Synthesis and Antihypertensive Activities of New 1,4-Dihydropyridine Derivatives Containing a Nitrooxy Moiety at the 3-Ester Position[1)]

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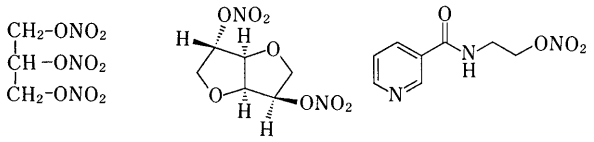
The synthesis of a new series of dihydropyridines containing a nitrooxy moiety at the 3-ester position is described. The antihypertensive activity of the compounds was examined and compared with that of nifedipine; some of them were relatively potent. The structure–activity relationship is also discussed.

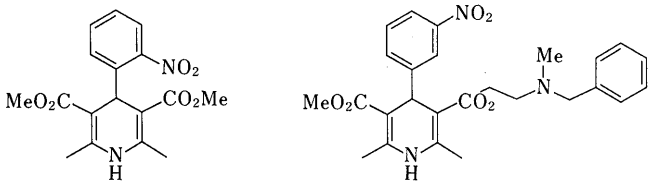
Keywords 1,4-dihydropyridine; calcium antagonist; antihypertensive effect; nitrate; cyclic GMP; structure–activity relationship

Organic nitrate compounds including nitroglycerine, isosorbide-dinitrate, and nicorandil increase the level of cyclic guanosine 5′-monophosphate (cyclic GMP) produced in various vascular smooth muscle tissues and promote relaxation.[2)] On the other hand, 4-aryl-1,4-dihydropyridine derivatives (nifedipine, nicardipine) have a high affinity for the voltage-dependent calcium channel, which results in potent vasodilator effects.[3)] They are therefore useful in treatment of hypertension and angina pectoris. Simultaneous use of calcium antagonist and nitrate compounds enhances the antihypertensive action with little side-effects.[4)] So the combination of nitro-like and calcium-blocking actions in a single molecule was expected to have a potential vasodilating activity superior to that of known 1,4-dihydropyridines. To test the hypothesis, we synthesized novel dihydropyridine derivatives having a nitrate moiety in one of the ester chains and evaluated their antihypertensive properties. The results are presented here.



