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New 1,4-Dihydropyridine Derivatives with Potent and Long-Lasting Hypotensive Effect[1)]

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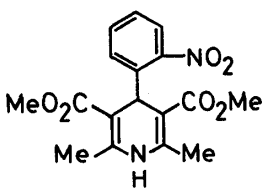
In a search for new 1,4-dihydropyridine derivatives with a long-lasting effect on the cardiovascular system, a series of piperazinylalkyl esters (I) bearing a lipophilic substituent on the 4-nitrogen of the piperazine ring was synthesized and tested for hypotensive effect in spontaneously hypertensive rats (SHR). Compounds I, especially those having a diphenylmethyl moiety on the piperazine ring, showed extremely potent and long-lasting hypotensive properties. Analogues related to I were also prepared, and the structure–activity relationships are discussed.

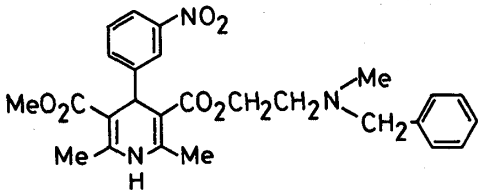
Keywords——1,4-dihydropyridine derivative; piperazinylalkyl ester; calcium antagonist; hypotensive activity; spontaneously hypertensive rat; structure–activity relationship

4-Aryl-1,4-dihydropyridine derivatives,[2)] such as nifedipine[3)] and nicardipine,[4)] are highly potent calcium antagonists and are widely used clinically for the treatment of hypertension, angina pectoris, and peripheral and cerebral vascular diseases.

Although nifedipine and nicardipine have been proven to be clinically useful and several other analogues are undergoing clinical testing, the rather short duration of action of this class of drugs is disadvantageous. A long-acting compound would be especially valuable for treating hypertension or for preventing angina pectoris.



nifedipine



nicardipine

Fig. 1. Known 1,4-Dihydropyridine Derivatives

We therefore attempted to synthesize new and long-acting 1,4-dihydropyridine derivatives by introducing functional groups that are expected to have both high lipophilicity and high affinity for the vascular tissues, so that the distribution and/or pharmacokinetics of the drugs could be modulated. Piperazine moieties with lipophilic substituents (*e.g.* diphenylmethyl, phenyl, benzoyl, *etc.*) were chosen for this purpose, because they are often present in cardiovascular agents such as peripheral α_1-adrenoceptor blockers (*e.g.* prazosin,[5)] urapidil[6)]), and vasodilators (*e.g.* cinnarizine,[7)] flunarizine[7)]).

Thus, a variety of piperazinylalkyl esters (I, Chart 1) and related compounds were prepared and tested for antihypertensive activity in spontaneously hypertensive rats (SHR).

Chemistry

Compounds **1**—**50** listed in Table I were prepared by one of the variations of the classical

