1H, s), 5.67 (1H, br s), 6.9—7.4 (3H, m), 7.25 (5H, s)
1B	3450, 1686, 1616, 1464, 1298, 1116, 1098	0.86 (6H, s), 2.09 (3H, s), 2.27 (8H, s), 3.46 (2H, s), 3.61 (3H, s), 3.93 (2H, s), 5.48 (1H, s), 5.80 (1H, br s), 6.9—7.3 (3H, m), 7.25 (5H, s)
2A	3450, 1688, 1616, 1464, 1300, 1272, 1138, 1114, 1106	2.17 (3H, s), 2.30 (6H, s), 2.68 (2H, t, J=6 Hz), 3.47 (2H, s), 3.60 (3H, s), 4.16 (2H, t, J=6 Hz), 5.42 (1H, s), 5.64 (1H, br s), 6.9—7.3 (8H, m)
2B	3450, 1688, 1618, 1464, 1300, 1116, 1100, 1012	0.86 (6H, s), 2.10 (3H, s), 2.28 (8H, s), 3.47 (2H, s), 3.62 (3H, s), 3.82 (1H, d, J=11 Hz), 4.05 (1H, d, J=11 Hz), 5.46 (1H, s), 5.60 (1H, br s), 6.8—7.3 (8H, m)
3A	3450, 1688, 1616, 1452, 1296, 1268, 1116, 1100	2.19 (3H, s), 2.31 (6H, s), 2.62 (2H, t, J=6 Hz), 3.50 (2H, s), 3.61 (3H, s), 4.14 (2H, t, J=6 Hz), 5.25 (1H, s), 5.68 (1H, br s), 6.8—7.3 (8H, m)
3B	3460, 1688, 1616, 1454, 1298, 1268, 1116, 1098	0.86 (3H, s), 0.89 (3H, s), 2.09 (3H, s), 2.29 (5H, s), 2.33 (3H, s), 3.46 (2H, s), 3.64 (3H, s), 3.90 (2H, s), 5.27 (1H, s), 5.71 (1H, br s), 6.8—7.3 (8H, m)
4A	3450, 1692, 1618, 1464, 1366, 1300, 1272, 1110	2.19 (3H, s), 2.30 (6H, s), 2.67 (2H, t, J=6 Hz), 3.50 (2H, s), 3.63 (3H, s), 4.20 (2H, t, J=6 Hz), 5.26 (1H, s), 5.81 (1H, br s), 7.2—7.4 (3H, m), 7.26 (5H, s)
4B	3450, 1688, 1598, 1458, 1360, 1294, 1106, 1090	0.86 (3H, s), 0.87 (3H, s), 2.10 (3H, s), 2.28 (8H, s), 3.47 (2H, s), 3.65 (3H, s), 3.89 (1H, d, J=11 Hz), 4.04 (1H, d, J=11 Hz), 5.34 (1H, s), 5.70 (1H, br s), 7.1—7.4 (8H, m)
5A	3450, 1692, 1616, 1466, 1354, 1300, 1272, 1114	2.17 (3H, s), 2.31 (6H, s), 2.59 (2H, t, J=6 Hz), 3.47 (2H, s), 3.60 (3H, s), 4.16 (2H, t, J=6 Hz), 5.50 (1H, s), 5.75 (1H, br s), 7.1—7.7 (3H, m), 7.25 (5H, s)
