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Novel 1,4-Dihydropyridine Calcium Antagonists. II. Synthesis and Antihypertensive Activity of 3-[4-(Substituted Amino)phenylalkyl]ester Derivatives

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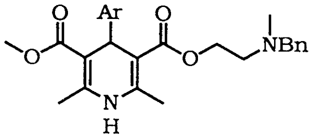
Novel 1,4-dihydropyridine derivatives bearing 3-[4-(substituted amino)phenylalkyl]ester side chains were prepared and tested for their antihypertensive activity in spontaneously hypertensive rats. Most compounds showed a more potent antihypertensive effect and a longer duration of action than nicardipine. The derivatives with a benzhydrylpiperazinyl and a benzhydrylpiperidinyl group were distinctive. 2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (4e), its 4-(4-cyano-2-pyridyl) analogue (4f), its 3-[4-(4-benzhydryl-1-piperazinyl)phenyl]propyl ester analogue (4h), its 2-[4-(4-benzhydryl-1-piperidinyl)phenyl]ethyl ester analogue (4j), and its 2-[4-(1-benzhydryl-4-piperidinyl)phenyl]ethyl ester analogue (4k) were selected as candidates for further pharmacological investigations.

Keywords 1,4-dihydropyridine-3-[4-(substituted amino)phenylalkyl]ester; calcium antagonist; antihypertensive effect; benzhydrylpiperazinyl group; benzhydrylpiperidinyl group; spontaneously hypertensive rat

Introduction

In a previous paper,1) we reported the syntheses and hypotensive effects of 4-(substituted pyridyl)-1,4-dihydropyridine derivatives, and three compounds (**1**, **2**, and **3**) were selected as candidates for further elaboration of their structures (Fig. 1).

We prepared 1,4-dihydropyridine calcium antagonists which have a novel ester side chain containing one or more amine functions and a benzene ring placed between the amine and the alkylene groups, expecting that the metabolism could be delayed to some extent by introducing such functions. We are interested in how the lipophilic benzene ring interacts with a receptor and influence its pharmacological properties. Although there are a few reports2) on such derivatives bearing alkyl-, alkoxy-, or halo-substituted phenylalkyl ester side chains, their pharmacological profiles have never been reported in detail. Alkylamino and aralkylamino, in particular, either piperidinyl or piperazinyl with a benzhydryl group were selected as functional groups for the substituent on the benzene ring, because this type of moiety has been employed in some vasodilating drugs (*e.g.*, cinnarizine3) and flunarizine3)) and a dihydropyridine calcium antagonist CV-4093 (manidipine).4)

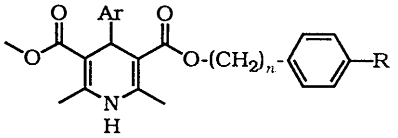


1 : Ar= 4-CN-2-Py

2 : Ar= $3-CF_3-2-Py$

3 : Ar= $2-CF_3-3-Py$

Fig. 1



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Ar : $3-NO_2-Ph$, 4-CN-2-Py, and $3-CF_3-2-Py$

R : dimethylamino, dibenzylamino, benzhydrylpiperazino, and benzhydrylpiperidinyl

n = 2 or 3

Fig. 2

Thus, we synthesized the series of compounds shown in Fig. 2 and some related compounds and tested for their antihypertensive effects in spontaneously hypertensive rats (SHR); the results are described in this paper.

Chemistry Methods for the Construction of 1,4-Dihydropyridine Skeleton Prepared compounds (**4a**—**m**) are listed in Table I. For the substituent at the 4-position of the 1,4-dihydropyridine ring, we employed 4-cyano-2-pyridyl and 2-trifluoromethyl-3-pyridyl groups, which were originally developed in our laboratory,1) in addition to the most popular 3-nitrophenyl group. They were synthesized either *via* the Hantzsch reaction (method A),5) its modified reaction (method B), or through the esterification reaction of 1,4-dihydropyridine monocarboxylic acid (**9**) with alcohols (**10**) (method C)6) (Chart 1).

Method for the Synthesis of Side Chains Alcohols employed in the preparation of the ester side chians of each derivatives were synthesized as shown in Charts 2, 3 and 4.

Preparation of Side Chains of 4c—g, 4i, 4j and 4l (Charts 2 and 3) Compound **10b**, the side chain of **4c** and **4d**, were obtained by direct dibenzylation of *p*-aminophenethyl alcohol (**12**). Compounds **10c** and **10d**, the side chains of **4e**—**g** and **4i**, were easily derived from **12** by treatment with bis(2-chloroethyl)amine hydrochloride in refluxing BuOH,7) and the following benzhydrylation with benzhydryl bromide and 4,4′-difluorobenzhydryl bromide, respectively. Compound **10e**, the side chain of **4l**, was also synthesized from **12** *via* **15**. The reductive amination of **14** with **12** using $NaBH_3CN$ as a reducing agent gave **15** in moderate yield.8) Compound **15** was then methylated by reductive alkylation

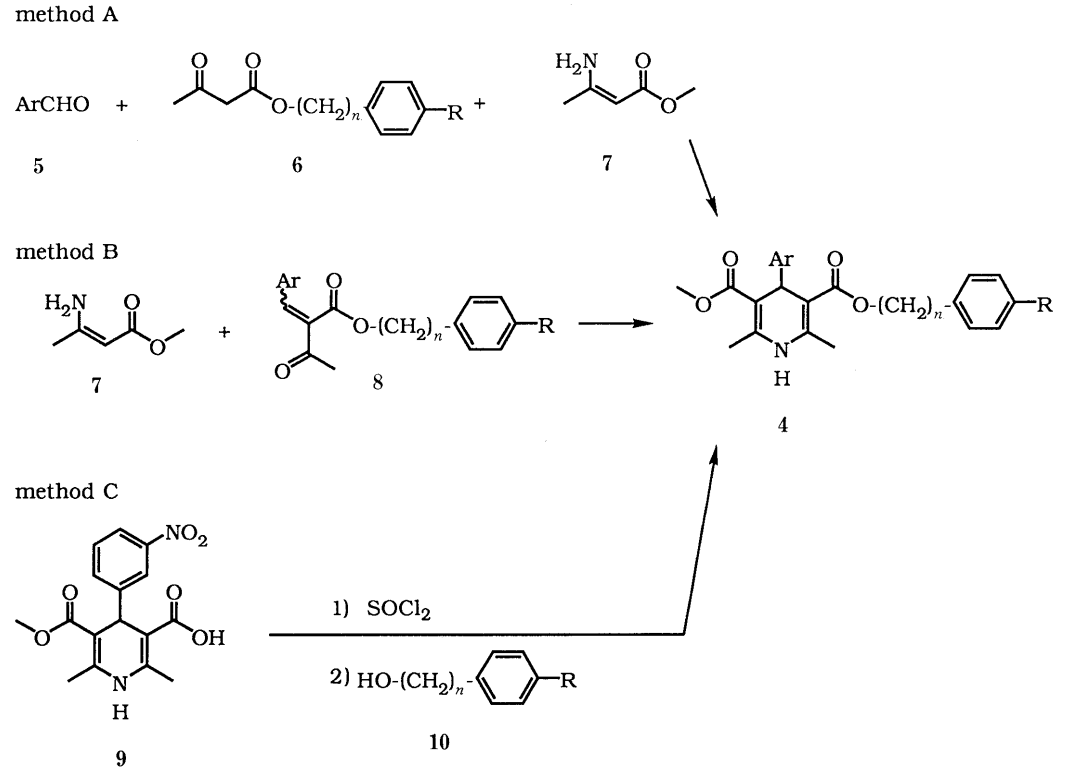
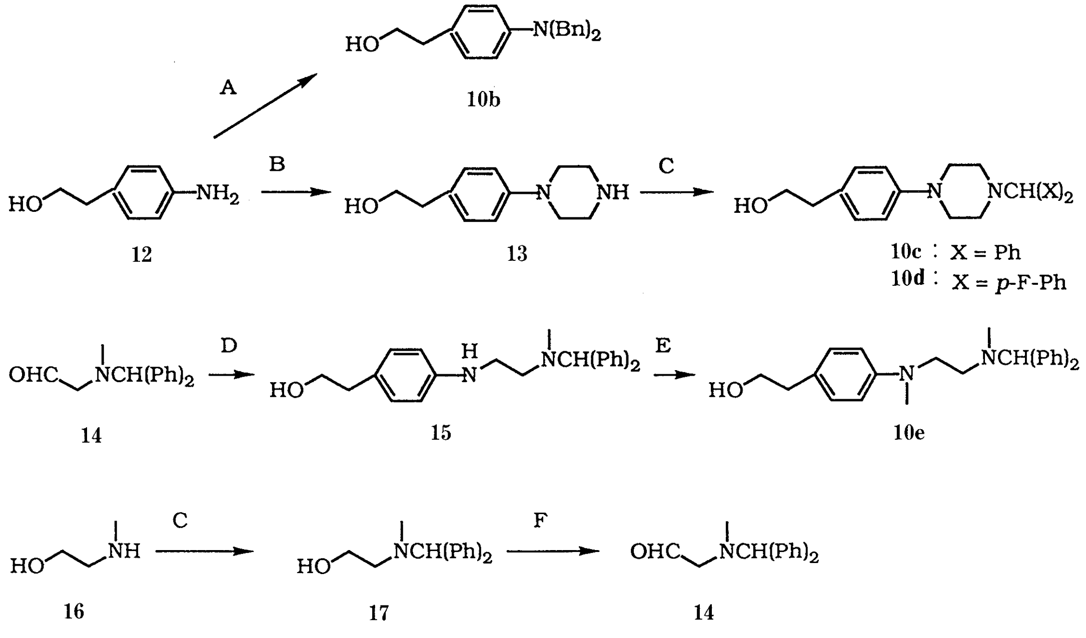