nitroglycerin isosorbidedinitrate nicorandil

Fig. 1



nifedipine nicardipine

known 1,4-dihydropyridines

Fig. 2

Chemistry

The 1,4-dihydropyridine derivatives (I) listed in Table I

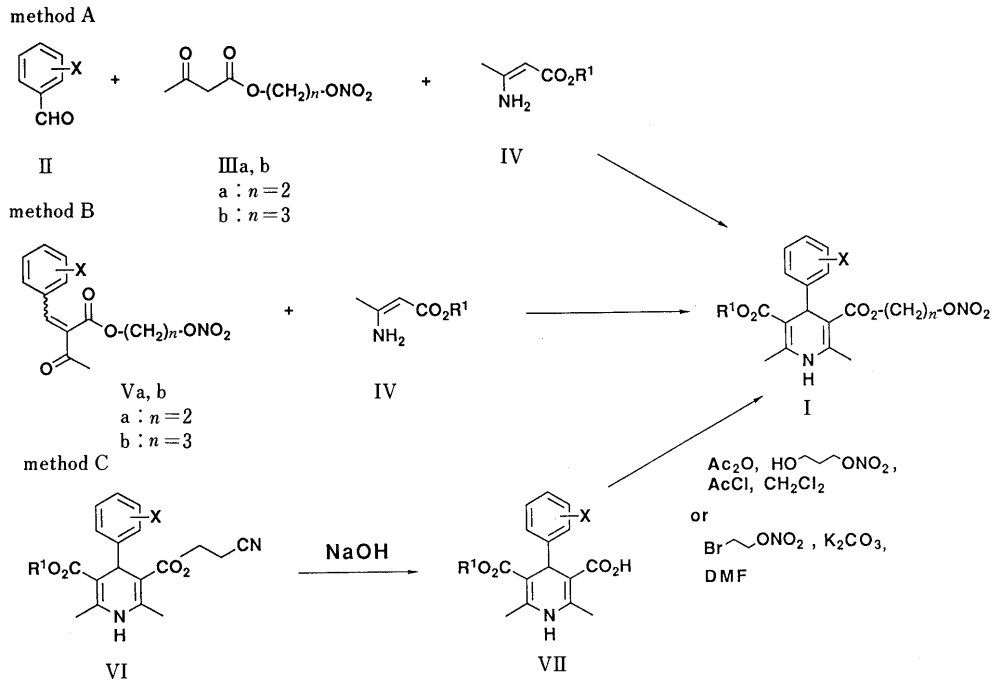


Chart 1

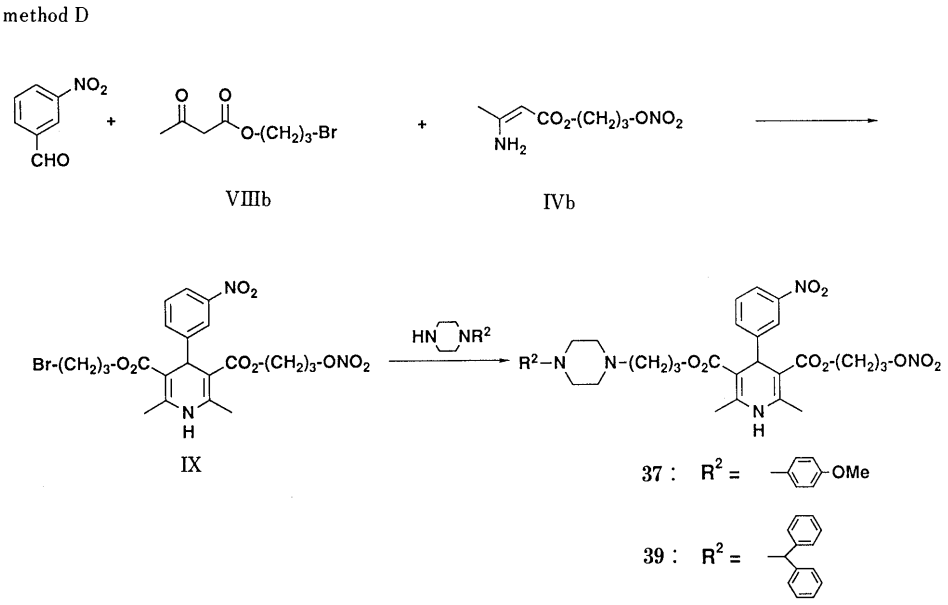


Chart 2

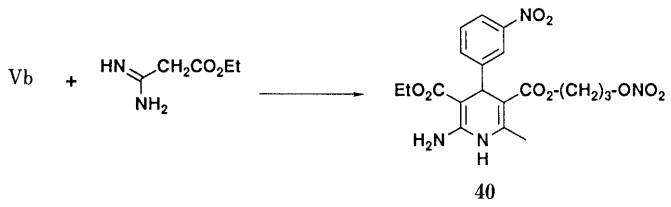


Chart 3

were prepared by three synthetic routes (Chart 1), which involved modifications of the Hantzsch reaction.[5] The reaction of 3-aminocrotonates (IV) with acetoacetates (IIIa, b) and benzaldehyde (II) in 2-propanol under reflux gave the 1,4-dihydropyridine derivatives (I) in 18.5—35.9% yields (method A). The second pathway (method B) involved the reaction of 3-aminocrotonates (IV) with benzylideneacetoacetates (Va, b), which were readily obtained by means of the Knoevenagel reaction from the corresponding aldehydes (II) and alkyl acetoacetates (IIIa, b), prepared by the reaction of diketene with alcohols (XI). This method gave good yields (21.8—67.7%), and purification was straightforward.

An alternative route to I, which is more suitable for large-scale preparation, involves esterification of the half-carboxylic acid (VII) prepared by removal of the cyanoethyl group in VI (method C).[6] Treatment of VII with acetic anhydride gave the mixed anhydride,[7] which reacted with the 3-nitrooxypropyl alcohol (X) in the presence of a catalytic amount of acetyl chloride to give I in moderate to good yields in most instances.

Compounds I were also obtained in good yields from VII by esterification of 2-nitrooxyethyl bromide in dimethylformamide in the presence of potassium carbonate. The 1,4-dihydropyridines **37** and **39** were also prepared from the bromo compound (IX) with piperazine derivatives in acetonitrile in the presence of potassium carbonate (Chart 2).

For further structure–activity studies, the following compounds were also synthesized. Compounds **41** and **42** having a carbamoyl or a cyano group were prepared by the route illustrated in Charts 4 and 5. The 2-amino-1,4-dihydropyridine (**40**) was prepared by the reaction shown in Chart 3. The denitro compound (**43**) of **1** was prepared from VII by esterification of 2-bromoethanol (Chart 6).

The starting materials (IIIa, b and IVb) were prepared as follows. The reaction of the 3-nitrooxypropanol (X)[8] with diketene almost exclusively afforded the acetoacetate (IIIb), which was treated with ammonia in tetrahydrofuran to give 3-nitrooxypropyl 3-aminocrotonate (IVb). 2-Nitrooxyethyl acetoacetate (IIIa) was obtained from VIIIa by using silver nitrate[9] in acetonitrile.

Results and Discussion

The antihypertensive activities and their duration of the new dihydropyridine derivatives (I) are shown in Tables I and II.

The screening test for vasodilating activity was carried out by measurement of femoral and vertebral blood flow in anesthetized dogs. The test drugs were administered into the artery. The potency was represented as the amplitude of the maximum increase in blood flow and its duration was represented as the half duration of the peak effect. The vasodilating activity was expressed as the ratio of the potency to that of nifedipine.

First, the 1,4-dihydropyridine (**2**), in which one carboxylate group of the 1,4-dihydropyridine-3,5-dicarboxylates was replaced by a nitrooxy alkyl ($n=2$) ester, showed more potent and/or longer-lasting antihypertensive activity than the known dihydropyridine, nifedipine. As regards the other functionality R^1 in the dihydropyridines prepared, the compounds with a small alkyl group such as methyl (**1**) and isopropyl (**3**) ester showed activity equal to or greater than that of nifedipine. As regards the size of the R^1, long chain alkyl, unsaturated alkyl and aralkyl substitution as well as alkoxyalkyl substitution (**6** and **8** except for **7**) generally caused a decrease in activity. This trend may be seen throughout Table I.

Next, when the alkyl chain of R^1 was lengthened from ethylene to trimethylene ($n=2\rightarrow3$, **13**—**22** except for **18**), all of these compounds were much less potent than their