5B	3450, 1684, 1600, 1462, 1360, 1298, 1110	0.86 (6H, s), 2.10 (3H, s), 2.29 (8H, s), 3.47 (2H, s), 3.61 (3H, s), 3.82 (1H, d, J=11 Hz), 4.05 (1H, d, J=11 Hz), 5.53 (1H, s), 5.67 (1H, br s), 7.1—7.6 (3H, m), 7.26 (5H, s)
6A	3440, 1692, 1614, 1462, 1348, 1300, 1114, 1100	2.18 (3H, s), 2.33 (6H, s), 2.61 (2H, t, J=6 Hz), 3.49 (2H, s), 3.61 (3H, s), 4.14 (2H, t, J=6 Hz), 5.32 (1H, s), 5.73 (1H, br s), 7.06 (1H, t, J=8 Hz), 7.26 (5H, s), 7.5—7.9 (2H, m)
6B	3450, 1684, 1606, 1464, 1348, 1180, 1116, 1096	0.87 (3H, s), 0.89 (3H, s), 2.10 (3H, s), 2.31 (5H, s), 2.33 (3H, s), 3.47 (2H, s), 3.63 (3H, s), 3.92 (2H, s), 5.34 (1H, s), 5.85 (1H, br s), 7.1—7.3 (6H, m), 7.5—7.9 (2H, m)
7A	3450, 1690, 1616, 1464, 1344, 1304, 1116, 1100	2.18 (3H, s), 2.35 (6H, s), 2.61 (2H, t, J=6 Hz), 3.49 (2H, s), 3.61 (3H, s), 4.14 (2H, t, J=6 Hz), 5.31 (1H, s), 5.76 (1H, br s), 7.00 (1H, dd, J=9 Hz), 7.25 (5H, s), 7.9—8.3 (2H, m)
7B	3450, 1686, 1616, 1466, 1346, 1308, 1118, 1100	0.86 (3H, s), 0.89 (3H, s), 2.10 (3H, s), 2.30 (2H, s), 2.33 (3H, s), 2.36 (3H, s), 3.47 (2H, s), 3.64 (3H, s), 3.91 (2H, s), 5.34 (1H, s), 5.83 (1H, br s), 7.03 (1H, dd, J=9 Hz), 7.25 (5H, s), 7.9—8.1 (1H, m), 8.19 (1H, dd, J=3, 6 Hz)
8B	3450, 1692, 1620, 1464, 1344, 1304, 1116, 1094, 1012	0.87 (6H, s), 2.10 (3H, s), 2.28 (2H, s), 2.32 (6H, s), 3.46 (2H, s), 3.61 (3H, s), 3.87 (1H, d, J=10 Hz), 4.01 (1H, d, J=10 Hz), 5.49 (1H, s), 5.87 (1H, br s), 7.25 (5H, s), 7.36 (1H, d, J=9 Hz), 7.86 (1H, dd, J=3, 9 Hz), 8.21 (1H, d, J=3 Hz)
9B	3460, 1692, 1616, 1468, 1300, 1272, 1116, 1102	0.87 (3H, s), 0.90 (3H, s), 2.10 (3H, s), 2.30 (5H, s), 2.34 (3H, s), 3.48 (2H, s), 3.64 (3H, s), 3.91 (2H, s), 5.24 (1H, s), 5.68 (1H, br s), 6.82 (1H, dd, J=9 Hz), 6.9—7.3 (7H, m)