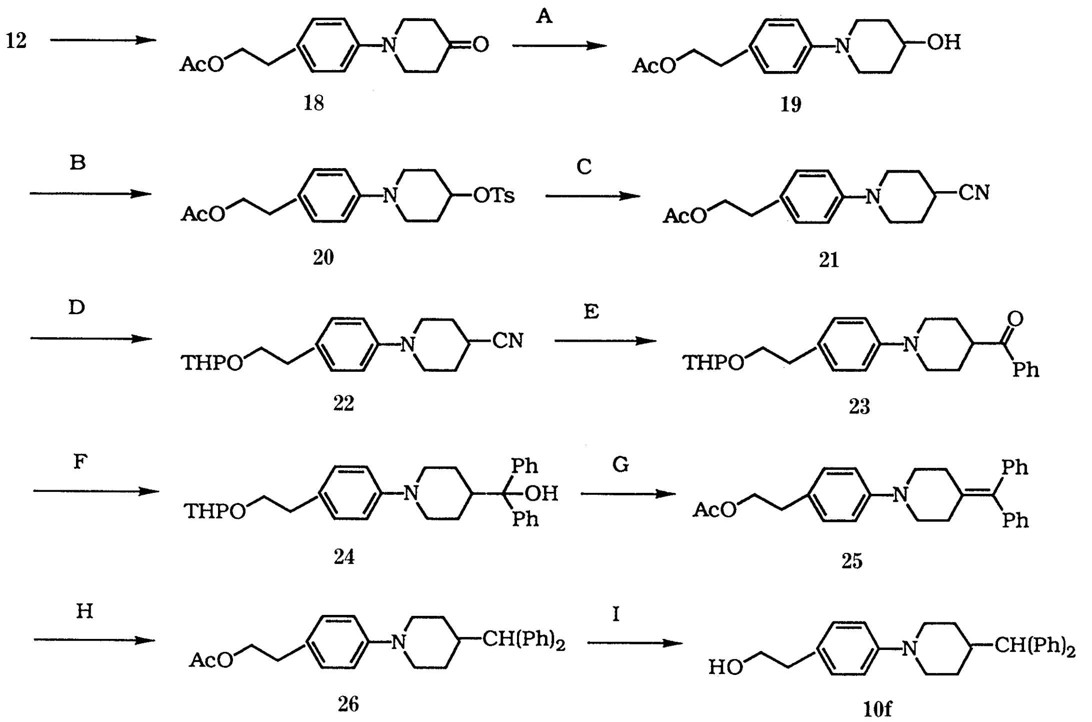
Chart 1



A) BnBr, K_2CO_3/DMF, r.t. (94%) B) $(ClCH_2CH_2)_2NH \cdot HCl$/BuOH, refl. (79%) C) $(Ph)_2CHBr$ or $(p\text{-F-Ph})_2CHBr$, K_2CO_3/DMF, r.t. (**10c**, 57%; **10d**, 50%; **17**, 59%) D) 12, $NaBH_3CN$/MeOH, r.t. (51%) E) 37% aq. HCHO, $NaBH_3CN$/MeOH, r.t. (66%) F) DMSO, DCC, H_3PO_4, r.t. (30%)

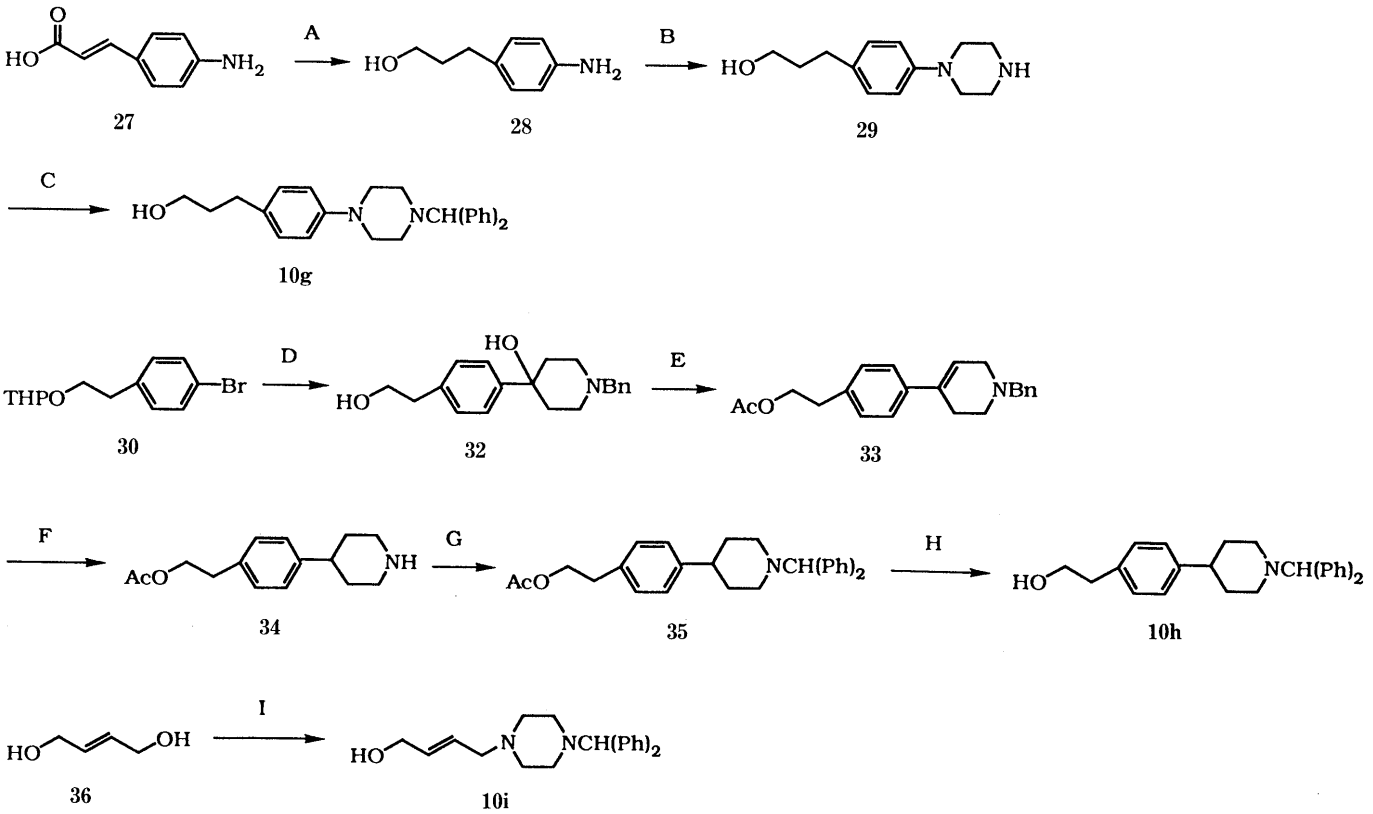
Chart 2

with HCHO. Aldehyde **14** was derived from aminoalcohol **16** by *N*-benzhydrylation, followed by oxidation of the obtained intermediate **17**. The method for the synthesis of **10f**, the side chain of **4j**, was as follows: Compound **18** derived from **12** by known methods[9] was reduced with $NaBH_4$ to give the corresponding alcohol **19**, which was treated with *p*-toluenesulfonyl chloride in pyridine. The tosyloxy leaving group of **20** was replaced by a cyano group by the method of Henbest and Jackson,[10] namely, **20** was treated with NaCN in *N*-methyl-2-pyrrolidone and *tert*-BuOH at 80—90 °C to give **21** in moderate yield. After the protecting group of the primary alcohol of **21** was changed into a tetrahydropyranyl (THP) group, **22** was treated with phenylmagnesium bromide twice to afford **24** in good yield. Dehydration and a concomitant exchange of THP for acetyl (Ac) was performed by treatment of **24** with H_2SO_4–AcOH