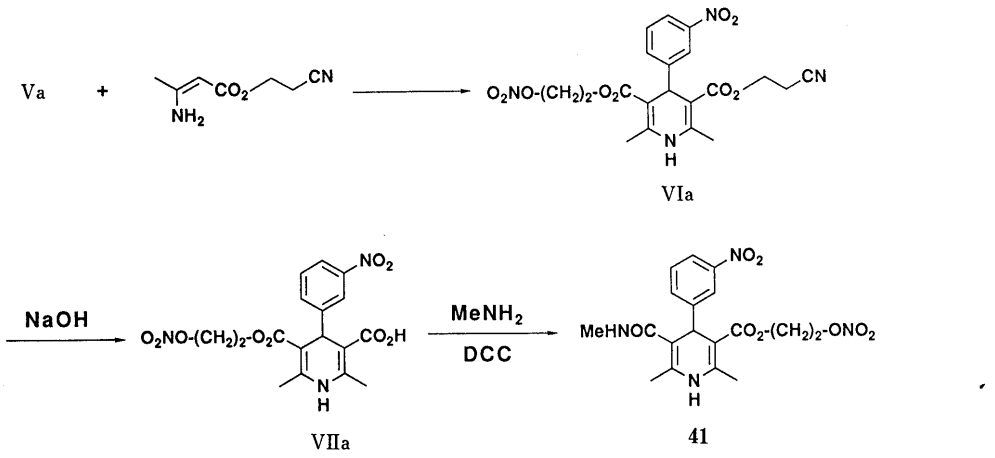


Chart 4

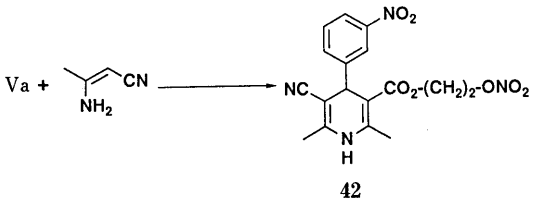


Chart 5

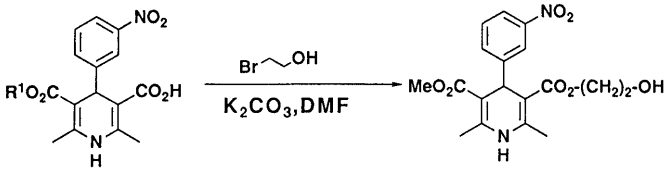
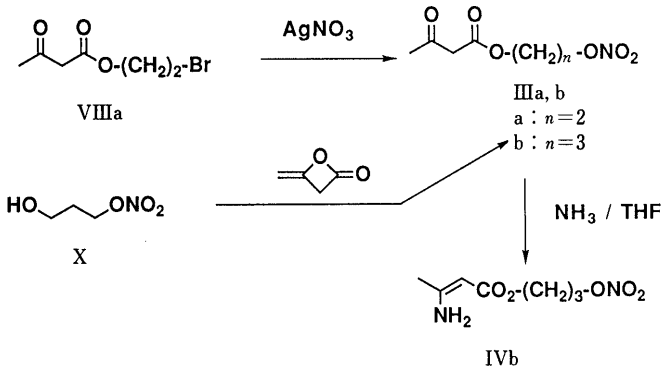


Chart 6



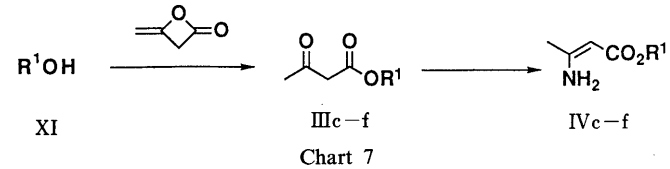


Chart 7

ethylene analogues (**1**—**3**). In the ethylene series, the compound with 2-nitrophenyl (**12**) at the 4-position is as potent as the parent compound **2**, while in the trimethylene series, the 2-nitrophenyl compounds (**23** and **24**) are more potent than the 3-nitrophenyl materials (**13** and **14**) and as potent as nifedipine.

When various substituents were introduced into the benzene ring at the 4-position of the dihydropyridine ring instead of the nitro group, the dihydropyridine (**26**—**33**) with 2-fluoro, 3-fluoro, 2-trifluoromethyl, 3-trifluoromethyl, 3-chloro, and 2,3-dichloro moieties showed reduced potency. Compounds **34** and **35**, possessing an electron-releasing group (3-methyl or 3,4-methylenedioxy) showed slightly lower activities. The replacement of the alkylester groups by the 2-(*N*-benzyl-*N*-methylamino)ethylester (**36**) or 3-(4-methoxyphenyl-1-piperazinyl)propylester groups (**37**) resulted in similar potency to that of **1** and **2**, while the *N*-benzhydrylpiperazinyl compounds (**38** and **39**) are less potent than **36** and **37** in the femoral artery. The 2-amino analogue (**40**), retaining the above-mentioned structural requirement, showed lower the activity. The 1,4-dihydropyridines (**41** and **42**), in which a carboxylate group was replaced by a carbamoyl or a cyano group, showed weaker antihypertensive activity than the corresponding carboxylate compounds.

As a derivative (**43**) of **1**, synthesized as shown in Chart 6, showed only weak activity, a nitrooxy group was confirmed to be required for potent activity.

In conclusion, we can say that substitution of one carboxylate group of 1,4-dihydropyridine-3,5-dicarboxylate with a nitrooxy lower alkyl ester is a potentially useful approach to obtain effective topical calcium antagonists.

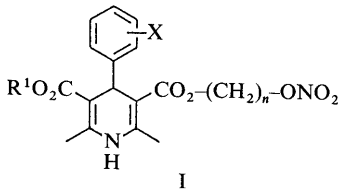
Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO DS-301 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 (200 MHz) spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm. The following abbreviations are used: s=single, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were measured on a Shimadzu LKB 9000 spectrometer. Column chromatography was performed on 70—230 mesh silica gel from Merck.

General Procedure for the Synthesis of Acetoacetate Derivatives IIIa—f. 2-Nitrooxyethyl Acetoacetate (IIIa) Silver nitrate (203.84 g, 1.2 mol) was added to a solution of 2-bromoethyl acetoacetate (VIIIa) (209.04 g, 1 mol) in MeCN (1000 ml), and the mixture was stirred at room temperature for 2 d. The precipitate was filtered off, and washed with MeCN. The filtrate was evaporated under reduced pressure. The residue was subjected to chromatography on silica gel to give IIIa (166.93 g, 87.4%) as a pale yellow oil. MS *m/z*: 191 (M^+).

3-Nitrooxypropyl Acetoacetate (IIIb) Diketene (100.88 g, 1.2 mol) was added dropwise to stirred, preheated (50—60 °C) 3-nitrooxypropyl alcohol (X) (121.09 g, 1 mol) in the presence of triethylamine (10.12 g, 0.1 mol),