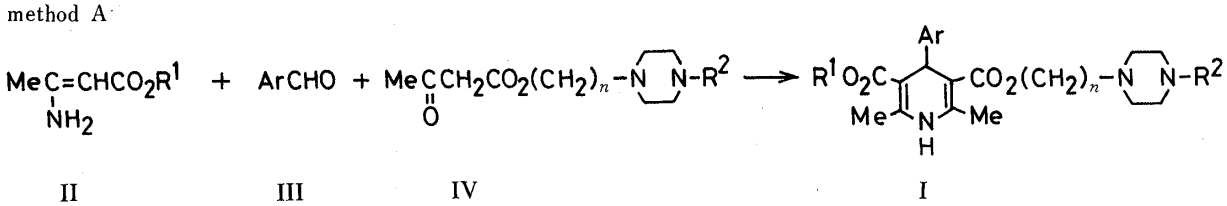


Chart 1

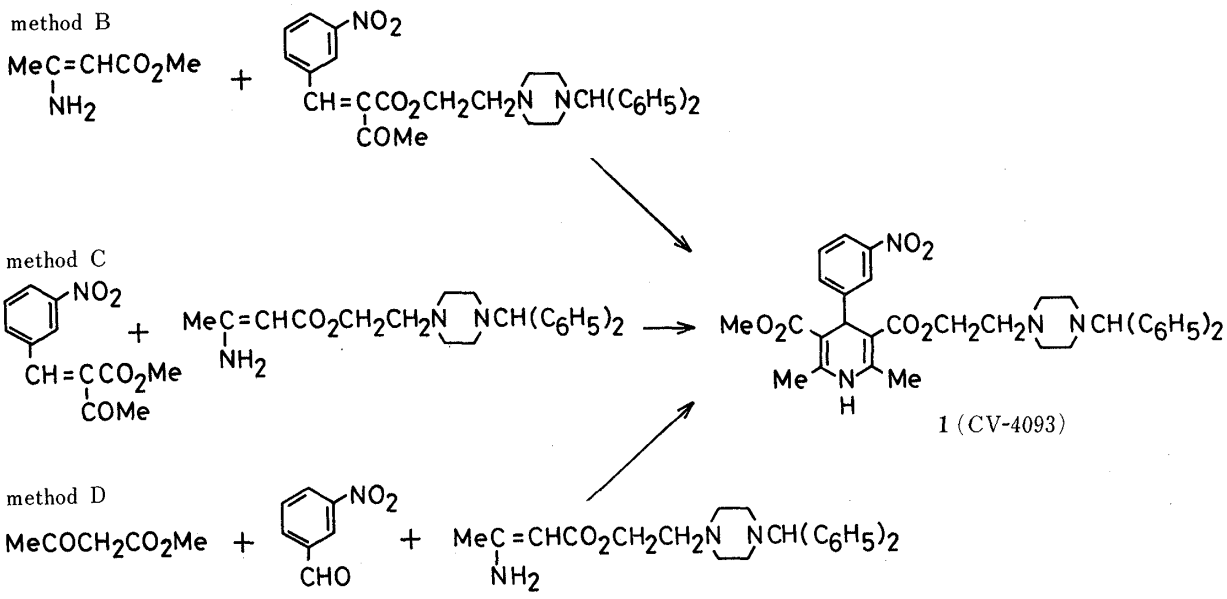


Chart 2

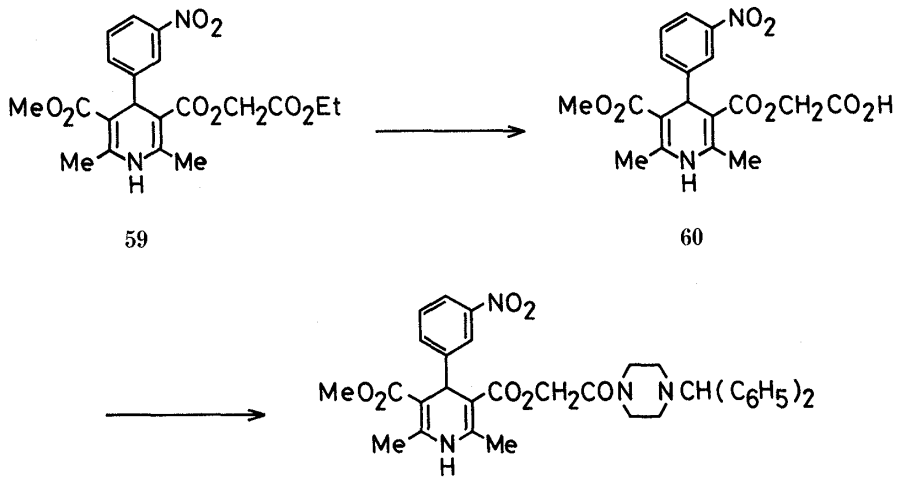
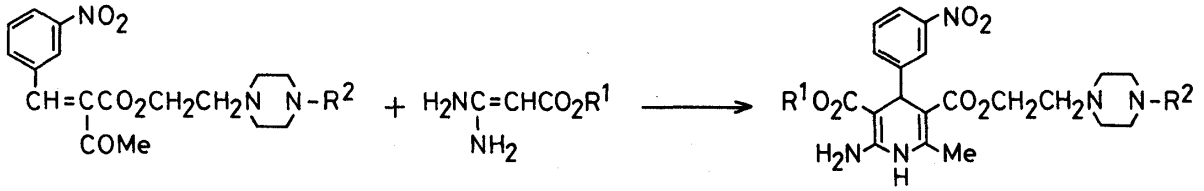


Chart 3

Hantzsch synthesis,[2] *i.e.* one-pot condensation of aminocrotonates (II), aryl aldehydes (III), and acetoacetates (IV) in refluxing 2-propanol (Chart 1, method A).

One of the most promising compounds as a potent and long-acting antihypertensive drug, 2-(4-diphenylmethyl-1-piperazinyl)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**1**, CV-4093), was also prepared by other variations of the Hantzsch synthesis (Chart 2, methods B—D). A large-scale preparation of **1** was perform-



V VI VII

Chart 4

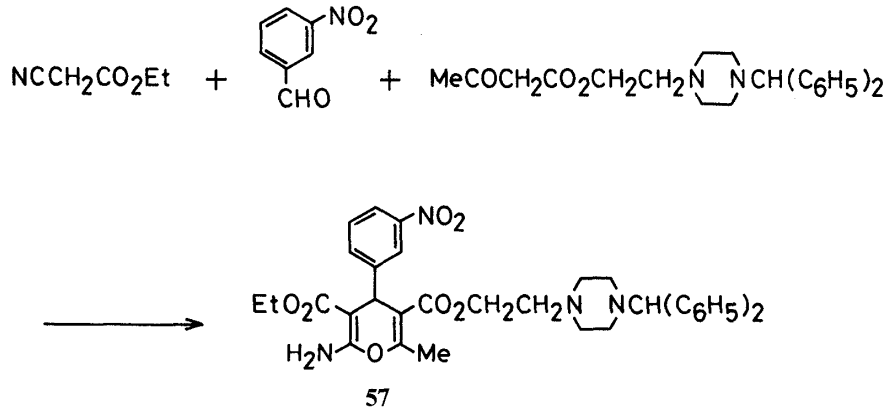


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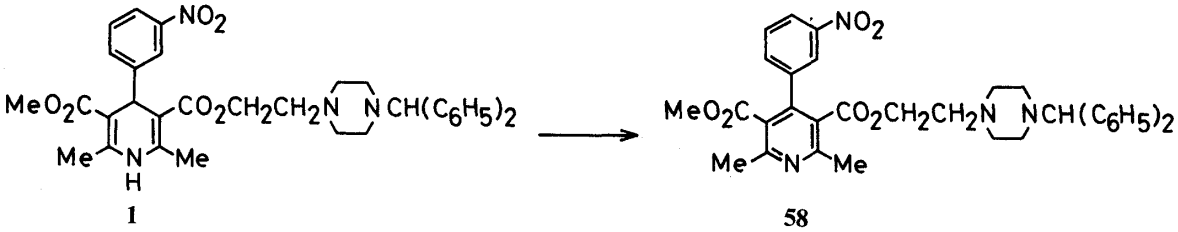
Chart 5



1 58

Chart 6

ed successfully by method B as described in Experimental.

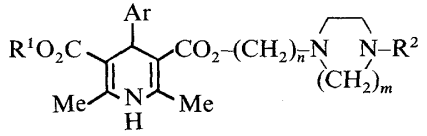
Other analogues such as those having a homopiperazine ring (*e.g.* **3**) and a piperidine ring (*e.g.* **51**, **52**, Table II), were prepared similarly.

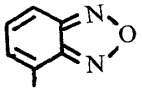
For further structure–activity studies, the following compounds were also synthesized. Compound **53**, in which the piperazine ring was connected through an amide bond, was prepared starting with **59** by the route illustrated in Chart 3. The reactions shown in Charts 4 and 5 afforded the 2-amino-1,4-dihydropyridines (VII) (*i.e.* **54**—**56**) and the oxa-analogue **57**, respectively. Oxidation of **1** with nitric acid gave the corresponding pyridine derivative **58** (Chart 6).

Pharmacological Methods

Male spontaneously hypertensive rats (10 to 11 weeks old, 3 to 6 rats per group), whose systolic blood pressures were about 200 mmHg, were used. The test compounds, prepared as a suspension in 5% gum arabic solution, were orally administered to the rats at a dose of 10 mg/kg. Rats administered 5% gum arabic solution alone were used as the control group. The systolic blood pressure in the caudal artery was measured with an Ueda USM-105R automatic blood pressure meter, 1, 5, 8, and 24 h after each test compound had been administered.[8] Hypotensive effects are shown as maximum reductions in blood pressure (mmHg) from the basal values. The duration of action is shown in hours during which a statistically significant reduction was observed. Changes of the blood pressure in the control groups were less than ± 5 mmHg in all experiments.