A) NaBH$_4$/MeOH, r.t. (96%) B) TsCl/pyridine, r.t. (81%) C) NaCN/*N*-methyl-2-pyrrolidone and *tert*-BuOH, 80—90 °C (45%) D) i) K_2CO_3/MeOH, r.t.; ii) DHP, TsOH/CH_2Cl_2, r.t. (80%) E) i) PhMgBr/Et_2O, r.t.; ii) 12 N H_2SO_4, ice-water cooling (66%) F) i) PhMgBr/Et_2O–THF, r.t; ii) 25% NH_4Cl (96%) G) H_2SO_4–AcOH (2:8), r.t. (66%) H) H_2, 10% Pd on charcoal/AcOH–$HClO_4$, 65—70 °C (79%) I) K_2CO_3/MeOH, r.t. (91%)

Chart 3



A) i) H_2, 5% Pd on charcoal/MeOH, r.t.; ii) HCl/MeOH, refl.; iii) $LiAlH_4$/THF, 22—23 °C (91%) B) $(ClCH_2CH_2)_2NH \cdot HCl$/BuOH, refl. (62%) C) $(Ph)_2CHBr$, K_2CO_3/DMF, r.t. (60%) D) i) BuLi/THF, < −60 °C; ii) 1-benzyl-4-piperidone (**31**), −60— −40 °C; iii) 10% HCl/MeOH, r.t. (76%) E) H_2SO_4–AcOH (2:8), r.t. (51%) F) H_2, 10% Pd on charcoal/AcOH–$HClO_4$, 65—70 °C (96%) G) $(Ph)_2CHBr$, K_2CO_3/DMF, r.t. (73%) H) K_2CO_3/MeOH, r.t. (89%) I) i) MsCl, NEt_3/THF–CH_2Cl_2, r.t.; ii) 1-benzhydrylpiperazine, K_2CO_3/DMF, r.t. (30%)

Chart 4

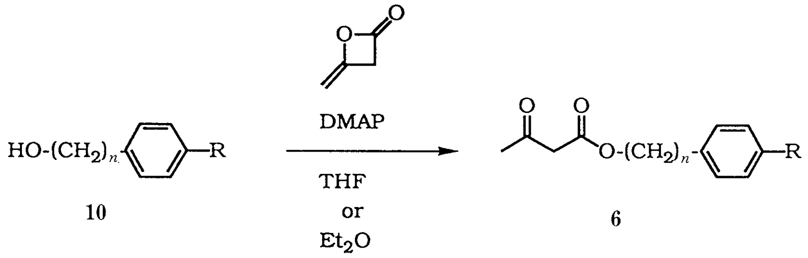
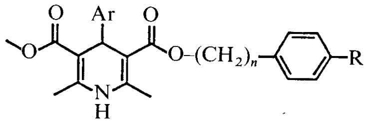


Chart 5

Table I. Physical and Biological Data of 1,4-Dihydropyridines (4)



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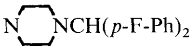
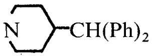
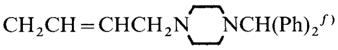
Compd. No.	Ar[a]	Method	R	n	Yield (%)	mp (°C)	Recrystn. solvent[b]	HR-SIMS[c] Found (Calcd)	Max. reduction of SBP (%)	Duration (h)
4a	4-CN-2-Py	A	NMe_2	2	45	184—186	M	461.2255 (461.2187)	4	—
4b	2-CF_3-3-Py	A	NMe_2	2	43	199—204	M	504.2131 (504.2109)	19	5
4c	4-CN-2-Py	A	NBn_2	2	40	194.5—197	M–C	613.2842 (613.2813)	20	11
4d	2-CF_3-3-Py	A	NBn_2	2	37	141—142	IPE–M–C	656.2703 (656.2733)	13	—
4e	3-NO_2-Ph	A, B, C		2	92[d]	Amorph.	—	—[g]	35	13
4f	4-CN-2-Py	A, B		2	48[e]	218—220	IPE–C	668.3168 (668.3234)	29	9
4g	2-CF_3-3-Py	A		2	13	Amorph.	—	711.3196 (711.3156)	29	16
4h	3-NO_2-Ph	C		3	73	Amorph.	—	637.2994 (637.3023)	46	22
4i	3-NO_2-Ph	C		2	94	Amorph.	—	701.3385 (701.3337)	34	16
4j	3-NO_2-Ph	C		2	75	Amorph.	—	723.3027 (723.2992)	42	20
4k	3-NO_2-Ph	C		2	48	Amorph.	—	686.3263 (686.3228)	42	>24
4l	3-NO_2-Ph	C	$NMeCH_2CH_2NMeCH(Ph)_2$	2	53	Amorph.	—	686.3204 (686.3228)	38	4
4m	3-NO_2-Ph	A			27	Amorph.	—	689.3358 (689.3337)	12	—
Nicardipine·HCl									10	—
Manidipine·2HCl									42	6

a) 4-CN-2-Py, 4-cyano-2-pyridyl; 2-CF_3-3-Py, 2-trifluoromethyl-3-pyridyl; 3-NO_2-Ph, 3-nitrophenyl. b) C, $CHCl_3$; IPE, isopropyl ether; M, MeOH. c) Compounds were converted to corresponding hydrochlorides and then analyzed. The method of conversion was described in Experimental section. d) The yield by method C. e) The yield by method B. f) Whole ester group. g) Compound 4e was converted to dihydrochloride and used for elemental analysis. The data are shown in Experimental section. Amorph. = amorphous.

(2 : 8, v/v) to afford **25**, which was hydrogenated in AcOH using 10% Pd on charcoal in the presence of $HClO_4$ to yield **26**. Compound **26** was hydrolyzed in a methanolic base to afford **10f** in high yield.

Preparation of Side Chain of 4h, 4k and 4m (Chart 4) Successive treatment of **27** with H_2 over 5% Pd on charcoal in MeOH, dry HCl in MeOH, and $LiAlH_4$ in tetrahydrofuran (THF) gave **28** in high yield. Compound **10g**, the side chain of **4h**, was derived from **28** as in the case of **12**. Compound **10h**, the side chain of **4k**, was obtained in the following manner: Lithiated **30**[11] was treated with *N*-benzyl-4-piperidone (**31**), and the following deprotection of the primary alcohol gave **32**, which was dehydrated and acetylated at the same time by treatment with H_2SO_4–AcOH (2 : 8, v/v) to give **33**. Treatment of **33** with H_2 over 10% of Pd on charcoal in AcOH–$HClO_4$ was followed by benzhydrylation of the secondary amine to give **35**. Compound **10h** was obtained by hydrolysis of **35** with K_2CO_3 in MeOH. Compound **10i**, the side chain of **4m**, was obtained by one pot reaction of (*E*)-2-butene-1,4-diol (**36**) with methanesulfonyl chloride in THF followed by an amination with 1-benzhydrylpiperazine. 2-(4-Dimethylaminophenyl)ethyl alcohol (**10a**) is commercially available.

In cases where 1,4-dihydropyridine derivatives were prepared by method A or B, the corresponding alcohols obtained above were converted to acetoacetic acid esters **6** by treatment with diketene in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) in THF or Et_2O as shown in Chart 5.[12)]

Results and Discussion

Antihypertensive activity and duration of action of the 1,4-dihydropyridine derivatives (**4a**—**m**) are shown in Table I.

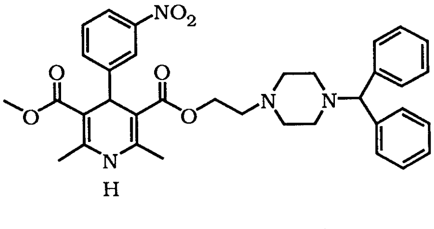
Most of the compounds synthesized except **4a** have more potent antihypertensive activity than nicardipine which was used as a control compound.

Concerning the substituent at the 4-position of the 1,4-dihydropyridine ring, the derivatives with 2-trifluoromethyl-3-pyridyl group showed longer duration than those with a 4-cyano-2-pyridyl or a 3-nitrophenyl group (*e.g.*, **4a** < **4b**, **4c** < **4d**, and **4e**, **4f** < **4g**) like the previous examples (*e.g.*, **1** < **3**).[1)] However, there seemed to be no distinct relationship between the potency of antihypertensive effect and the substituents used at 4-position.

The derivatives which have a piperazine moiety with a benzhydryl group (**4e**—**g**) showed more potent and longer lasting antihypertensive activity than the compounds without such a group (**4a**—**d**), and when the alkylene was lengthened from ethylene to trimethylene ($n=2 \rightarrow n=3$, *i.e.*, **4e**→**4h**) the antihypertensive effect and duration were increased. However, the introduction of a fluorine atom into the 4-position on each benzene ring of the benzhydryl moiety had little influence on the antihypertensive action (**4e** *vs.* **4i**).