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



I

Compd. No.	X	R^1	n	Method	Yield (%)	mp (°C)	Recrystn. solvent[b]	Formular[c]	Vasodilating activity[d] FBF	VBF
1	3-NO_2	Me	2	A, B, C	50.1[e]	109—111	D–IPE	$C_{18}H_{19}N_3O_9$	0.9 (1.2)	1.1 (0.9)
2	3-NO_2	Et	2	C	43.7	146—147	D–H	$C_{19}H_{21}N_3O_9$	1.2 (1.6)	1.4 (1.0)
3	3-NO_2	iso-Pr	2	C	49.9	126—127	D–IPE	$C_{20}H_{23}N_3O_9$	1.2 (1.9)	1.2 (1.9)
4	3-NO_2	iso-Bu	2	C	43.2	95—96	D–E	$C_{21}H_{25}N_3O_9$	0.7 (1.3)	0.6 (0.8)
5	3-NO_2	iso-Amyl	2	C	48.2	103—104	D–H	$C_{22}H_{27}N_3O_9$	0.6 (1.9)	0.8 (1.0)
6	3-NO_2	CH_2CH_2OMe	2	C	25.8	113—115	D–H	$C_{20}H_{23}N_3O_{10}$	0.3 (1.3)	NT
7	3-NO_2	CH_2CH_2OEt	2	B	49.1	82—84	D–E	$C_{21}H_{25}N_3O_{10}$	0.9 (1.6)	1.1 (1.0)
8	3-NO_2	$CH_2CH_2OCHMe_2$	2	B	36.5	90—91	D–IPE	$C_{22}H_{27}N_3O_{10}$	0.4 (1.3)	0.9 (3.5)
9	3-NO_2	$CH_2CH=CMe_2$	2	B	56.4	140—142	M–EA	$C_{22}H_{25}N_3O_9$	0.8 (0.4)	0.5 (0.9)
10	3-NO_2	$CH_2C_6H_4OMe$-4	2	B	43.8	114—116	D–IPE	$C_{25}H_{25}N_3O_{10}$	0.6 (1.2)	0.5 (0.5)
11	2-NO_2	Me	2	A	23.8	84—85	D–IPE	$C_{18}H_{19}N_3O_9$	0.6 (1.0)	1.1 (2.7)
12	2-NO_2	Et	2	A	21.2	72—74	D–IPE	$C_{19}H_{21}N_3O_9$	1.2 (2.6)	1.1 (1.9)
13	3-NO_2	Me	3	A, B, C	65.5[e]	114—116	H–EA	$C_{19}H_{21}N_3O_9$	0.8 (1.1)	0.9 (1.0)
14	3-NO_2	Et	3	B	66.0	129—130	H–EA	$C_{20}H_{23}N_3O_9$	0.4 (1.3)	NT
15	3-NO_2	iso-Pr	3	B	61.2	99—102	D–IPE	$C_{21}H_{25}N_3O_9$	0.7 (2.2)	0.8 (1.8)
16	3-NO_2	iso-Bu	3	B	58.6	123—125	D–IPE	$C_{22}H_{27}N_3O_9$	0.7 (2.2)	0.6 (1.8)
17	3-NO_2	iso-Amyl	3	B	63.6	71—72	H–EA	$C_{23}H_{29}N_3O_9$	0.6 (1.0)	0.7 (3.0)
18	3-NO_2	CH_2CH_2OMe	3	B	63.1	75—76	H–EA	$C_{21}H_{25}N_3O_{10}$	1.0 (2.2)	0.9 (1.8)
19	3-NO_2	CH_2CH_2OEt	3	B	59.5	89—91	D–IPE	$C_{22}H_{27}N_3O_{10}$	0.6 (1.5)	0.5 (1.1)
20	3-NO_2	$CH_2CH_2OCHMe_2$	3	B	53.3	63—64	D–IPE	$C_{23}H_{29}N_3O_{10}$	0.8 (2.3)	0.9 (1.9)
21	3-NO_2	$CH_2CH=CMe_2$	3	B	65.3	72—74	D–IPE	$C_{23}H_{27}N_3O_9$	0.7 (1.9)	0.8 (1.6)
22	3-NO_2	$CH_2C_6H_4OMe$-4	3	B	57.8	86—88	D–IPE	$C_{26}H_{27}N_3O_{10}$	0.6 (1.8)	0.5 (1.5)
23	2-NO_2	Me	3	A	18.5	114—115	D–IPE	$C_{19}H_{21}N_3O_9$	1.0 (1.2)	1.0 (1.3)
24	2-NO_2	Et	3	A	25.3	111—113	D–IPE	$C_{20}H_{23}N_3O_9$	0.9 (1.8)	1.1 (2.4)
25	2-NO_2	iso-Pr	3	A	22.5	75—76	D–IPE	$C_{21}H_{25}N_3O_9$	0.8 (1.3)	0.7 (1.1)
26	2-F	Me	2	C	58.4	108—109	D–IPE	$C_{18}H_{19}FN_2O_7$	0.8 (0.6)	0.9 (0.6)
27	2-F	Me	3	C	55.1	77—79	D–IPE	$C_{19}H_{21}FN_2O_7$	0.8 (0.9)	0.9 (0.8)
28	3-F	Me	2	C	67.5	124—125	D–IPE	$C_{18}H_{19}FN_2O_7$	0.5 (0.5)	0.4 (0.5)
29	3-F	Me	3	C	69.2	74—76	D–IPE	$C_{19}H_{21}FN_2O_7$	0.8 (1.2)	0.9 (1.0)
30	2-CF_3	Me	2	C	48.4	119—120	D–IPE	$C_{19}H_{19}F_3N_2O_7$	0.7 (1.0)	0.8 (0.8)
31	3-CF_3	Me	2	C	63.1	81—84	D–IPE	$C_{19}H_{19}F_3N_2O_7$	0.5 (0.5)	0.6 (0.5)
32	2,3-Cl_2	Me	2	C	49.4	125—127	D–IPE	$C_{18}H_{18}Cl_2N_2O_7$	0.5 (1.8)	0.4 (1.5)
33	3-Cl	Me	2	C	62.9	132—133	D–IPE	$C_{18}H_{19}ClN_2O_7$	0.6 (0.7)	0.6 (0.5)
34	3-Me	Me	2	B	21.8	105—106	D–IPE	$C_{19}H_{22}N_2O_7$	0.4 (0.3)	0.3 (0.3)
35	3,4-OCH_2O–	Me	2	C	41.9	80—82	D–IPE	$C_{19}H_{20}N_2O_9$	0.5 (0.2)	0.6 (0.2)
36	3-NO_2	$(CH_2)_2N(Me)CH_2Ph$	2	B	35.3	115—117	Amorphous[f]	$C_{27}H_{30}N_4O_9$	1.1 (2.4)	0.7 (1.9)
37	3-NO_2	$(CH_2)_3$NN–C_6H_4OMe-4	3	D	66.5	130—131	D–IPE	$C_{32}H_{39}N_5O_{10}$	1.0 (2.7)	0.7 (2.0)
38	3-NO_2	$(CH_2)_2$NNCHPh_2	2	B	45.1	80—81	D–IPE	$C_{36}H_{39}N_5O_9$	0.2 (0.2)	0.7 (2.6)
39	3-NO_2	$(CH_2)_3$NNCHPh_2	3	D	53.9	63—65	Amorphous[f]	$C_{38}H_{43}N_5O_9$	0.4 (2.5)	0.6 (2.2)

a) Structures of all compounds were confirmed by the IR, mass and NMR spectra. For a typical example, see Experimental. *b*) Solvents for recrystallization: A, acetone; D, dichloromethane; IPE, diisopropyl ether; E, ether; EA, ethyl acetate; H, *n*-hexane; M, methanol. *c*) All compounds were analyzed for C, H, and N. Analytical results obtained for these elements were within 0.4% of the calculated values for the formulae shown. *d*) For the biological method, see Experimental. NT: not tested. The figures represent the ratio of the increase in blood flow; the increase induced by nifedipine was taken as 1.0. The figures shown in the parentheses are half-maximum duration in minutes of the increased blood flow. Half-maximum duration means the period for which the increase in blood flow was above half of the maximum increase in blood flow. Abbreviations: FBF, femoral arterial blood flow; VBF, vertebral arterial blood flow. *e*) Yield by method C. *f*) Yield of the amorphous powder which was first isolated by chromatography (analytically pure).

and the mixture was stirred for 1—3 h at 50—60 °C. Then saturated $NaHCO_3$ was added, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with water, and dried (Na_2SO_4). The solvent was evaporated to dryness to give the acetoacetate as a pale yellow oil (179.93 g, 87.7%). MS *m/z*: 205 (M^+).