TABLE I. Physical and Biological Properties of 1,4-Dihydropyridines (I)

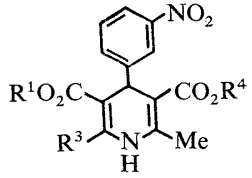


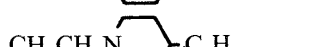
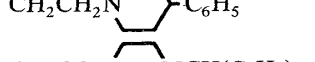
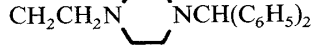
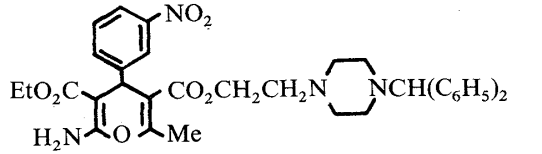
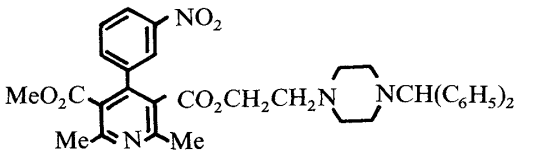
Compd. No.	Ar	R^1	*m*	*n*	R^2	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypotensive action	
										Maximum (mmHg)	Duration (h)
1·2HCl[d]	3-NO_2–C_6H_4	Me	2	2	$(C_6H_5)_2CH$	75.2[e]	174—180[f]	Et–A[f]	$C_{35}H_{38}N_4O_6 \cdot 2HCl$	−91	*ca.* 24
2	3-NO_2–C_6H_4	Et	2	2	$(C_6H_5)_2CH$	48.3	Amorph.	—	$C_{36}H_{40}N_4O_6$	−101	8—24
3	3-NO_2–C_6H_4	Me	3	2	$(C_6H_5)_2CH$	31.7	Amorph.	—	$C_{36}H_{40}N_4O_6$	−38	5—8
4	3-NO_2–C_6H_4	CH_2CH_2OMe	2	2	$(C_6H_5)_2CH$	19.5	Amorph.	—	$C_{37}H_{42}N_4O_7$	−48	8—24
5	2-Cl–C_6H_4	Me	2	2	$(C_6H_5)_2CH$	30.8	Amorph.	—	$C_{35}H_{38}ClN_3O_4$	−80	8—24
6·2HCl	3-Cl–C_6H_4	Me	2	2	$(C_6H_5)_2CH$	28.3[e]	159—161	Ch–M–EA	$C_{35}H_{38}ClN_3O_4 \cdot 2HCl \cdot H_2O$	−97	8—24
7·2HCl	3-Cl–C_6H_4	Et	2	2	$(C_6H_5)_2CH$	43.3[e]	179—182	Ch–M–EA[f]	$C_{36}H_{40}ClN_3O_4 \cdot 2HCl$	−93	8—24
8	2,3-Cl_2–C_6H_3	Me	2	2	$(C_6H_5)_2CH$	51.6	Amorph.	—	$C_{35}H_{37}Cl_2N_3O_4$	−33	8—24
9	2,3-Cl_2–C_6H_3	Et	2	2	$(C_6H_5)_2CH$	30.7	Amorph.	—	$C_{36}H_{39}Cl_2N_3O_4$	−79	*ca.* 24
10·2HCl	3-CF_3–C_6H_4	Me	2	2	$(C_6H_5)_2CH$	52.5[e]	168—170	M–E	$C_{36}H_{38}F_3N_3O_4 \cdot 2HCl \cdot 1/2\,H_2O$	−66	8—24
11·2HCl		Me	2	2	$(C_6H_5)_2CH$	45.0	192—198	M	$C_{35}H_{37}N_5O_5 \cdot 2HCl \cdot 1/2\,H_2O$	−98	8—24
12·2HCl	3-NO_2–C_6H_4	Me	2	2	$(4\text{-F–}C_6H_4)_2CH$	33.3[e]	190—193	M	$C_{35}H_{36}F_2N_4O_6 \cdot 2HCl$	−98	*ca.* 24
13·2HCl	3-NO_2–C_6H_4	Me	2	2	$(4\text{-Cl–}C_6H_4)_2CH$	57.8[e]	208—211	Et–E	$C_{35}H_{36}Cl_2N_4O_6 \cdot 2HCl$	−87	*ca.* 24
14·2HCl	3-NO_2–C_6H_4	Me	2	2	$(4\text{-Me–}C_6H_4)_2CH$	53.1[e]	182—183	Et–E	$C_{37}H_{42}N_4O_6 \cdot 2HCl$	−98	*ca.* 24
15	3-NO_2–C_6H_4	Et	2	2	$(4\text{-Me–}C_6H_4)_2CH$	50.8	Amorph.	—	$C_{38}H_{44}N_4O_6$	−77	8—24
16	3-NO_2–C_6H_4	Me	2	2	$(4\text{-MeO–}C_6H_4)_2CH$	39.3	Amorph.	—	$C_{37}H_{42}N_4O_8$	−88	8—24
17	3-Cl–C_6H_4	Et	2	2	$(4\text{-Me–}C_6H_4)_2CH$	48.4	Amorph.	—	$C_{38}H_{44}ClN_3O_4$	−60	8—24
18	2,3-Cl_2–C_6H_3	Me	2	2	$(4\text{-F–}C_6H_4)_2CH$	52.9	Amorph.	—	$C_{35}H_{35}Cl_2F_2N_3O_4$	−34	8—24
19	2,3-Cl_2–C_6H_3	Me	2	2	$(4\text{-Cl–}C_6H_4)_2CH$	43.2	Amorph.	—	$C_{35}H_{35}Cl_4N_3O_4$	−32	*ca.* 8
20	2,3-Cl_2–C_6H_3	Et	2	2	$(4\text{-Me–}C_6H_4)_2CH$	27.3	Amorph.	—	$C_{38}H_{43}Cl_2N_3O_4$	−49	*ca.* 8
21	3-CF_3–C_6H_4	Et	2	2	$(4\text{-Me–}C_6H_4)_2CH$	44.1	Amorph.	—	$C_{39}H_{44}F_3N_3O_4$	−48	8—24