Interestingly, replacement of either nitrogen atom of the piperizine ring in **4e** by a carbon atom gave rise to increased antihypertensive effect and, in particular, prolongation of the duration of action (**4j** and **4k**). From these results, neither nitrogen atom of the piperazine ring is necessarily required for the antihypertensive activity. In addition, the fact that the straight chain analogue **4l** preserves activity suggests the structural flexibility of this portion of the molecule to show the antihypertensive activity.

Although manidipine (Fig. 3),[4)] which will soon come onto the market, showed a potent antihypertensive activity, the duration of action was not as long (*ca.* 6 h; see Table I). It is remarkable to note that compound **4e**, in which a benzene ring is introduced between the alkylene and the piperazine ring of manidipine, has somewhat less antihypertensive activity and yet the duration of action is more than twice as long as manidipine. This would be due, at least in part, to a tardiness of the metabolism or an increase of the affinity to a drug receptor caused by the introduced benzene ring.



CV-4093 (manidipine)

Fig. 3

Among the compounds described above, **4e** (AE0047), **4f**, **4h**, **4i** and **4k** were selected as candidates for further pharmacological investigations. One of the investigations indicated that AE0047 had a potent and selective vasodilating action to canine vertebral artery, and this property is thought to be an additional benefit to an antihypertensive drug.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 spectrometer. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Hitachi R-24 (60 Mc) or a BRUKER AC-200 spectrometer with tetramethylsilane (TMS) as an internal standard. Secondary ion mass spectra (SIMS) were measured on a Hitachi M-2000 instrument, and precise mass analysis were performed by high resolution SIMS (HR-SIMS). 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) plates were used for thin layer chromatography (TLC).

2-(4-Dibenzylaminophenyl)ethyl Alcohol (10b) To a solution of **12** (1.04 g, 7.6 mmol) in *N*,*N*-dimethylformamide (DMF) (9 ml), K_2CO_3 (4.20 g, 30 mmol) and benzyl bromide (2.99 g, 18 mmol) were added successively at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After addition of H_2O, the resulting mixture was extracted with Et_2O. The extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (98 : 2, v/v) to give the product (**10b**) as a pale yellow oil (2.28 g, 94%). IR (film): 3350, 3025, 1620, 1520, 1495, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (1H, s), 2.69 (2H, t, $J=6$ Hz), 3.71 (2H, t, $J=6$ Hz), 4.56 (4H, s), 6.62, 6.92 (4H, A_2B_2-q, $J=8.5$ Hz), 7.18 (10H, s).

2-[4-(1-Piperazinyl)phenyl]ethyl Alcohol (13) A mixture of **12** (10.15 g, 74 mmol), bis(2-chloroethyl)amine hydrochloride (6.61 g, 37 mmol) and BuOH (66 ml) was refluxed for 23.5 h. After cooling to room temperature, the resulting solution was poured into H_2O, which was made alkaline with 15% NaOH to pH 10—11 with ice-water cooling. The resulting mixture was extracted with $CHCl_3$, the extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (1 : 1, v/v) to yield the product (**13**) as a pale yellow solid (6.00 g, 79%). IR (KBr): 3300, 1615, 1515, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, s), 2.75 (2H, t, $J=6$ Hz), 2.8—3.2 (8H, m), 3.77 (2H, t, $J=6$ Hz), 6.7—6.95 (2H, m), 6.95—7.15 (2H, m).

2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethyl Alcohol (10c) To a solution of **13** (6.00 g, 29 mmol) in DMF (33 ml) were added successively, K_2CO_3 (8.03 g, 58 mmol) and benzhydryl bromide (7.54 g, 31 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 h. The resulting mixture was poured into H_2O, and then extracted with Et_2O. The extract was washed with brine, dried, and the solvent was removed. The product (**10c**) was isolated by chromatography on silica gel with AcOEt–hexane (1 : 1, v/v) to give a colorless oil (6.19 g, 57%). IR ($CHCl_3$): 3600, 2950, 1615, 1490, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71 (1H, s), 2.35—2.65 (4H, m), 2.71 (2H, t, $J=6$ Hz), 2.95—3.3 (4H, m), 3.72 (2H, t, $J=6$ Hz), 4.23 (1H, s), 6.65—6.9 (2H, m), 6.9—7.55 (12H, m).

2-[4-{4-(4,4′-Difluorobenzhydryl)-1-piperazinyl}phenyl]ethyl alcohol (**10d**) was obtained by similar treatment of **13** with 4,4′-difluorobenzhydryl bromide as a colorless solid (yield 50%). IR (KBr): 3300, 2850, 1605, 1505, 1455 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (1H, br s), 2.72 (2H, t, $J=6$ Hz), 2.4—2.6 (4H, m), 3.0—3.2 (2H, m), 3.75 (2H, t, $J=6$ Hz), 4.20 (1H, s), 6.7—7.5 (12H, m).

2-(*N*-Benzhydryl-*N*-methylamino)ethyl alcohol (**17**) was obtained by similar treatment of *N*-methylethanolamine (**16**) with benzhydryl bromide as a colorless oil (yield 59%). IR (film): 3300, 2950, 2750, 1590, 1490, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.70 (2H, t, $J=7$ Hz), 3.48 (2H, t, $J=7$ Hz), 4.37 (1H, s), 7.0—7.5 (10H, br).

2-[4-{2-(*N*-Benzhydryl-*N*-methylamino)ethylamino}phenyl]ethyl Alcohol (15) To a solution of **17** (5.00 g, 21 mmol) and *N*,*N*-dicyclohexylcarbodiimide (16.50 g, 80 mmol) in dimethyl sulfoxide (DMSO) (100 ml) was added, 1.0 M H_3PO_4 in DMSO (10 ml) at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After removing the precipitated dicyclohexylurea by filtration, 1 M K_2CO_3 was added to the filtrate, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. The obtained residue was chromatographed on silica gel with AcOEt–hexane (1 : 5, v/v) to give aldehyde **14** (1.54 g, 30%), which was used immediately in the next reaction. To a solution of aldehyde **14** (780 mg, 3.3 mmol) and **12** (1.34 g, 9.8 mmol) in MeOH (50 ml), $NaBH_3CN$ (163 mg, 2.6 mmol) was added at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After the solvent was removed, the residue was purified by chromatography on silica gel with AcOEt–hexane (1 : 1, v/v). The product (**15**) was obtained as a pale yellow oil (600 mg, 51%). IR (film): 3300, 2875, 1610, 1495, 1450 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.61 (2H, t, $J=6$ Hz), 2.74 (2H, t, $J=6.5$ Hz), 3.17 (2H, t, $J=6$ Hz), 3.77 (2H, t, $J=6.5$ Hz), 4.44 (1H, s), 6.56, 7.01 (4H, A_2B_2-q, $J=8.5$ Hz), 7.15—7.40 (10H, m).

2-[4-[*N*-{2-(*N*-Benzhydryl-*N*-methylamino)ethyl}-*N*-methylamino]-phenyl]ethyl Alcohol (10e) To a solution of **15** (44 mg, 0.12 mmol) in CH_3CN (10 ml) were added successively, 37% aqueous HCHO (10 mg, 0.12 mmol) and $NaBH_3CN$ (8 mg, 0.10 mmol) at room temperature. After the resulting mixture was stirred at the same temperature for 2 h, the solvent was removed. H_2O was added to the mixture, and then the mixture was extracted with Et_2O. The extract was washed with brine and dried. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane (1 : 1, v/v) to give the product (**10e**) as a pale yellow oil (30 mg, 66%). IR (film): 3300, 2850, 1610, 1500, 1455 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.54 (1H, br s), 2.25 (3H, s), 2.55 (2H, t, $J=7$ Hz), 2.73 (2H, t, $J=6.5$ Hz), 2.84 (3H, s), 3.44 (2H, t, $J=7$ Hz), 3.76 (2H, t, $J=6.5$ Hz), 4.39 (1H, s), 6.49, 6.98 (4H, A_2B_2-q, $J=8.5$ Hz), 7.0—7.4 (10H, m).

2-[4-(4-Hydroxy-1-piperidinyl)phenyl]ethyl Acetate (19) To a solution of **18** (2.17 g, 8.9 mmol) in MeOH (22 ml), $NaBH_4$ (168 mg, 4.4 mmol) was added with ice-water cooling. After the reaction mixture was stirred at the same temperature for 30 min, the resulting solution was poured into H_2O, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. Purification by chromatography on silica gel with AcOEt–hexane (2 : 1, v/v) gave the product (**19**) as a pale yellow oil (2.10 g, 96%). IR (film): 3400, 2975, 1740, 1620, 1520, 1470, 1245 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.6—1.8 (2H, m), 1.9—2.05 (2H, m), 2.03 (3H, s), 2.67 (1H, br s), 2.84 (2H, t, $J=7$ Hz), 2.8—2.95 (2H, m), 3.51 (2H, dt, $J=13$, 4 Hz), 3.7—3.9 (1H, m), 4.22 (2H, t, $J=7$ Hz), 6.8—6.95 (2H, m), 7.05—7.2 (2H, m).