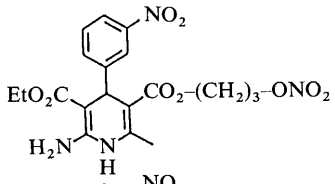
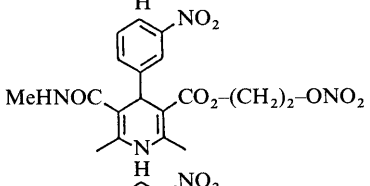
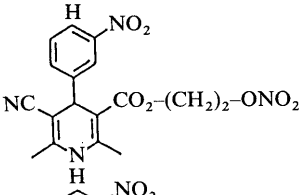
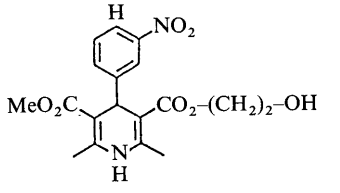
The acetoacetate (IIIb) thus obtained was used in the next reaction without further purification or after brief purification by column chromatography on silica gel. Other acetoacetate (IIIc—f) used for the preparation of 1,4-dihydropyridines related to I were prepared similarly and their spectral and physical data are listed in Table III.

General Procedure for the Synthesis of 3-Aminocrotonate Derivatives (IVb—f) Ammonia was bubbled for 3 h into a solution of substituted acetoacetate (IIIb—f) (0.5 mol) in tetrahydrofuran (THF, 300 ml) at 0 °C. The reaction flask was tightly stoppered and the mixture was stirred at 0 °C for 24 h. The solvent and excess NH_3 were evaporated off to give the corresponding crude 3-aminocrotonate derivative (IVb—f), which was used for the next step.

3-Nitrooxypropyl 3-Aminocrotonate (IVb): MS *m/z*: 204 (M^+). IR (neat) cm^{-1}: 3438 (NH), 1626 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.93 (3H, s), 2.08 (2H, m), 4.16 (2H, t, J=6 Hz), 4.51 (1H, s), 4.56 (2H, t, J=6 Hz), 7.88 (1H, br s).

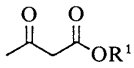
Ethoxyethyl 3-Aminocrotonate (IVc): MS *m/z*: 173 (M^+). IR (neat) cm^{-1}: 3445 (NH), 1667 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 1.92 (3H, s), 3.56 (2H, q, J=7 Hz), 3.76 (2H, t, J=5 Hz),

TABLE II. Physical and Biological Properties of Compounds Related to I[a)]

Compd. No.		Method	Yield (%)	mp (°C)	Recrystn. solvent[b)]	Formula[c)]	Vasodilating activity[d)] FBF	VBF
40			28.4	146—148	A–H	$C_{19}H_{22}N_4O_9$	0.15	NT
41			43.5	178—181	D–IPE	$C_{18}H_{20}N_4O_8$	0.4	0.5
42		B	38.7	137—138	D–IPE	$C_{17}H_{16}N_4O_7$	0.1 (0.3)	NT
43		C	46.3	155—156	D–IPE	$C_{18}H_{20}N_2O_7$	0.5 (0.2)	0.4 (0.2)

a—d) See footnotes *a—d*) in Table I.

TABLE III. Yields and Spectral Data for Acetoacetic Acid Esters (IIIa—f)



Compd. No.	R^1	bp (°C)/Torr	Yield (%)	IR (neat) (cm^{-1}) C=O	^{1}H-NMR ($CDCl_3$) δ (ppm)
IIIa	$CH_2CH_2ONO_2$	*a*)	87.4	1752	2.30 (3H, s), 3.53 (2H, s), 4.44 (2H, m), 4.69 (2H, m)
IIIb	$CH_2CH_2CH_2ONO_2$	*b*)	87.7	1728	2.12 (2H, m), 2.28 (3H, s), 3.50 (2H, m), 4.28 (2H, m), 4.58 (2H, t, J=5 Hz)
IIIc	$CH_2CH_2ONO_2$	81— 83/0.4	45.9	1746 1718	1.22 (3H, t, J=7 Hz), 2.29 (3H, s), 3.51 (2H, s), 3.55 (2H, q, J=7 Hz), 3.66 (2H, t, J=5 Hz), 4.32 (2H, t, J=5 Hz)
IIId	$CH_2CH_2OCHMe_2$	95— 98/0.4	77.9	1746 1719	1.18 (6H, d, J=6 Hz), 2.30 (3H, s), 3.49 (2H, s), 3.63 (1H, m), 3.66 (2H, t, J=5 Hz), 4.30 (2H, t, J=5 Hz)
IIIe	$CH_2CH=CMe_2$	76— 79/0.5	81.7	1719	1.75 (6H, d, J=8 Hz), 2.28 (3H, s), 3.45 (2H, s), 4.65 (2H, d, J=6 Hz), 5.37 (1H, m)
IIIf	$CH_2C_6H_4OMe$-4	164—166/0.5	45.0	1742 1718	2.23 (3H, s), 3.48 (2H, s), 3.81 (3H, s), 5.13 (2H, s), 6.82—7.37 (4H, m)

a) MS m/z: 191 (M^+). *b*) MS m/z: 205 (M^+).

4.23 (2H, t, J=5 Hz), 4.60 (1H, s), 7.50 (1H, br s).

Isopropoxyethyl 3-Aminocrotonate (IVd): MS m/z: 187 (M^+). IR (neat) cm^{-1}: 3436 (NH), 1667 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.18 (6H, d, J=6 Hz), 1.91 (3H, s), 3.61 (2H, d, J=5 Hz), 3.64 (1H, m), 4.19 (2H, t, J=5 Hz), 4.59 (1H, s), 7.50 (2H, br s).