22	3-CO_2Me–C_6H_4	Et	2	2	(4-Me–C_6H_4)$_2$CH	47.5	Amorph.	—	$C_{40}H_{47}N_3O_6$	−42	*ca.* 8
23·2HCl	3-NO_2–C_6H_4	Me	2	3	(C_6H_5)$_2$CH	34.3	168—173	M	$C_{36}H_{40}N_4O_6 \cdot 2HCl \cdot 1/2\,H_2O$	−63	*ca.* 8
24·2HCl	3-Cl–C_6H_4	Me	2	3	(C_6H_5)$_2$CH	45.6	169—172	M	$C_{36}H_{40}ClN_3O_4 \cdot 2HCl$	−50	8—24
25	3-NO_2–C_6H_4	Me	2	2	(C_6H_5)$_2$$CHCH_2$	36.4	Amorph.	—	$C_{36}H_{40}N_4O_6$	−58	*ca.* 8
26	3-NO_2–C_6H_4	Me	2	2	C_6H_5	51.2	129—130	E	$C_{28}H_{32}N_4O_6$	−60	*ca.* 8
27·HCl	3-NO_2–C_6H_4	Me	2	2	4-F–C_6H_4	76.4[e]	219—221	M–A	$C_{28}H_{31}FN_4O_6 \cdot HCl$	−51	8—24
28	3-NO_2–C_6H_4	Et	2	2	4-F–C_6H_4	45.3	129—131.5	EA–H	$C_{29}H_{33}FN_4O_6$	−67	*ca.* 24
29	3-NO_2–C_6H_4	Me	2	2	2-Cl–C_6H_4	46.5	153—154	E–H	$C_{28}H_{31}ClN_4O_6$	−44	8—24
30·HCl	3-NO_2–C_6H_4	Me	2	2	3-Cl–C_6H_4	58.5[e]	192—196	M	$C_{28}H_{31}ClN_4O_6 \cdot HCl$	−77	8—24
31	3-NO_2–C_6H_4	Me	2	2	4-Cl–C_6H_4	55.7	141.5—143	E–H	$C_{28}H_{31}ClN_4O_6$	−57	8—24
32	3-NO_2–C_6H_4	Me	2	2	2-Me–C_6H_4	72.1	156—157	IPE–H	$C_{29}H_{34}N_4O_6$	−69	8—24
33	3-NO_2–C_6H_4	Me	2	2	2-MeO–C_6H_4	55.6	157—158	E	$C_{29}H_{34}N_4O_7$	−35	*ca.* 5
34	3-NO_2–C_6H_4	Me	2	2	4-MeO–C_6H_4	62.1	169—171	IPE	$C_{29}H_{34}N_4O_7$	−41	5—8
35	3-NO_2–C_6H_4	Me	2	2	3-CF_3–C_6H_4	82.7	134—136	E	$C_{29}H_{31}F_3N_4O_6$	−68	8—24
36	3-NO_2–C_6H_4	Me	2	2	2,3-Cl_2–C_6H_3	75.7	189—190	E–H	$C_{28}H_{30}Cl_2N_4O_6$	−39	8—24
37	3-NO_2–C_6H_4	Me	2	2	2,5-Cl_2–C_6H_3	54.9	170—172	IPE–H	$C_{28}H_{30}Cl_2N_4O_6$	−46	*ca.* 8
38	3-NO_2–C_6H_4	Me	2	2	3-Cl-4-Me–C_6H_3	54.8	155—157	E–H	$C_{29}H_{33}ClN_4O_6$	−85	8—24
39	2-Cl–C_6H_4	Me	2	2	3-Cl–C_6H_4	24.1	130—132	IPE–H	$C_{28}H_{31}Cl_2N_3O_4$	−38	*ca.* 8
40	3-Cl–C_6H_4	Me	2	2	C_6H_5	44.2	147—148.5	IPE–H	$C_{28}H_{32}ClN_3O_4$	−30	5—8
41	3-Cl–C_6H_4	Me	2	2	4-F–C_6H_4	34.1	135—136.5	A–IPE	$C_{28}H_{33}ClFN_3O_4$	−35	8—24
42	3-Cl–C_6H_4	Me	2	2	2-Cl–C_6H_4	52.6	161.5—163	IPE–H	$C_{28}H_{31}Cl_2N_3O_4$	−39	*ca.* 8
43	3-Cl–C_6H_4	Me	2	2	4-Cl–C_6H_4	47.5	127—131	IPE–H	$C_{28}H_{31}Cl_2N_3O_4$	−58	8—24
44	3-Cl–C_6H_4	Me	2	2	2-Me–C_6H_4	48.6	151—153	IPE–H	$C_{29}H_{34}ClN_3O_4$	−54	*ca.* 8
45	3-Cl–C_6H_4	Me	2	2	4-MeO–C_6H_4	50.9	163.5—164.5	IPE	$C_{29}H_{34}ClN_3O_5$	−33	5—8
46	2,3-Cl_2–C_6H_3	Me	2	2	4-F–C_6H_4	34.9	146—148	EA–E	$C_{28}H_{30}FCl_2N_3O_4$	−54	8—24
47	2,3-Cl_2–C_6H_3	Me	2	2	3-Cl–C_6H_4	29.2	140—143	E–H	$C_{28}H_{30}Cl_3N_3O_4$	−44	8—24
48	3-CF_3–C_6H_4	Me	2	2	3-Cl–C_6H_4	44.6	141—143	E–H	$C_{29}H_{31}ClF_3N_3O_4$	−40	*ca.* 8
49	3-NO_2–C_6H_4	Me	2	2	C_6H_5CO	42.2	Amorph.	—	$C_{29}H_{32}N_4O_7$	−3	—
50·2HCl	3-NO_2–C_6H_4	Me	2	2	Me	45.3	187—190	M	$C_{23}H_{30}N_4O_6 \cdot 2HCl$	−10	<5
Nifedipine										−45	<5
Nicardipine·HCl										−38	<5

a) Yield by method A. *b*) A, acetone; Ch, chloroform; E, ethyl ether; EA, ethyl acetate; Et, ethanol; H, hexane; IPE, isopropyl ether; M, methanol. *c*) All compounds were analyzed for C, H and N; the analytical results were within ±0.4% of the calculated values. *d*) Also referred to as CV-4093 (2HCl). *e*) Yield of the amorphous powder which was first isolated by chromatography and is analytically pure. *f*) For details, see Experimental.

TABLE II. Physical and Biological Properties of Compounds Related to I



Compd. No.	R^1	R^3	R^4	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]	Hypotensive action	
								Maximum (mmHg)	Duration (h)
51	Me	Me		29.9[c]	Amorph.	—	$C_{36}H_{39}N_3O_6$	−73	8—24
52	Me	Me		14.2[d]	159—160	Pr	$C_{29}H_{33}N_3O_6$	−58	8—24
53	Me	Me		29.7[e]	177—180	EA–IPE	$C_{35}H_{36}N_4O_7$	+6	—
54·$(CO_2H)_2$	Et	NH_2		60.5[f]	152—153	Et–E	$C_{35}H_{39}N_5O_6 \cdot C_2H_2O_4$	−82	8—24
55·$(CO_2H)_2$	iso-Pr	NH_2		69.5[f]	157—160	Et–E	$C_{30}H_{37}N_5O_6 \cdot C_2H_2O_4$	−81	8—24
56·$(CO_2H)_2$	Et	NH_2		38.0	153—155	Et–E	$C_{36}H_{40}N_4O_6 \cdot C_2H_2O_4$	−61	8—24
57				71.0	Amorph.	—	$C_{35}H_{38}N_4O_7$	0	—
58				90.1	Amorph.	—	$C_{35}H_{36}N_4O_6$	+4	—

a) E, ethyl ether; EA, ethyl acetate; Et, ethanol; IPE, isopropyl ether; Pr, 2-propanol. *b*) See footnote *c*) in Table I. *c*) Prepared by method A. *d*) Prepared by method B. *e*) For details, see Experimental. *f*) See footnote *e*) in Table I.