2-[4-{4-(*p*-Toluenesulfonyloxy)-1-piperidinyl}phenyl]ethyl Acetate (20) To a solution of **19** (100 mg, 0.38 mmol) in pyridine (1 ml), *p*-toluenesulfonyl chloride (109 mg, 0.57 mmol) was added with ice-water cooling. The reaction mixture was stirred at room temperature for 17 h under N_2 atmosphere. After addition of H_2O to the mixture and acidification with 5 N AcOH to *ca.* pH 4, the resulting mixture was extracted with Et_2O. The extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 2, v/v) to give the product (**20**) as a pale yellow oil (115 mg, 81%). IR (film): 2950, 1735, 1615, 1515, 1360, 1240, 1180 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.85—2.0 (4H, m), 2.03 (3H, s), 2.7—2.85 (1H, m), 2.86 (2H, t, $J=7$ Hz), 3.0—3.15 (2H, m), 3.35—3.45 (2H, m), 4.23 (2H, t, $J=7$ Hz), 6.85—6.95 (2H, m), 7.1—7.2 (2H, m).

2-[4-(4-Cyano-1-piperidinyl)phenyl]ethyl Acetate (21) To a solution of **20** (2.47 g, 5.9 mmol) in *N*-methyl-2-pyrrolidone (161 ml) and *tert*-BuOH (8.5 ml), NaCN (3.48 g, 71 mmol) was added at room temperature and stirred at 80—90 °C for 15 h under N_2 atmosphere. The resulting solution was poured into crushed ice and the mixture was extracted with Et_2O. The extracts was washed with brine, dried, and the solvent was removed. The product was isolated by chromatography on silica gel with AcOEt–hexane (1 : 2, v/v) to afford **21** as a pale yellow oil (731 mg, 45%). IR (film): 2975, 2250, 1740, 1615, 1520, 1425, 1240 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.95—2.1 (4H, m), 2.03 (3H, s), 2.7—2.85 (1H, m), 2.86 (2H, t, $J=7$ Hz), 3.0—3.15 (2H, m), 3.35—3.45 (2H, m), 4.23 (2H, t, $J=7$ Hz), 6.85—6.95 (2H, m), 7.1—7.2 (2H, m).

4-Cyano-1-[4-{2-(tetrahydropyran-2-yloxy)ethyl}phenyl]piperidine (22) To a solution of **21** (719 mg, 2.6 mmol) in MeOH (10 ml), a catalytic amount of K_2CO_3 (*ca.* 3 mol%) was added at room temperature, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was poured into 10% K_2CO_3, and then extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. After the obtained residue (600 mg) was dissolved in CH_2Cl_2 (10 ml), 3,4-dihydro-2*H*-pyran (DHP) (328 mg, 4.6 mmol), *p*-toluenesulfonic acid (644 mg, 3.4 mmol), and pulverized molecular sieves 3A (350 mg) were added successively to the solution, and then the mixture was stirred at room temperature for 1.5 h. Molecular sieves were filtered off and the filtrate was poured into 10% K_2CO_3. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 2, v/v) to give the product (**22**) as a pale yellow oil (663 mg, 80%). IR (film): 2950, 2225, 1615, 1515, 1445, 1140, 1120 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.45—1.9 (6H, m), 1.9—2.1 (4H, m), 2.2—2.4 (1H, m), 2.87 (2H, t, $J=7$ Hz), 2.95—3.1 (2H, m), 3.35—3.5 (2H, m), 3.4—3.8 (2H, m), 3.5—4.0 (2H, m), 4.59 (1H, t, $J=3$ Hz), 6.8—6.9 (2H, m), 7.1—7.2 (2H, m).

4-Benzoyl-1-[4-{2-(tetrahydropyran-2-yloxy)ethyl}phenyl]piperidine (23) To a solution of PhMgBr in Et_2O (1.37 N, 0.90 ml, 1.2 mmol) was added, a solution of **22** (175 mg, 0.56 mmol) in Et_2O (2 ml) with ice-water cooling under N_2 atmosphere. After stirring at room temperature for 1.5 h, H_2O was added to the mixture, and then 12 N H_2SO_4 was added with ice-water cooling until the colorless solid precipitate had disappeared. The organic layer was separated, and after the aqueous layer was made alkaline with K_2CO_3 to pH 11, the solution was extracted with AcOEt. The combined extracts were washed with brine, dried, and the solvent was removed. Purification of the residue by chromatography on silica gel with AcOEt–hexane (1 : 3, v/v) gave the product (**23**) as a colorless solid (145 mg, 66%). IR (KBr): 2950, 2850, 1665, 1615, 1595, 1580, 1520, 1455, 1140 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.45—1.9 (6H, m), 1.9—2.05 (4H, m), 2.75—2.9 (4H, m), 3.3—3.55 (2H, m), 3.5—3.95 (5H, m), 4.60 (1H, t, $J=3$ Hz), 6.85—6.95 (2H, m), 7.1—7.2 (2H, m), 7.4—7.55 (3H, m), 7.95—8.05 (2H, m).

4-(1-Hydroxy-1,1-diphenyl)methyl-1-[4-{2-(tetrahydropyran-2-yloxy)-ethyl}phenyl]piperidine (24) To a solution of PhMgBr in Et_2O (1.37 N, 3.5 ml, 4.8 mmol) was added dropwise, a solution of **23** in THF (8 ml) with ice-water cooling, following this addition, the reaction mixture was stirred at room temperature for 40 min. To the resulting mixture were added successively, 25% NH_4Cl and H_2O, and then the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 7, v/v) to give the product (**24**) as a pale yellow oil (1.04 g, 96%). IR (film): 3400, 2950, 1610, 1515, 1445, 1120 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.45—1.85 (11H, m), 2.5—2.8 (3H, m), 2.82 (2H, t, $J=7.5$ Hz), 3.4—3.9 (6H, m), 4.59 (1H, t, $J=3$ Hz), 6.8—6.9 (2H, m), 7.05—7.15 (2H, m), 7.15—7.45 (6H, m), 7.45—7.55 (4H, m).

2-[4-(Benzhydrylidene-1-piperidinyl)phenyl]ethyl Acetate (25) A mixture of **24** (1.04 g, 2.2 mmol) and H_2SO_4–AcOH (2 : 8, v/v) (10 ml) was stirred at room temperature for 1 h. After the reaction mixture was poured into H_2O and made alkaline with K_2CO_3 to pH 11, the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. The product was isolated by chromatography on silica gel with AcOEt–hexane (1 : 6, v/v) to give **25** as a pale yellow oil (603 mg, 66%). IR (film): 2950, 1740, 1615, 1515, 1490, 1460, 1440, 1240 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.02 (3H, s), 2.50 (4H, t, $J=6$ Hz), 2.84 (2H, t, $J=7$ Hz), 3.24 (4H, t, $J=6$ Hz), 4.23 (2H, t, $J=7$ Hz), 6.8—6.9 (2H, m), 7.05—7.35 (12H, m).

2-[4-(4-Benzhydryl-1-piperidinyl)phenyl]ethyl Acetate (26) To a solution of **25** (600 mg, 1.5 mmol) in AcOH (10 ml), 70% $HClO_4$ (0.3 ml) was added. After 10% Pd on charcoal (600 mg) was added to the solution under N_2 atmosphere, N_2 was replaced by H_2, and then the mixture was stirred at 65—70 °C for 3 h. The catalyst was filtered off, and the filter was washed with MeOH and CH_2Cl_2. After evaporation of the solvent, 10% K_2CO_3 was added to the residue, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 7, v/v) to afford the product (**26**) as a pale yellow oil (476 mg, 79%). IR (film): 2925, 1735, 1615, 1515, 1490, 1450, 1240 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.3—1.45 (2H, m), 1.67 (2H, d, $J=13$ Hz), 2.02 (3H, s), 2.24 (1H, dt, $J=11$, 3.5 Hz), 2.65 (2H, td, $J=12$, 2.5 Hz), 2.83 (2H, t, $J=7$ Hz), 3.53 (1H, d, $J=11$ Hz), 3.55—3.65 (2H, m), 4.22 (2H, t, $J=7$ Hz), 6.8—6.9 (2H, m), 7.05—7.15 (2H, m), 7.15—7.4 (10H, m).