s), 3.91 (2H, s), 4.53 (1H, s), 7.3 (5H, m). *Anal.* Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.05; H, 9.00; N, 9.49.

3-(*N*-Benzyl-*N*-methylamino)-2,2-dimethylpropyl Methyl 4-(2-Fluoro-5-nitrophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (7B) Method A: To a solution of 2-fluoro-5-nitrobenzaldehyde (169 mg, 1.00 mmol) in 2-propanol (1 ml) was added **16** (290 mg, 0.99 mmol) and methyl 3-aminocrotonate (115 mg, 1.00 mmol). This mixture was refluxed for 8 h. The solvent was removed and the residue was purified by chromatography on silica gel eluting with hexane–AcOEt (2:1, v/v) to provide **7B** (184 mg, 34%). Recrystallization from hexane–AcOEt gave analytically pure crystals, mp 126—127 °C. *Anal.* Calcd for $C_{29}H_{34}FN_3O_6$: C, 64.55; H, 6.35; N, 7.79. Found: C, 64.58; H, 6.33; N, 7.77. Spectral data of **7B** are shown in Table III.

Hydrochloride of **7B** (TC-81): A solution of **7B** in CH_2Cl_2 was treated with 1 N HCl. The CH_2Cl_2 phase was separated, washed with H_2O and dried over Na_2SO_4. The solvent was removed and the residue was crystallized from acetone to give **7B**·HCl as pale yellow crystals, mp 204—210 °C. IR (KBr): 1672, 1486, 1346, 1206 cm^{-1}. *Anal.* Calcd for $C_{29}H_{34}FN_3O_6$·HCl: C, 60.47; H, 6.12; N, 7.29. Found: C, 60.41; H, 6.23; N, 7.12.

Method B: A mixture of 2-fluoro-5-nitrobenzaldehyde (6.76 g, 40.0 mmol) and methyl acetoacetate (4.74 g, 40.9 mmol) in toluene (100 ml) was cooled with ice water. Gaseous hydrogen chloride was bubbled through the solution for 15 min and the solution was stirred for another 1 h and allowed to stand overnight at room temperature. The reaction mixture was washed with water (100 ml) and brine (2 × 100 ml). Removal of the solvent gave a yellow oil (13.1 g). To the oil was added 2-propanol (80 ml), **17** (11.6 g, 40.0 mmol) and triethylamine (5.6 ml) and the mixture was refluxed for 3 h. The solvent was removed and AcOEt (40 ml) was added to the residue. The organic phase was washed with H_2O and brine. To the solution was added AcOEt (40 ml), hexane (40 ml) and 1 N HCl (50 ml). The upper organic phase was removed by decantation and the lower phase was extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4 and the solvent was removed to afford **7B**·HCl. Recrystallization from acetone gave pure **7B**·HCl (10.7 g, 47%).

Method C: A mixture of methyl 2-(2-fluoro-5-nitrobenzylidene)acetoacetate (807 mg, 3.02 mmol) and **17** (896 mg, 3.09 mmol) in 2-propanol (5 ml) was refluxed for 2 h. The solvent was removed and to the residue was added CH_2Cl_2 and 1 N HCl. The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent afforded an orange oil which was crystallized from acetone to give **7B**·HCl (1.15 g, 66%).

Dihydropyridines **1A**—**7A**, **1B**, **2B**, **8B** and **9B** were synthesized similarly by method A. Compounds **3B**—**5B** were prepared by method B. Compound **6B** was obtained by method A, B and C, respectively. The physical data of these compounds and their hydrochlorides are shown in Tables I and III.

Antihypertensive Activity i) In Normotensive Rats: Three or four male Wistar rats (weighing about 300—350 g) per group were used. The rats were anesthetized with urethane (500 mg/kg) and α-chloralose (100 mg/kg) administered intraperitoneally. The test compounds, prepared as a solution of physiological saline containing 10% or a lower amount of ethanol, were intravenously injected through a catheter inserted into the femoral vein of the rats. The blood pressure was recorded with a pressure transducer *via* the catheter inserted into the femoral artery. Antihypertensive activity of the test compound was indicated by the dose (ED_{20} nmol/kg) required to decrease blood pressure by 20% as compared with that before administration. To determine the duration of antihypertensive action of the test compound, half-life of the action ($T_{1/2}$) was measured. These values were calculated from dose–response curves or time-course curves of mean blood pressure.

ii) In SHR: Three or four male SHR per group were used. A polyethylene catheter was inserted into the femoral artery of male SHR under ether anesthesia and was connected to a pressure transducer. The rats were then fixed in Bollman cages. After one hour or more following the rats recovery from anesthesia, the test compounds prepared as a suspension in 0.5% carboxymethyl cellulose sodium salts were administered orally. Antihypertensive activity of the test compound was indicated by 20% effective

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dose (ED_{20} mg/kg) and the duration of action was measured by 50% recovery time ($T_{1/2}$) from maximal hypotension.

References and Notes

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