Results and Discussion

The hypotensive properties of the new dihydropyridine derivatives (I) and related compounds in SHR are shown in Tables I and II.

In general, compounds I possessing an electron-attracting group at the *ortho*- or *meta*-position of the phenyl ring at the 4-position showed more potent and/or longer-lasting hypotensive action than the known dihydropyridines, nifedipine and nicardipine. In particular, a highly potent and long-lasting effect was seen with compounds having a nitro- or a chlorophenyl group at the 4-position in combination with an *N*-diphenylmethyl substituent on the piperazinylethyl side chain (*e.g.* **1**, **2**, **5**, **6**, **7**). Compound **11**, which has a 2,1,3-benzoxadiazol-4-yl moiety, as in dazodipine (PY-108-068[9]), also had very potent activity. Compounds containing substituents, such as fluorine, chlorine, methyl and methoxy, on the aromatic rings of the diphenylmethyl group retained the hypotensive properties (*e.g.* **12**—**22**).

Although the insertion of another methylene in the three different directions of the diphenylmethylpiperazinylethyl moiety of **1** or **6** resulted in a decrease of potency and duration of action (see **3**, **23**, **24**, and **25**), these compounds still have better properties as antihypertensive agents than the known dihydropyridines.

Compounds having a phenyl or a substituted phenyl group as an *N*-substituent of the piperazine ring tend to have less-potent and shorter-lasting activity than the corresponding diphenylmethyl derivatives, but they also appeared to be superior to nifedipine and nicardipine in terms of potency and/or duration of action, as seen in compounds **26**—**48**. The variation of the substituents on the *N*-phenyl ring did not cause marked changes in activity, but the pharmacological properties of **28**, **30**, **32**, **35** and **38** seem to be prominent.

While the *N*-benzoyl- and *N*-methylpiperazine derivatives **49** and **50** were almost inactive, the 4-diphenylmethyl- and 4-phenylpiperidine derivatives **51** and **52** (Table II), deaza-analogues of **1** and **26**, had potent activity. These results show that the 4-nitrogen of the piperazine ring is not essential, but the presence of the diphenylmethyl or the phenyl moiety at the particular site of an appropriate heterocyclic ring is a very important structural feature for remarkable hypotensive action. However, elimination of the basicity of the 1-nitrogen from the piperazine by transforming it to an amide-nitrogen as in **53** resulted in complete loss of activity despite the presence of the diphenylmethyl group. The basic nitrogen at this site appears to be important, as in the case of nicardipine.[4]

The 2-amino analogues (**54**—**56**), retaining the above-mentioned structural requirements, also had potent activity. The pyridine analogue (**58**) and the dihydropyran analogue (**57**), however, lacked activity, clearly indicating that the 1,4-dihydropyridine skeleton is essential for the hypotensive action of this series of compounds.

As regards the other ester functionality R^1 in the dihydropyridines synthesized, there seems to be no significant difference among the activities of methyl, ethyl and isopropyl esters.

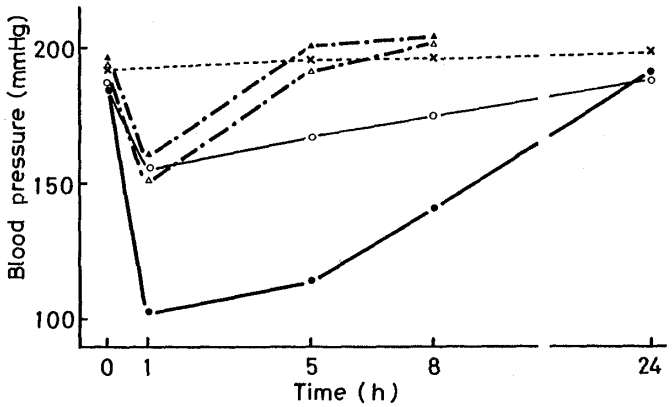


Fig. 2. Hypotensive Action of **1** (CV-4093) in SHR

---×---, control; —●—, CV-4093 (2HCl) (10 mg/kg, *p.o.*); —○—, CV-4093 (2HCl) (3 mg/kg, *p.o.*); ---▲---, nicardipine·HCl (10 mg/kg, *p.o.*); ---△---, nifedipine (10 mg/kg, *p.o.*).

The methoxyethyl ester, however, showed slightly lower activity (**1**, **2** *vs.* **4**).

The hypotensive profile of **1** (CV-4093) is illustrated in Fig. 2 and compared with those of nifedipine and nicardipine. A detailed pharmacological study of CV-4093 is in progress and the results will be published elsewhere.[10]

Experimental

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 or a Hitachi IR-260-10 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm. The following abbreviations are used: s=singlet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were measured on a JEOL JMS-01SC instrument. Column chromatography was performed on 70—230 mesh silica gel from Merck.

General Procedure for Piperazinylalkyl Acetoacetates (IV)——Diketene (0.01—0.011 mol) was added to stirred, preheated (70—80 °C) 4-substituted 1-piperazinealkanols (0.01 mol) or their toluene solutions at a rate such that the temperature could be kept at 70—80 °C without further heating. After addition was complete, the mixture was stirred for 1—3 h at 70—80 °C. The acetoacetates (IV) thus formed were used in the next reaction without further purification or after brief purification by column chromatography on silica gel.

Other acetoacetates used for the preparation of 1,4-dihydropyridines related to I were prepared similarly.

2-(4-Diphenylmethyl-1-piperazinyl)ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (1, CV-4093)——Method A: A solution of 3-nitrobenzaldehyde (2.66 g), 2-(4-diphenylmethyl-1-piperazinyl)ethyl acetoacetate (6.09 g) and methyl 3-aminocrotonate (2.03 g) in 2-propanol (25 ml) was refluxed for 6 h with stirring. The solvent was removed and the residue was purified by chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give **1** as an oil. A solution of the oil in a small amount of isopropyl ether was treated with hexane at 0 °C with stirring to yield analytically pure **1** as a pale yellow powder (7.35 g, 75.2%). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1680. *Anal.* Calcd for $C_{35}H_{38}N_4O_6$: C, 68.83; H, 6.27; N, 9.17. Found: C, 68.97; H, 6.27; N, 9.05.