3-Methyl-2-butenyl 3-Aminocrotonate (IVe): MS m/z: 169 (M^+). IR (neat) cm^{-1}: 3457 (NH), 1666 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.74 (6H, d, J=8 Hz), 1.91 (3H, s), 3.75 (1H, m), 4.56 (2H, d, J=6 Hz), 5.39 (1H, m), 7.78 (1H, br s).

(4-Methoxyphenyl)methyl 3-Aminocrotonate (IVf): MS m/z: 221 (M^+). IR (neat) cm^{-1}: 3450 (NH), 1665 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.90 (3H, s), 3.80 (3H, s), 4.57 (1H, s), 5.05 (2H, s), 6.82—7.37 (4H, m), 7.73 (1H, br s).

General Procedure for the Synthesis of Dihydropyridines (I). 2-Nitrooxyethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (1) Method A: A solution of 3-nitrobenzaldehyde (II) (1.51 g, 10 mmol), 2-nitrooxyethyl acetoacetate (IIIa) (1.91 g, 10 mmol), and methyl 3-aminocrotonate (IV) (1.15 g, 10 mmol) in 2-propanol (30 ml) was refluxed for 3 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** (1.51 g, 35.9%) as yellow crystals, mp 109—111 °C. MS m/z: 421 (M^+). IR (KBr) cm^{-1}: 3371 (NH), 1708, 1685 (C=O). *Anal.* Calcd for $C_{18}H_{19}N_3O_9$: C, 51.31; H, 4.55; N, 9.97. Found: C, 51.12; H, 4.60; N, 9.60.

Method B: A solution of II (30.22 g, 20 mmol), IIIa (38.23 g, 20 mmol), AcOH (0.24 g, 4 mmol), and piperidine (0.34 g, 4 mmol) in benzene (500 ml) 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 2-nitrooxyethyl 2-(3-nitrobenzylidene)acetoacetate (Va)[10] as colorless crystals, mp 108—115 °C (from CH_2Cl_2–iso-Pr_2O). The