2-[4-(4-Benzhydryl-1-piperidinyl)phenyl]ethyl Alcohol (10f) To a solution of **26** (469 mg, 1.1 mmol) in MeOH (5 ml) was added, a catalytic amount of K_2CO_3 (*ca.* 3 mol%) at room temperature, and the obtained mixture was stirred at the same temperature for 1 h. After the reaction mixture was poured into 10% K_2CO_3, the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed. Purification of the residue by chromatography on silica gel with AcOEt–hexane (2 : 5, v/v) gave the product (**10f**) as a colorless solid (387 mg, 91%). IR (KBr): 3325, 2900, 1610, 1515, 1490, 1450 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.25—1.45 (3H, m), 1.6—1.7 (2H, m), 2.25 (1H, dt, $J=11$, 3.5 Hz), 2.66 (2H, td, $J=12$, 2.5 Hz), 2.77 (2H, t, $J=6.5$ Hz), 3.56 (1H, d, $J=11$ Hz), 3.55—3.65 (2H, m), 3.80 (2H, br s), 6.8—6.9 (2H, m), 7.05—7.15 (2H, m), 7.15—7.4 (10H, m).

3-(4-Aminophenyl)propyl Alcohol (28) To a solution of **27** (8.04 g, 40 mmol) in MeOH (340 ml), 5% Pd on charcoal (870 mg) was added under N_2 atmosphere. After N_2 was replaced by H_2, the mixture was stirred at room temperature for 55 min. The catalyst was filtered off, and the filter was rinsed with MeOH. The filtrate was evaporated to dryness to give a colorless solid (8.03 g). A mixture of the solid (8.03 g) and 10% dry HCl in MeOH (126 ml) was refluxed for 1.5 h. After cooling in an ice-water bath, the reaction mixture was poured into ice-water and made alkaline with K_2CO_3 to pH 9—10. The resulting solution was extracted with $CHCl_3$, and then the extract was washed with brine, dried, and the solvent was evaporated to dryness to yield a colorless solid (7.17 g). To a suspension of $LiAlH_4$ (2.73 g, 72 mmol) in THF (87 ml), a solution of the solid (7.17 g) obtained above in THF (95 ml) was added dropwise at 8—15 °C with ice-water cooling. After the addition was completed, the reaction mixture was stirred at 22—23 °C for 1.5 h. The resulting mixture was worked up as usual to give a crude mixture, which was purified by chromatography on silica gel with $CHCl_3$–MeOH (94 : 6, v/v) to afford the product (**28**) as a colorless oil (5.54 g, 91%). IR (film): 3300, 2925, 1620, 1515, 1450 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.5—2.05 (2H, m), 2.4—2.7 (2H, m), 2.91 (3H, br s), 3.54 (2H, t, $J=6.5$ Hz), 6.4—6.7 (2H, m), 6.75—7.05 (2H, m).

3-[4-(1-Piperazinyl)phenyl]propyl Alcohol (29) Compound **29** was obtained as a pale yellow solid (yield 62%) by the same method as used for the synthesis of **13**. IR (KBr): 3250, 2900, 2825, 1615, 1520, 1445 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.65—2.1 (2H, m), 2.13 (2H, s), 2.45—2.8 (2H, m), 2.8—3.25 (8H, m), 3.57 (2H, t, $J=6.5$ Hz), 6.65—6.9 (2H, m), 6.9—7.15 (2H, m).

3-[4-(4-Benzhydryl-1-piperazinyl)phenyl]propyl Alcohol (10g) Compound **10g** was obtained as a slightly yellow oil (yield 60%) by the same method as used for the synthesis of **10c**. IR ($CHCl_3$): 3600, 2950, 2825, 1615, 1510, 1490, 1455 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.45—2.05 (2H, m), 2.35—2.75 (6H, m), 2.95—3.25 (4H, m), 3.55 (2H, t, $J=6$ Hz), 4.19 (1H, s), 6.6—6.85 (2H, m), 6.85—7.05 (2H, m).

2-[4-(1-Benzyl-4-piperidinyl)phenyl]ethyl Alcohol (32) To a solution of **30** (7.53 g, 26 mmol) in THF (70 ml), BuLi in hexane (10 w/v%, 16.9 ml, 26 mmol) was added dropwise at below −60 °C under N_2 atmosphere. After the addition was completed, the solution was stirred at the same temperature for 30 min. Keeping the temperature below −60 °C, a solution of **31** (5.00 g, 26 mmol) in THF (30 ml) was added dropwise to the reaction mixture, and stirred for 2.5 h. After the solution was allowed to warm to *ca.* −40 °C, H_2O was added and then the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and the solvent was removed to give a pale yellow oil (10.95 g). To a solution of the oil (10.95 g) in MeOH (120 ml), 10% HCl (60 ml) was added at room temperature. After the reaction mixture was stirred at the same temperature for 1 h, the solution was poured into H_2O, which was made alkaline with K_2CO_3. After extraction of the resulting mixture with CH_2Cl_2, the extract was washed with brine, dried, and the solvent was removed. The product (**32**) was obtained by chromatography on silica gel with $CHCl_3$–MeOH (86 : 14, v/v) as a pale yellow oil (6.21 g, 76%). IR ($CHCl_3$): 3625, 3450, 2975, 2850, 1515, 1500, 1480 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.69 (2H, d, $J=12$ Hz), 2.15 (2H, td, $J=13, 4.5$ Hz), 2.53 (2H, td, $J=12, 2$ Hz), 2.3—2.7 (2H, br), 2.7—2.8 (2H, br), 2.81 (2H, t, $J=6.5$ Hz), 3.62 (2H, s), 3.80 (2H, t, $J=6.5$ Hz), 7.1—7.5 (9H, m).

2-[4-(1-Benzyl-1,2,5,6-tetrahydro-4-pyridyl)phenyl]ethyl Acetate (33) Compound **33** was obtained as a pale yellow oil (yield 51%) by the same method as used for the synthesis of **25**. IR (film): 2900, 2800, 1740, 1515, 1495, 1240 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.02 (3H, s), 2.5—2.6 (2H, br), 2.65—2.75 (2H, m), 2.91 (2H, t, $J=7$ Hz), 3.15, 3.18 (2H, A_2B_2-q, $J=3$ Hz), 3.63 (2H, s), 4.26 (2H, t, $J=7$ Hz), 6.0—6.1 (1H, m), 7.1—7.4 (9H, m).

2-[4-(4-Piperidinyl)phenyl]ethyl Acetate (34) Compound **34** was obtained as a slightly yellow oil (yield 96%) by the same method as used for the synthesis of **26**. IR (film): 2925, 2825, 1735, 1510, 1440, 1240 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.6—1.95 (4H, m), 2.04 (3H, s), 2.59 (1H, dt, $J=12$, 4 Hz), 2.78 (2H, dt, $J=12$, 2.5 Hz), 2.90 (2H, t, $J=7$ Hz), 3.26 (2H, d, $J=12$ Hz), 3.66 (1H, br s), 4.26 (2H, t, $J=7$ Hz), 7.16 (4H, s).

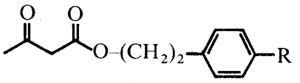
2-[4-(1-Benzhydryl-4-piperidinyl)phenyl]ethyl Acetate (35) Compound **35** was obtained as a slightly yellow oil (yield 73%) by the same method as used for the synthesis of **10c**. IR (film): 2950, 2800, 1740, 1600, 1520, 1495, 1460, 1240 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.7—2.0 (6H, m), 2.03 (3H, s), 2.3—2.6 (1H, m), 2.89 (2H, t, $J=7$ Hz), 3.00 (2H, d, $J=10.5$ Hz), 4.26 (2H, t, $J=7$ Hz), 4.29 (1H, s), 7.1—7.5 (14H, m).

2-[4-(1-Benzhydryl-4-piperidinyl)phenyl]ethyl Alcohol (10h) Compound **10h** was obtained as a slightly yellow oil (yield 89%) by the same method as used for the synthesis of **10f**. IR (film): 3325, 2925, 2800, 1600, 1515, 1490, 1450 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.5—2.0 (7H, m), 2.4—2.6 (1H, m), 2.81 (2H, t, $J=6.5$ Hz), 3.00 (2H, d, $J=10.5$ Hz), 3.82 (2H, t, $J=6.5$ Hz), 4.29 (1H, s), 7.1—7.5 (14H, m).

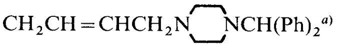
4-(4-Benzhydryl-1-piperazinyl)-(*E*)-2-buten-1-ol (10i) To a solution of **36** (3.04 g, 35 mmol, $E:Z=3:1$) and NEt_3 (2.32 g, 23 mmol) in CH_2Cl_2 (5 ml) and THF (6 ml), methanesulfonyl chloride (2.63 g, 23 mmol) in THF (8 ml) was added dropwise at room temperature. After the addition was completed, the mixture was stirred at the same temperature for 1.5 h. After the precipitated $Et_3N \cdot HCl$ was filtered off, the filtrate was evaporated to dryness to give a pale yellow oil. To a solution of 1-benzhydrylpiperazine (5.87 g, 23 mmol) in DMF (20 ml), K_2CO_3 (3.18 g, 23 mmol) and a solution of the oil in DMF (10 ml) were added successively at room temperature. After stirring at 65—70 °C for 1 h under N_2 atmosphere, the resulting mixture was poured into H_2O, and then extracted with Et_2O. The extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (10 : 1, v/v) to give the product (**10i**) as a colorless oil (2.12 g, 30%). IR (film): 3400, 2950, 2800, 1600, 1495, 1460 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.45 (8H, s), 2.59 (1H, s), 2.9—3.1 (2H, m), 4.0—4.15 (2H, m), 4.22 (1H, s), 5.55—5.95 (2H, m), 7.05—7.55 (10H, m).