Dihydrochloride Monohydrate: A solution of the free base of **1** (3.90 g) obtained above in CH_2Cl_2 (10 ml) was treated with a slight excess of HCl/dioxane, and a small amount of water was added thereto at 0 °C with stirring. The precipitated crystals were collected, washed with Et_2O and dried to afford **1**·2HCl·H_2O (4.23 g, 94.4%). The crystals were dissolved in CH_2Cl_2–MeOH, and the solvents were evaporated off. The residue was then dissolved in AcOEt, and a small amount of water was added thereto with ice-cooling to give light yellow crystals, mp 167—170 °C. IR ν_{max}^{Nujol} cm^{-1}: 3420 (br), 3320, 2430 (br), 1710, 1645. *Anal.* Calcd for $C_{35}H_{38}N_4O_6 \cdot 2HCl \cdot H_2O$: C, 59.90; H, 6.03; N, 7.99. Found: C, 60.06; H, 5.79; N, 7.84.

Method B: A solution of 3-nitrobenzaldehyde (307 mg) and 2-(4-diphenylmethyl-1-piperazinyl)ethyl acetoacetate (668 mg) in benzene (20 ml) containing a catalytic amount of piperidine was refluxed for 2 h with continuous removal of water by a Dean–Stark apparatus. The benzene layer was washed with water, dried (Na_2SO_4) and concentrated to give crude 2-(4-diphenylmethyl-1-piperazinyl)ethyl 2-(3-nitrobenzylidene)acetoacetate as an oil. A solution of the oil and methyl 3-aminocrotonate (280 mg) in 2-propanol (10 ml) was refluxed for 2 h with stirring. After removal of the solvent, the residue was purified by chromatography on silica gel to yield **1** (725 mg, 67.6%), which was then treated in the same manner as in method A to give **1**·2HCl·H_2O (460 mg, 38.3%), mp 166—169 °C.

Compound **52** (Table II) was prepared by this method.

Method C: An excess amount of 20% NH_3/EtOH was added to a solution of 2-(4-diphenylmethyl-1-piperazinyl)ethyl acetoacetate (3.0 g) in EtOH (5 ml), and the mixture kept in a refrigerator overnight. The solvent was removed *in vacuo* to give crude 2-(4-diphenylmethyl-1-piperazinyl)ethyl 3-aminocrotonate as an oil. A solution of the oil and methyl 2-(3-nitrobenzylidene)acetoacetate (1.97 g) in 2-propanol (30 ml) was refluxed for 10 h with stirring. Concentration followed by treatment in the same manner as in method A or B gave **1**·2HCl·H_2O (0.83 g, 15.0%), mp 164—169 °C.

Method D: A solution of crude 2-(4-diphenylmethyl-1-piperazinyl)ethyl 3-aminocrotonate prepared from the corresponding acetoacetate (3.21 g), 3-nitrobenzaldehyde (0.88 g) and methyl acetoacetate (1.15 g) in 2-propanol (15 ml) was refluxed for 6 h with stirring. The solvent was removed and the residue treated in the same manner as in method A or B to yield **1**·2HCl·H_2O (1.06 g, 17.8%), mp 166—169 °C.

Large-Scale Preparation on **1**·2HCl by Method B: Diketene (175 ml) was added dropwise to a stirred and heated (*ca.* 70 °C) 4-diphenylmethyl-1-piperazineethanol (oil; 552 g) at a rate such that the temperature did not exceed 80 °C. After the addition was complete, the mixture was stirred at 70—80 °C for 2 h. Excess diketene was distilled off *in vacuo* to give crude 2-(4-diphenylmethyl-1-piperazinyl)ethyl acetoacetate (739.8 g) as a light brown oil. A mixture of this oil, 3-nitrobenzaldehyde (281.0 g), piperidine (30 ml) and benzene (2000 ml) was heated under reflux for 5 h with continuous removal of water by a Dean–Stark apparatus. The benzene layer was washed with water and dried ($MgSO_4$). Removal of the solvent gave crude 2-(4-diphenylmethyl-1-piperazinyl)ethyl 2-(3-nitrobenzylidene)-acetoacetate as an oil.[11] A solution of this oil and methyl 3-aminocrotonate (200 g) in 2-propanol (2500 ml) was

then refluxed for 7 h with stirring. The solvent was removed *in vacuo* and the residue was partitioned between $CHCl_3$ (3500 ml) and water (1000 ml). The $CHCl_3$ layer was separated, washed with water (1000 ml), and dried ($MgSO_4$). After removal of the solvent, the residue was treated with 16.2% HCl/MeOH (502 g) and concentrated *in vacuo*. The residue was dissolved in hot AcOEt (1200 ml), diluted with Et_2O (700 ml) and left standing overnight at room temperature. The resulting yellow precipitate was filtered off and washed with acetone to give **1**·2HCl (467.9 g, 36.8%). The pure anhydrous **1**·2HCl was obtained in two crystalline forms (α- and β-forms) as follows.

α-Form: The crude **1**·2HCl (461.1 g) was dissolved in hot 95% EtOH (3300 ml) and the solution was left to stand at room temperature overnight. The precipitate was filtered off, washed with EtOH (*ca.* 400 ml) and dreid at 60 °C *in vacuo* to give yellow crystals of α-form (316.4 g), mp 157—163 °C. IR ν_{max}^{Nujol} cm^{-1}: 3370, 2390 (br), 1634, 1625. *Anal.* Calcd for $C_{35}H_{38}N_4O_6 \cdot 2HCl$: C, 61.49; H, 5.90; N, 8.20. Found: C, 61.18; H, 6.02; N, 7.90.

β-Form: A suspension of the α-form (314.2 g) in acetone (5000 ml) was stirred for 3 h and then allowed to stand overnight at room temperature, druing which time the yellow crystals of α-form were converted to light-yellow fine crystals of β-form. The crystals were filtered off, washed with acetone (1000 ml), and dried *in vacuo* at 75—80 °C. Yield 273.4 g. mp 174—180 °C. This sample showed mp 204—206.5 °C (dec.) when measured in an open capillary tube. IR ν_{max}^{Nujol} cm^{-1}: 3350, 2350 (br), 2170 (br), 1720, 1627. NMR (DMSO-d_6) δ: 2.27 (3H, s), 2.33 (3H, s), 3.12 (4H, br), 3.50 (6H, br), 3.53 (3H, s), 4.37 (2H, br), 4.97 (1H, s), 5.45 (1H, br), 7.2—7.9 (14H, m), 9.24 (1H, s). *Anal.* Calcd for $C_{35}H_{38}N_4O_6 \cdot 2HCl$: C, 61.49; H, 5.90; N, 8.20. Found: C, 61.50; H, 5.81; N, 8.32. This sample showed a different X-ray diffraction pattern from that of the α-form obtained above.