TABLE IV. Spectral Data for 1,4-Dihydropyridines (I) Listed in Table I

Compd. No.	IR (KBr) cm^{-1} (NH)	(CO)	^{1}H-NMR ($CDCl_3$) δ (ppm)
1	3371	1708, 1685	2.37 (6H, s), 3.66 (3H, s), 4.32 (2H, m), 4.63 (2H, t, J=5 Hz), 5.09 (1H, s), 6.14 (1H, s), 7.33—8.20 (4H, m)
2	3380	1698	1.25 (3H, t, J=6 Hz), 2.36 (6H, s), 4.10 (2H, m), 4.32 (2H, m), 4.60 (2H, t, J=6 Hz), 5.07 (1H, s), 5.88 (1H, s), 7.32—8.15 (4H, m)
3	3382	1694	1.12 (3H, d, J=6 Hz), 1.28 (3H, d, J=6 Hz), 2.37 (6H, s), 4.33 (2H, m), 4.64 (2H, t, J=5 Hz), 4.96 (1H, m), 5.06 (1H, s), 6.01 (1H, s), 7.33—8.04 (4H, m)
4	3366	1703	0.85 (3H, d, J=8 Hz), 0.90 (3H, d, J=8 Hz), 1.91 (1H, m), 2.46 (3H, s), 2.50 (3H, s), 3.83 (2H, dd, J=8, 2 Hz), 4.35 (2H, m), 4.63 (2H, t, J=5 Hz), 5.11 (1H, s), 5.97 (1H, br s), 7.33—8.22 (4H, m)
5	3368	1709	0.87 (3H, d, J=6 Hz), 0.89 (3H, d, J=6 Hz), 1.49 (4H, m), 1.56 (1H, m), 2.36 (3H, s), 2.38 (3H, s), 4.06 (2H, m), 4.34 (2H, m), 4.63 (2H, m), 5.08 (1H, s), 6.03 (1H, s), 7.32—8.13 (4H, m)
6	3326	1708, 1681	2.38 (3H, s), 2.39 (3H, s), 3.36 (3H, s), 3.55 (2H, m), 4.19 (2H, m), 4.32 (2H, m), 4.60 (2H, m), 5.09 (1H, s), 5.97 (1H, s), 7.32—8.15 (4H, m)
7	3386	1698	1.20 (3H, t, J=6 Hz), 2.38 (6H, s), 3.50 (2H, q, J=6 Hz), 3.61 (2H, t, J=5 Hz), 4.19 (2H, m), 4.33 (2H, m), 4.51 (2H, m), 5.10 (1H, s), 5.95 (1H, br s), 7.32—8.17 (4H, m)
8	3366	1702	1.14 (3H, d, J=7 Hz), 1.18 (3H, d, J=7 Hz), 2.38 (6H, s), 3.49 (1H, q, J=7 Hz), 3.59 (2H, m), 4.18 (2H, m), 4.32 (2H, m), 4.61 (2H, m), 5.10 (1H, s), 5.98 (1H, br s), 7.33—8.14 (4H, m)
9	3369	1707	1.98 (3H, s), 2.09 (3H, s), 2.70 (6H, s), 4.77 (2H, m), 4.87 (2H, d, J=7 Hz), 4.96 (2H, t, J=5 Hz), 5.40 (1H, s), 5.64 (1H, t, J=7 Hz), 6.53 (1H, br s), 7.65—8.50 (4H, m)
10	3369	1698	2.35 (3H, s), 2.37 (3H, s), 3.82 (3H, s), 4.30 (2H, m), 4.58 (2H, t, J=5 Hz), 4.94 (1H, d, J=12 Hz), 5.05 (1H, s), 5.07 (1H, d, J=12 Hz), 5.94 (1H, br s), 6.78—8.08 (8H, m)
11	3344	1712, 1684	2.32 (3H, s), 2.37 (3H, s), 3.58 (3H, s), 4.29 (2H, m), 4.60 (2H, t, J=5 Hz), 5.75 (1H, s), 5.89 (1H, br s), 7.21—7.75 (4H, m)
12	3325	1700, 1680	1.18 (3H, t, J=7 Hz), 2.35 (3H, s), 2.37 (3H, s), 4.14 (2H, q, J=7 Hz), 4.33 (2H, m), 4.61 (2H, t, J=5 Hz), 5.78 (1H, br s), 5.83 (1H, s), 7.21—7.78 (4H, m)
13	3378	1698, 1684	2.03 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 3.67 (3H, s), 4.16 (2H, m), 4.38 (2H, t, J=6 Hz), 5.09 (1H, s), 6.10 (1H, s), 7.35—8.16 (4H, m)
14	3371	1702	1.24 (3H, t, J=7 Hz), 2.02 (2H, m), 2.37 (3H, s), 2.39 (3H, s), 4.10 (2H, m), 4.16 (2H, m), 4.37 (2H, t, J=6 Hz), 5.08 (1H, s), 5.93 (1H, s), 7.32—8.15 (4H, m)
15	3372	1700	1.04 (3H, d, J=6 Hz), 1.27 (3H, d, J=6 Hz), 2.02 (2H, m), 2.36 (3H, s), 2.39 (3H, s), 4.15 (2H, m), 4.37 (2H, t, J=6 Hz), 4.98 (1H, m), 5.05 (1H, s), 5.80 (1H, s), 7.33—8.15 (4H, m)
16	3343	1698, 1653	0.86 (3H, d, J=6 Hz), 0.91 (3H, d, J=6 Hz), 1.91 (1H, m), 2.05 (2H, m, J=6 Hz), 2.89 (6H, s), 3.84 (2H, dd, J=8, 2 Hz), 4.17 (2H, m), 4.40 (2H, t, J=6 Hz), 5.10 (1H, s), 5.97 (1H, s), 7.35—8.14 (4H, m)
17	3343	1698	0.90 (6H, d, J=6 Hz), 1.50 (2H, m), 1.55 (1H, m), 2.05 (2H, m), 2.36 (3H, s), 2.38 (3H, s), 3.96 (2H, m), 4.17 (2H, m), 4.39 (2H, m), 5.08 (1H, s), 5.95 (1H, s), 7.31—8.18 (4H, m)
18	3333	1697	2.02 (2H, m), 2.35 (3H, s), 2.39 (3H, s), 3.37 (3H, s), 3.56 (2H, t, J=6 Hz), 4.15 (2H, m), 4.19 (2H, m), 4.37 (2H, t, J=6 Hz), 5.10 (1H, s), 5.98 (1H, s), 7.33—8.14 (4H, m)
19	3330	1697, 1654	1.20 (3H, t, J=6 Hz), 2.02 (2H, m), 2.34 (3H, s), 2.39 (3H, s), 3.52 (2H, q, J=6 Hz), 3.62 (2H, t, J=5 Hz), 4.15 (2H, m), 4.21 (2H, m), 4.37 (2H, t, J=6 Hz), 5.12 (1H, s), 6.00 (1H, s), 7.33—8.15 (4H, m)
20	3329	1696, 1654	1.16 (3H, d, J=7 Hz), 1.19 (3H, d, J=7 Hz), 2.02 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 3.60 (1H, m), 3.62 (2H, t, J=5 Hz), 4.12 (2H, m), 4.17 (2H, m), 4.34 (2H, t, J=6 Hz), 5.11 (1H, s), 6.06 (1H, s), 7.31—8.17 (4H, m)
21	3374	1703	1.66 (3H, s), 1.75 (3H, s), 2.02 (2H, m), 2.34 (3H, s), 2.39 (3H, s), 4.15 (2H, m), 4.37 (2H, t, J=6 Hz), 4.57 (2H, m), 5.08 (1H, s), 5.30 (1H, m), 5.85 (1H, s), 7.32—8.14 (4H, m)
22	3328	1697	1.98 (2H, m), 2.33 (3H, s), 2.35 (3H, s), 3.82 (3H, s), 4.11 (2H, m), 4.33 (2H, t, J=6 Hz), 4.95 (1H, d, J=11 Hz), 5.05 (1H, s), 5.09 (1H, d, J=11 Hz), 5.90 (1H, s), 6.77—8.17 (8H, m)
23	3326	1699, 1680	2.03 (2H, m), 2.31 (3H, s), 2.39 (3H, s), 3.60 (3H, s), 4.12 (2H, m), 4.29 (2H, t, J=6 Hz), 5.74 (1H, s), 5.84 (1H, s), 7.22—7.44 (4H, m)
24	3326	1698, 1680	1.29 (3H, t, J=6 Hz), 2.02 (2H, m), 2.33 (3H, s), 2.38 (3H, s), 4.10 (2H, m), 4.12 (2H, q, J=6 Hz), 5.76 (1H, br s), 5.80 (1H, s), 7.20—7.78 (4H, m)
25	3347	1700, 1652	1.02 (3H, d, J=6 Hz), 1.23 (3H, d, J=6 Hz), 2.02 (2H, m), 2.33 (3H, s), 2.35 (3H, s), 4.22 (2H, m), 4.39 (2H, t, J=6 Hz), 4.98 (1H, m), 5.72 (1H, br s), 5.85 (1H, s), 7.21—7.80 (4H, m)
26	3350	1688, 1669	2.32 (6H, s), 3.63 (3H, s), 4.28 (2H, m), 4.60 (2H, m), 5.22 (1H, s), 5.95 (1H, br s), 6.85—7.33 (4H, m)
27	3359	1681	2.02 (2H, m), 2.33 (3H, s), 2.36 (3H, s), 3.64 (3H, s), 4.11 (2H, m), 4.35 (2H, t, J=6 Hz), 5.25 (1H, s), 5.85 (1H, br s), 6.86—7.35 (4H, m)
28	3348	1686, 1666	2.36 (6H, s), 3.65 (3H, s), 4.36 (2H, m), 4.62 (2H, m), 4.98 (1H, s), 5.80 (1H, br s), 6.79—7.28 (4H, m)
29	3359	1680	2.02 (2H, m), 2.33 (3H, s), 2.36 (3H, s), 3.63 (3H, s), 4.10 (2H, m), 4.35 (2H, t, J=6 Hz), 5.23 (1H, s), 5.74 (1H, br s), 6.85—7.35 (4H, m)
30	3342	1712, 1682	2.32 (3H, s), 2.35 (3H, s), 3.60 (3H, s), 4.20 (1H, m), 4.39 (1H, m), 4.57 (2H, m), 5.54 (1H, s), 5.77 (1H, br s), 7.18—7.77 (4H, m)
31	3360	1687, 1650	2.34 (6H, s), 3.76 (3H, s), 4.32 (2H, m), 4.60 (2H, m), 5.04 (1H, s), 6.15 (1H, br s), 7.28—7.52 (4H, m)
32	3347	1684, 1662	2.31 (3H, s), 2.35 (3H, s), 3.64 (3H, s), 4.29 (2H, m), 4.61 (2H, m), 5.46 (1H, s), 5.91 (1H, s), 7.02—7.37 (3H, m)
33	3346	1687, 1651	2.36 (6H, s), 3.66 (3H, s), 4.33 (2H, m), 4.60 (2H, m), 4.95 (1H, s), 5.80 (1H, s), 7.10—7.23 (4H, m)
34	3345	1686, 1650	2.30 (3H, s), 2.33 (3H, s), 2.34 (3H, s), 3.66 (3H, s), 4.31 (2H, m), 4.60 (2H, m), 4.93 (1H, s), 5.92 (1H, br s), 6.90—7.27 (4H, m)