General Method for the Synthesis of Acetoacetic Acid Esters (6) To a THF or Et_2O solution of **10**, diketene (1.2 eq of **10**) and a catalytic amount of DMAP were added with ice-salt cooling. After the addition of the reagents, the reaction mixture was stirred at the same temperature for 30 min and at room temperature for 3—16 h. To the mixture, 0.1% NaOH

TABLE II. Yields and Spectral Data of Acetoacetic Acid Esters (6)



6

Compd. No.	R	Yield (%)	IR ν_{max} (cm^{-1})	^1H-NMR ($CDCl_3$) δ (ppm)
6a	NMe_2	76	2925, 2800, 1740, 1710, 1615, 1520, 1450 (KBr)	2.20 (3H, s), 2.84 (2H, t, $J=7$ Hz), 2.89 (6H, s), 3.38 (2H, s), 4.27 (2H, t, $J=7$ Hz), 6.63, 7.02 (2H, A_2B_2q, $J=9$ Hz)
6b	NBn_2	82	3025, 2925, 1740, 1720, 1620, 1520, 1495, 1455 (film)	2.15 (3H, s), 2.81 (2H, t, $J=6$ Hz), 3.36 (2H, s), 4.25 (2H, t, $J=6$ Hz), 4.57 (4H, s), 6.5—6.75 (2H, m), 6.8—7.1 (2H, m), 7.19 (10H, s)
6c	 N NCH(Ph)$_2$	100	3025, 2975, 2800, 1740, 1720, 1620, 1520, 1495, 1450 (film)	2.18 (3H, s), 2.4—2.7 (4H, m), 2.85 (2H, t, $J=6.5$ Hz), 3.0—3.35 (4H, m), 3.39 (2H, s), 4.24 (1H, s), 4.29 (2H, t, $J=6.5$ Hz), 6.65—6.9 (2H, m), 6.9—7.6 (2H, m)
6d	 $CH_2CH=CHCH_2N$ NCH(Ph)$_2$[a]	75	2925, 2800, 1740, 1720, 1600, 1495, 1450 (film)	2.20 (3H, s), 2.44 (8H, br s), 5.64 (2H, d, $J=5.5$ Hz), 3.41 (2H, s), 4.22 (1H, s), 4.59 (2H, d, $J=5.5$ Hz), 5.69 (1H, ddd, $J=15.5$, 6, 5.5 Hz), 5.83 (1H, ddd, $J=15.5$, 6, 5.5 Hz), 7.1—7.4 (10H, m)

[a] Whole ester group.

was added and then the resulting mixture was extracted with Et_2O or CH_2Cl_2. The extract was washed with 0.1% NaOH (twice) and brine, dried, and the solvent was evaporated to dryness to give the acetoacetic acid ester (**6**), which was used in the next reaction either without further purification or after purification by chromatography on silica gel. Yields and spectral data are shown in Table II.

Typical Procedure for Method A 2-(4-Dimethylaminophenyl)ethyl Methyl 4-(4-Cyano-2-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**4a**): A solution of 4-cyano-2-pyridinecarboxaldehyde (1.01 g, 7.6 mmol), 2-(4-dimethylaminophenyl)ethyl acetoacetate (**6a**, 1.90 g, 7.6 mmol), and methyl 3-aminocrotonate (**7**, 903 mg, 7.6 mmol) in 2-propanol (10 ml) was stirred at 40—45 °C for 26 h. The solvent was removed and the residue was chromatographed on silica gel with AcOEt–hexane (9 : 1, v/v). The product (**4a**) was recrystallized from MeOH to give a colorless powder (1.58 g, 45%).

The other compounds were similarly prepared, except **4e** for which refluxing temperature was necessary.

Typical Procedure for Method B 2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethyl Methyl 4-(4-Cyano-2-pyridyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**4f**): A solution of 4-cyano-2-pyridinecarboxaldehyde (828 mg, 6.3 mmol) and 2-[4-(4-benzhydryl-1-piperazinyl)phenyl]ethyl acetoacetate (**6c**, 2.86 g, 6.3 mmol) in benzene (14 ml) containing piperidine (107 mg, 1.3 mmol) and AcOH (376 mg, 6.3 mmol) was refluxed for 1 h with azeotropic removal of H_2O using a Dean–Stark trap. After cooling to room temperature, the reaction mixture was washed with H_2O, aqueous saturated $NaHCO_3$, and brine. After drying, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with AcOEt–hexane (2 : 3, v/v) to give 2-[4-(4-benzhydryl-1-piperazinyl)phenyl]ethyl 2-(4-cyano-2-pyridylmethylidene)acetoacetate (2.36 g) as an amorphous solid. A solution of the amorphous solid and methyl 3-aminocrotonate (**7**, 447 mg, 3.9 mmol) in 2-propanol (18 ml) was refluxed for 4 h. The solvent was distilled off and the residue was chromatographed on silica gel with AcOEt–hexane (3 : 1, v/v). The product (**4f**) was recrystallized from isopropyl ether–$CHCl_3$ to give a slightly yellow powder (2.35 g, 59%).

Compound **4e** was prepared similarly by method B.

Typical Procedure for Method C 2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**4e**): To a suspension of carboxylic acid (**9**, 3.00 g, 9.0 mmol) in $CHCl_3$ (24 ml) and DMF (6 ml) was added $SOCl_2$ (1.18 g, 9.9 mmol) at 4—5 °C with ice-water cooling and this was then stirred for 2 h at the same temperature. The solution of **10c** (3.36 g, 9.0 mmol) in $CHCl_3$ (6 ml) was added to the reaction mixture at 5—7 °C and stirred for 1 h at 4—5 °C. The reaction mixture was diluted with $CHCl_3$ (30 ml), washed with 1 N NaOH and brine, dried, and the solvent was removed. The residue was purified by chromatography on silica gel with AcOEt–hexane (2 : 3, v/v) to give the product (**4e**) as a yellow amorphous powder (5.70 g, 92%). *Anal.*[13] Calcd for $C_{41}H_{42}N_4O_6 \cdot 2HCl$: C, 62.77; H, 6.01; N, 7.14; Cl, 9.04. Found: C, 63.01; H, 6.08; N, 7.05; Cl, 8.76.

The other compounds were prepared similarly by method C.

Spectral data of **4** are shown in Table III.

Method for the Preparation of Hydrochlorides of 4 To a solution of **4** (2.30 mmol) in CH_2Cl_2 (30 ml), a solution of HCl in dioxane (the same equivalent of HCl with **4**)[14] was added at room temperature. After the solution was stirred at the same temperature for 2.5 h, the solvent was removed. The residue was dissolved in EtOH (25 ml) and then the solvent