Preparation of Crystalline Free Base of **1**: A stirred suspension of **1**·2HCl (β-form, 6.0 g) in Et_2O was treated with 5% aq. NH_4OH. The Et_2O layer was separated, washed with water and dried ($MgSO_4$). The solvent was removed and the residue was recrystallized from isopropyl ether–hexane to give **1** (4.78 g, 89.2%) as light yellow crystals, mp 125—128 °C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1705, 1650. NMR ($CDCl_3$) δ: 2.33 (6H, s), 2.40 (8H, m), 2.58 (2H, t, J=6 Hz), 3.61 (3H, s), 4.15 (2H, t, J=6 Hz), 4.20 (1H, s), 5.10 (1H, s), 5.93 (1H, s), 7.1—8.1 (14H, m). *Anal.* Calcd for $C_{35}H_{38}N_4O_6$: C, 68.83; H, 6.27; N, 9.17. Found: C, 68.85; H, 6.24; N, 8.97.

Other compounds (**2**—**51**) were prepared by method A. Typical examples are given below.

2-(4-Diphenylmethyl-1-piperazinyl)ethyl Ethyl 4-(3-Chlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (7)——A solution of 3-chlorobenzaldehyde (1.11 g), 2-(4-diphenylmethyl-1-piperazinyl)ethyl acetoacetate (3.0 g) and ethyl 3-aminocrotonate (1.07 g) in 2-propanol (20 ml) was refluxed for 6 h with stirring. The solvent was removed and the residue was chromatographed on silica gel (200 g) with $CHCl_3$ to give **7** as an amorphous powder (2.1 g, 43.3%). IR ν_{max}^{Nujol} cm^{-1}: 3310, 1690, 1675. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.5 Hz), 2.30 (3H, s), 2.31 (3H, s), 2.41 (8H, br), 2.56 (2H, t, J=6 Hz), 3.93—4.25 (5H, m), 4.95 (1H, s), 5.63 (1H, br s), 6.9—7.5 (14H, m). *Anal.* Calcd for $C_{36}H_{40}ClN_3O_4$: C, 70.40; H, 6.56; N, 6.84. Found: C, 70.23; H, 6.66; N, 6.88.

Dihydrochloride: A solution of the free **7** (1.7 g) in a small amount of EtOH was treated with HCl/EtOH to give **7**·2HCl as crystals (1.80 g). The crystals were dissolved in $CHCl_3$–MeOH (3:1, v/v), and the solution was concentrated *in vacuo* without heating. Dilution with AcOEt gave colorless crystals (1.74 g, 91.6%), mp 179—182 °C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 2360 (br), 2150 (br), 1720, 1660. *Anal.* Calcd for $C_{36}H_{40}ClN_3O_4 \cdot 2HCl$: C, 62.93; H, 6.16; N, 6.12. Found: C, 62.67; H, 6.44; N, 6.00.

2-[4-(3-Chlorophenyl)-1-piperazinyl]ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (30)——A solution of 3-nitrobenzaldehyde (2.41 g), 2-[4-(3-chlorophenyl)-1-piperazinyl]ethyl acetoacetate (4.93 g) and methyl 3-aminocrotonate (1.83 g) in 2-propanol (70 ml) was refluxed for 7 h with stirring. The reaction mixture was concentrated and the residue was chromatographed on silica gel with Et_2O–AcOEt (10:1, v/v) to give an oil. This was further purified by reprecipitation from AcOEt–Et_2O–hexane to yield **30** as a powder (4.93 g, 58.5%). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1680 (br). NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.36 (3H, s), 2.6 (6H, br m), 3.1 (4H, m), 3.63 (3H, s), 4.22 (2H, t, J=6 Hz), 5.12 (1H, s), 5.89 (1H, s), 6.7—8.2 (8H, m). *Anal.* Calcd for $C_{28}H_{31}ClN_4O_6$: C, 60.59; H, 5.63; N, 10.09. Found: C, 60.42; H, 5.64; N, 9.77.

Hydrochloride: The free **30** (330 mg) was treated with HCl/MeOH to give **30**·HCl (333 mg, 94.7%). Recrystallization from MeOH gave yellow prisms, mp 192—196 °C. IR ν_{max}^{Nujol} cm^{-1}: 3200, 2430 (br), 1700. *Anal.* Calcd for $C_{28}H_{31}ClN_4O_6 \cdot HCl$: C, 56.86; H, 5.45; N, 9.47, Cl, 11.99. Found: C, 56.79; H, 5.48; N, 9.67; Cl, 11.85.

2-[4-(3-Chloro-4-methylphenyl)-1-piperazinyl]ethyl Methyl 1,4-Dihydro-4-(3-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (38)——A solution of 3-nitrobenzaldehyde (746 mg), 2-[4-(3-chloro-4-methylphenyl)-1-piperazinyl]ethyl acetoacetate (1.52 g) and methyl 3-aminocrotonate (568 mg) in 2-propanol (10 ml) was refluxed for 4 h with stirring. The solvent was removed and the residue was chromatographed on silica gel (100 g) with Et_2O. The product (**38**) was recrystallized from Et_2O–hexane to yield yellow crystals (1.40 g, 54.8%) mp 155—157 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1705, 1645. NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.33 (3H, s), 2.35 (3H, s), 2.5—2.7 (6H, m), 3.08 (4H, m), 3.62 (3H, s), 4.19 (2H, t, J=6 Hz), 5.10 (1H, s), 5.81 (1H, br s), 6.6—8.1 (7H, m). *Anal.* Calcd for $C_{29}H_{33}ClN_4O_6$: C, 61.21; H, 5.85; N, 9.85. Found: C, 61.35; H, 5.87; N, 9.78.

Ethoxycarbonylmethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (59)——A solution of 3-nitrobenzaldehyde (11.02 g), ethoxycarbonylmethyl acetoacetate (13.72 g) and methyl 3-aminocrotonate (8.39 g) in 2-propanol (35 ml) was refluxed for 7 h with stirring. After removal of the solvent, the product (**59**) was isolated by chromatography on silica gel (400 g) with hexane–AcOEt (3:2, v/v). Recrystallization from isopropyl

ether gave yellow crystals (22.66 g, 74.3%), mp 148—150 °C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1735, 1705. NMR ($CDCl_3$) δ: 1.22 (3H, t, J=6.6 Hz), 2.35 (6H, s), 3.62 (3H, s), 4.17 (2H, q, J=6.6 Hz), 4.57 (2H, s), 5.16 (1H, s), 6.28 (1H, br s), 7.33—8.13 (4H, m). *Anal.* Calcd for $C_{29}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.49; H, 5.43; N, 6.50.

Carboxymethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (60)——A solution of **59** (6.38 g) in EtOH (15 ml) was added to a solution of KOH (1.01 g) in EtOH (25 ml). The mixture was stirred at room temperarure for 3 h, diluted with water (100 ml) and extracted with $CHCl_3$. The $CHCl_3$ layer was worked up and the residue was crystallized from CH_2Cl_2–AcOEt to give **60** (3.81 g, 64.0%), mp 183 °C. Recrystallization from CH_2Cl_2–AcOEt gave yellow crystals, mp 184.5—185 °C. IR ν_{max}^{Nujol} cm^{-1}: 3370, 1745, 1705, 1660. NMR (DMSO-d_6) δ: 2.33 (6H, s), 3.61 (3H, s), 4.55 (2H, s), 5.14 (1H, s), 7.13 (1H, br s), 7.21—8.14 (4H, m). *Anal.* Calcd for $C_{18}H_{18}N_2O_8$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.30; H, 4.57; N, 7.10.

(4-Diphenylmethyl-1-piperazinyl)carbonylmethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (53)——Thionyl chloride (0.3 ml) was added dropwise to a stirred solution of **60** (500 mg) in $CHCl_3$ (10 ml). The mixture was stirred at room temperature for 20 min and then refluxed for 10 min. After removal of the solvent, the residue was treated with 1-diphenylmethylpiperazine (323 mg) and K_2CO_3 (212 mg) in benzene (10 ml) under reflux for 2 h. The reaction mixture was washed with water and worked up. The product (**53**) was isolated by chromatography on silica gel (80 g) with hexane–AcOEt (3:2, v/v). Recrystallization from AcOEt–isopropyl ether gave pale yellow crystals (238 mg, 29.7%), mp 177—180 °C. IR ν_{max}^{Nujol} cm^{-1}: 3290, 1705, 1680, 1645. NMR ($CDCl_3$) δ: 2.42—2.49 (4H, m), 2.34 (6H, s), 3.20—3.72 (4H, m), 3.59 (3H, s), 4.22 (1H, s), 4.53 (1H, d, J=13.5 Hz), 4.77 (1H, d, J=13.5 Hz), 5.13 (1H, s), 6.50 (1H, s), 7.06—8.12 (14H, m). *Anal.* Calcd for $C_{35}H_{36}N_4O_7$: C, 67.29; H, 5.81; N, 8.97. Found: C, 67.22; H, 5.79; N, 8.93.

5-[2-(4-Diphenylmethyl-1-piperazinyl)ethyl] 3-Ethyl 2-Amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (54) Oxalate——A solution of Na (200 mg) in abs. EtOH (10 ml) was added dropwise to a boiling solution of 2-(4-diphenylmethyl-1-piperazinyl)ethyl 2-(3-nitrobenzylidene)acetoacetate (4.37 g) and ethyl amidinoacetate hydrochloride (1.42 g) in abs. EtOH (10 ml) during 15 min. The mixture was refluxed for another 5 min and filtered to remove NaCl. The filtrate was concentrated and the residue was chromatographed on silica gel (120 g) with Et_2O–AcOEt (10:1, v/v) to give **54** as a yellow powder (3.22 g, 60.5%). A solution of **54** (2.48 g) in a small amount of EtOH was treated with a solution of oxalic acid in EtOH followed by addition of Et_2O. The precipitate was collected and recrystallized from EtOH–Et_2O to yield **54**·oxalate as a yellow crystalline powder (1.83 g), mp 152—153 °C. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3290, 1675, 1645. NMR (DMSO-d_6) δ: 1.09 (3H, t, J=7.2 Hz), 2.31 (3H, s), 2.23—3.03 (10H, m), 3.73—4.24 (4H, m), 4.31 (1H, s), 4.67 (1H, s), 6.13 (2H, br), 6.87 (2H, br s), 7.04—8.02 (14H, m), 9.11 (1H, s). *Anal.* Calcd for $C_{35}H_{39}N_5O_6 \cdot C_2H_2O_4$: C, 62.09; H, 5.77; N, 9.78. Found: C, 62.47; H, 6.09; N, 9.57.

Compounds **55** and **56** were prepared similarly.

5-[2-(4-Diphenylmethyl-1-piperazinyl)ethyl] 3-Ethyl 2-Amino-5-methyl-4-(3-nitrophenyl)-4*H*-pyran-3,5-dicarboxylate (57)——A solution of 3-nitrobenzaldehyde (900 mg), 2-(4-diphenylmethyl-1-piperazinyl)ethyl acetoacetate (2.06 g), ethyl cyanoacetate (674 mg) and piperidine (3 drops) in 2-propanol (10 ml) was refluxed for 4 h with stirring. The reaction mixture was concentrated, diluted with water and extracted with Et_2O. The extract was worked up and the product (**57**) was isolated by chromatography on silica gel (120 g) with hexane–AcOEt (3:2, v/v) as a white solid (2.41 g, 71.0%). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3300, 1705, 1685. NMR ($CDCl_3$) δ: 1.14 (3H, t, J=6.0 Hz), 2.38 (3H, s), 2.51 (2H, t, J=6.0 Hz), 4.79 (1H, s), 6.18 (2H, br s), 7.03—8.17 (14H, m). *Anal.* Calcd for $C_{35}H_{38}N_4O_7$: C, 67.08; H, 6.11; N, 8.94. Found: C, 66.71; H, 6.07; N, 8.61. MS m/z: 627 (M^+).

2-(4-Diphenylmethyl-1-piperazinyl)ethyl Methyl 2,6-Dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (58)——A mixture of **1**·2HCl (4.0 g), 2 N HNO_3 (25 ml) and dioxane (5 ml) was stirred at 70 °C for 1.5 h. The mixture was diluted with water (30 ml), made alkaline with 50% NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was worked up and the product (**58**) was isolated by chromatography on silica gel (120 g) with hexane–AcOEt (1:1, v/v) as a yellowish solid (3.21 g, 90.1%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735. NMR ($CDCl_3$) δ: 2.35 (10H, br s), 2.58 (3H, s), 2.61 (3H, s), 3.53 (3H, s), 4.07 (2H, t, J=6.0 Hz), 4.17 (1H, s), 6.99—7.62 and 8.07—8.27 (14H, m). *Anal.* Calcd for $C_{35}H_{36}N_4O_6$: C, 69.06; H, 5.96; N, 9.20. Found: C, 69.32; H, 6.00; N, 8.93.

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