TABLE III. Spectral Data of 1,4-Dihydropyridines (**4**) Listed in Table I

Compd. No.	IR (KBr) ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
4a	3200, 3100, 2950, 2225, 1705, 1665, 1620, 1600, 1520, 1500, 1440	2.25 (6H, s), 2.80 (2H, t, $J=6$ Hz), 2.91 (6H, s), 3.63 (3H, s), 4.24 (2H, t, $J=6$ Hz), 5.14 (1H, s), 6.62, 7.00 (4H, A_2B_2q, $J=8$ Hz), 7.05 (1H, s), 7.15—7.4 (2H, m), 8.52 (1H, d, $J=5$ Hz)
4b	3300, 3200, 3100, 2950, 1710, 1700, 1650, 1620, 1520, 1500, 1455, 1430, 1120	2.27, 2.30 (each 3H, s), 2.75 (2H, t, $J=7$ Hz), 2.89 (6H, s), 3.58 (3H, s), 4.16 (2H, t, $J=7$ Hz), 5.63 (1H, s), 6.01 (1H, s), 6.5—6.75 (2H, m), 6.9—7.15 (2H, m), 7.33 (1H, dd, $J=7.5$, 5 Hz), 7.84 (1H, d, $J=7.5$ Hz), 8.43 (1H, d, $J=5$ Hz)
4c	3325, 3200, 3075, 2950, 2225, 1700, 1660, 1620, 1600, 1545, 1495, 1450, 1430	2.19, 2.24 (each 3H, s), 2.74 (2H, t, $J=6$ Hz), 3.55 (3H, s), 4.18 (2H, t, $J=6$ Hz), 4.58 (4H, s), 5.17 (1H, s), 6.5—6.75 (2H, m), 6.8–7.05 (3H, m), 7.05—7.45 (12H, m), 8.50 (1H, d, $J=5$ Hz)
4d	3275, 3200, 3100, 2950, 1695, 1650, 1620, 1520, 1495, 1455, 1435	2.21, 2.27 (each 3H, s), 2.67 (2H, t, $J=6.5$ Hz), 3.56 (3H, s), 4.15 (2H, t, $J=6.5$ Hz), 4.59 (4H, s), 5.60 (1H, s), 5.91 (1H, s), 6.5—6.7 (2H, m), 6.75—7.0 (2H, m), 7.1—7.4 (11H, m), 7.86 (1H, d, $J=7.5$ Hz), 8.51 (1H, d, $J=5$ Hz)
4e	3325, 2950, 2800, 1680, 1615, 1520, 1480, 1450, 1430, 1345	2.30, 2.35 (each 3H, s), 2.45—2.65 (4H, m), 2.82 (2H, t, $J=7$ Hz), 3.05—3.25 (4H, m), 3.64 (3H, s), 4.23 (2H, t, $J=7$ Hz), 4.26 (1H, s), 5.07 (1H, s), 5.73 (1H, s), 6.80, 7.04 (4H, A_2B_2q, $J=8.5$ Hz), 7.1—7.6 (12H, m), 7.97 (1H, ddd, $J=8$, 2.5, 1 Hz), 8.06 (1H, t, $J=2.5$ Hz)
4f	3300, 3050, 2950, 2800, 2225, 1700, 1660, 1615, 1595, 1545, 1485, 1450, 1430	2.23, 2.27 (each 3H, s), 2.45—2.6 (4H, m), 2.80 (2H, t, $J=6.5$ Hz), 3.05—3.2 (4H, m), 3.62 (3H, s), 4.1—4.4 (2H, m), 4.26 (1H, s), 5.14 (1H, s), 6.79 (1H, s), 6.82, 7.05 (4H, A_2B_2q, $J=8.5$ Hz), 7.1—7.5 (12H, m), 8.60 (1H, dd, $J=5$, 0.5 Hz)
4g	3325, 2950, 2800, 1700, 1650, 1615, 1515, 1490, 1450, 1430, 1120	2.24, 2.28 (each 3H, s), 2.6—2.95 (6H, m), 2.95—3.3 (4H, m), 3.57 (3H, s), 3.95—4.45 (2H, m), 4.28 (1H, s), 5.59 (1H, s), 5.86 (1H, s), 6.6—7.0 (4H, m), 7.0—7.55 (11H, m), 7.89 (1H, d, $J=7.5$ Hz), 8.46 (1H, d, $J=5$ Hz)
4h	3375, 2950, 2800, 1690, 1650, 1615, 1530, 1490, 1455, 1435, 1350	1.75—2.1 (2H, m), 2.34, 2.36 (each 3H, s), 2.4—2.6 (4H, m), 3.05—3.2 (4H, m), 3.65 (3H, s), 3.9—4.15 (2H, m), 4.26 (1H, s), 5.12 (1H, s), 5.93 (1H, s), 6.80, 6.89 (4H, A_2B_2q, $J=9$ Hz), 7.1—7.5 (11H, m), 7.65 (1H, dt, $J=8$, 1.5 Hz), 7.98 (1H, ddd, $J=8$, 2.5, 2.5 Hz), 8.11 (1H, t, $J=2.5$ Hz)
4i	3350, 2950, 2800, 1680, 1650, 1610, 1520, 1480, 1430, 1345	2.31, 2.36 (each 3H, s), 2.45—2.6 (4H, m), 2.82 (2H, t, $J=7$ Hz), 3.1—3.25 (4H, m), 3.64 (3H, s), 4.22 (2H, t, $J=7$ Hz), 4.26 (1H, s), 5.07 (1H, s), 5.82 (1H, s), 6.78, 6.97 (4H, A_2B_2q, $J=8.5$ Hz), 7.0—7.55 (12H, m), 7.98 (1H, ddd, $J=8.5$, 2.5, 2.5 Hz), 8.06 (1H, t, $J=2.5$ Hz)
4j	3325, 2925, 1685, 1610, 1520, 1480, 1430, 1345	1.1—1.45 (2H, m), 1.70 (2H, br s), 2.1—2.35 (1H, m), 2.30, 2.35 (each 3H, s), 2.64 (2H, td, $J=12$, 2.5 Hz), 2.81 (2H, t, $J=7$ Hz), 3.5—3.65 (3H, m), 3.64 (3H, s), 4.22 (2H, t, $J=7$ Hz), 5.07 (1H, s), 5.77 (1H, s), 6.80, 7.02 (4H, A_2B_2q, $J=8.5$ Hz), 7.1—7.35 (11H, m), 7.51 (1H, dt, $J=8$, 1.5 Hz), 7.97 (1H, ddd, $J=8$, 2, 2 Hz), 8.06 (1H, t, $J=2$ Hz)
4k	3350, 3050, 2975, 1690, 1620, 1535, 1490, 1460, 1440, 1355	1.65—2.05 (6H, m), 2.28, 2.34 (each 3H, s), 2.4—2.6 (1H, m), 2.87 (2H, t, $J=7$ Hz), 3.00 (2H, t, $J=10.5$ Hz), 3.64 (3H, s), 4.26 (2H, t, $J=7$ Hz), 4.29 (1H, s), 5.07 (1H, s), 5.88 (1H, s), 7.05—7.55 (16H, m), 7.97 (1H, ddd, $J=8$, 2.5, 2.5 Hz), 8.07 (1H, t, $J=2.5$ Hz)
4l	3300, 2900, 1680, 1520, 1490, 1460, 1440, 1320	2.25 (3H, s), 2.31, 2.35 (each 3H, s), 2.54 (2H, t, $J=7.5$ Hz), 2.77 (2H, t, $J=7$ Hz), 2.82 (3H, s), 3.43 (2H, t, $J=7.5$ Hz), 3.64 (3H, s), 4.20 (2H, t, $J=7$ Hz), 4.39 (1H, s), 5.09 (1H, s), 5.80 (1H, s), 6.45, 6.93 (4H, A_2B_2q, $J=8.5$ Hz), 7.1—7.6 (11H, m), 7.54 (1H, dt, $J=8$, 1.5 Hz), 7.97 (1H, ddd, $J=8$, 2, 2 Hz), 8.08 (1H, t, $J=2$ Hz)
4m	3325, 2950, 2800, 1695, 1620, 1530, 1485, 1450, 1430, 1350	2.33, 2.34 (each 3H, s), 2.43 (8H, br s), 2.98 (2H, d, $J=5.5$ Hz), 3.60 (3H, s), 4.22 (1H, s), 4.52 (2H, d, $J=5.5$ Hz), 5.08 (1H, s), 5.6—5.85 (2H, m), 5.87 (1H, s), 7.15—7.45 (11H, m), 7.59 (1H, dt, $J=8$, 2 Hz), 7.94 (1H, ddd, $J=8$, 2, 2 Hz), 8.07 (1H, t, $J=2$ Hz)

was evaporated to dryness to give the hydrochloride of **4**. All hydrochlorides of **4** were obtained as amorphous solids and subjected to pharmacological testing.

Biological Test[15] The experiments were performed in groups of 3—6 male SHR (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 were converted to hydrochlorides and were prepared as a solution or a suspension in aqueous 0.3% Tween 80 solution and orally administered at a dose of 3 mg/kg (10 ml/kg). Antihypertensive effects are shown as maximum reductions in SBP (%) from 0 h values. Duration of antihypertensive effects, carefully estimated by time course curves of SBP, is shown in hours by which SBP recovered to half maximum reductions.

References and Notes

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11) Compound **30** was prepared from **12** by the usual Sandmeyer reaction, followed by protection of hydroxy group by THP group. See, *e.g.* B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1966); K. F. Bernady, M. B. Floyd, J. F. Poletto, and M. J. Weiss, *ibid.*, **44**, 1438 (1979).

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13) Dihydrochloride of **4e** was prepared in the following manner: **4e** (7.0 mmol) was dissolved in CH_2Cl_2 (20 ml) and HCl gas was bubbled into the solution at its reflux temperature for 30 min and then with ice-salt cooling for 20 min to give a precipitated solid. The mixture was allowed to warm to room temperature and then the precipitate was collected by filtration to afford **4e**·2HCl (4.5 g) as a pale yellow powder. Dihydrochloride of **4e** was elementally analyzed. Calculated values were made assuming 3.19% water content determined by Karl Fisher method.

14) Concentration of HCl was determined by titration with 1 N NaOH using phenolphthalein as an indicator.

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