TABLE IV. (continued)

Compd. No.	IR (KBr) cm^{-1} (NH)	(CO)	^{1}H-NMR ($CDCl_3$) δ (ppm)
35	3334	1674, 1651	2.32 (6H, s), 3.68 (3H, s), 4.34 (2H, m), 4.62 (2H, m), 4.90 (1H, s), 5.76 (1H, br s), 5.90 (2H, s), 6.62—6.80 (3H, m)
36	3343	1695	2.25 (3H, s), 2.36 (3H, s), 2.38 (3H, s), 2.70 (2H, t, J=6 Hz), 3.57 (2H, s), 4.22 (2H, t, J=6 Hz), 4.32 (2H, m), 4.59 (2H, t, J=5 Hz), 5.10 (1H, s), 6.05 (1H, s), 7.18—8.12 (9H, m)
37	3392	1699	1.85 (2H, m), 2.04 (2H, s), 2.38 (6H, s), 2.49 (2H, m), 2.58 (4H, m), 3.11 (4H, m), 3.77 (3H, s), 4.11 (2H, m), 4.15 (2H, m), 4.38 (2H, t, J=6 Hz), 5.09 (1H, s), 6.06 (1H, br s), 6.79—8.16 (4H, m)
38	3402	1698	2.35 (3H, s), 2.37 (3H, s), 2.49 (8H, m), 2.62 (2H, t, J=5 Hz), 4.19 (2H, m), 4.30 (2H, m), 4.59 (2H, t, J=5 Hz), 5.07 (1H, s), 6.01 (1H, br s), 7.11—8.11 (10H, m)
39	3333	1698	1.79 (2H, m), 2.02 (2H, m), 2.31 (2H, m), 2.33 (3H, s), 2.35 (3H, s), 2.40 (8H, m), 4.09 (2H, m), 4.11 (2H, m), 4.20 (1H, s), 4.36 (2H, t, J=5 Hz), 5.06 (1H, s), 5.88 (1H, s), 7.11—8.12 (14H, m)
40	3368, 3433	1700, 1673	1.13 (3H, t, J=6 Hz), 1.93 (2H, m), 2.33 (3H, s), 3.95 (2H, m), 4.00 (2H, m), 4.37 (2H, t, J=5 Hz), 4.86 (1H, s), 6.75 (2H, br s), 7.44—8.04 (4H, m), 8.86 (1H, s)[a]
41	3256, 3344	1685	2.24 (3H, s), 2.34 (3H, s), 2.78 (3H, d, J=5 Hz), 4.35 (2H, m), 4.65 (2H, t, J=5 Hz), 4.89 (1H, s), 5.33 (1H, d, J=5 Hz), 5.90 (1H, s), 7.39—8.17 (4H, m)
42	3344	1709, 1667	2.14 (3H, s), 2.41 (3H, s), 4.28 (2H, m), 4.52 (2H, m), 4.73 (1H, s), 6.08 (1H, s), 7.43—8.18 (4H, m)
43	3285, 3441	1702, 1680	1.60 (1H, br s), 2.38 (3H, s), 2.40 (3H, s), 3.65 (3H, s), 3.80 (2H, m), 4.20 (2H, m), 5.11 (1H, s), 5.79 (1H, br s), 7.32—8.18 (4H, m)

a) Measured in DMSO-d_6.

TABLE V. Spectral Data for 1,4-Dihydropyridins (VI)

Compd. No.	X	R^1	IR (KBr) cm^{-1} (NH)	(CO)	^{1}H-NMR ($CDCl_3$) δ (ppm)
VIa	3-NO_2	$CH_2CH_2ONO_2$	3370	1698	2.33 (3H, s), 2.36 (3H, s), 2.85 (2H, m), 4.16 (2H, t, J=5 Hz), 4.27 (2H, m), 4.68 (2H, t, J=5 Hz), 4.98 (1H, s), 7.46—8.07 (4H, m), 9.20 (1H, br s)[a]
VIb	3-NO_2	Et	3375	1698	1.25 (3H, t, J=8 Hz), 2.38 (3H, s), 2.40 (3H, s), 2.66 (2H, t, J=6 Hz), 4.11 (2H, q, J=8 Hz), 4.26 (2H, m), 5.11 (1H, s), 5.84 (1H, br s), 7.33—8.17 (4H, m)
VIc	3-NO_2	iso-Pr	3375	1695	1.11 (3H, d, J=5 Hz), 1.27 (3H, d, J=5 Hz), 2.38 (3H, s), 2.39 (3H, s), 2.66 (2H, d, J=6 Hz), 4.27 (2H, m), 4.95 (1H, m), 5.09 (1H, s), 6.01 (1H, br s), 7.34—8.18 (4H, m)
VId	3-NO_2	iso-Bu	3367	1703, 1687	0.85 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 1.90 (1H, m), 2.40 (3H, s), 2.42 (3H, s), 2.68 (2H, t, J=6 Hz), 3.83 (2H, dd, J=8, 2 Hz), 4.29 (2H, m), 5.12 (1H, s), 5.89 (1H, br s), 7.33—8.17 (4H, m)
VIe	3-NO_2	iso-Amyl	3370	1695	0.85 (3H, d, J=5 Hz), 0.86 (3H, d, J=5 Hz), 1.51 (2H, m), 2.39 (6H, s), 2.68 (2H, t, J=6 Hz), 3.89 (1H, m), 4.08 (2H, m), 4.29 (2H, m), 5.11 (1H, s), 5.89 (1H, br s), 7.35—8.15 (4H, m)
VIf	3-NO_2	MeO	3369	1697	2.38 (3H, s), 2.40 (3H, s), 2.77 (2H, t, J=7 Hz), 3.37 (3H, s), 3.58 (2H, m), 4.18 (2H, m), 4.26 (2H, m), 5.13 (1H, s), 6.00 (1H, br s), 7.35—8.18 (4H, m)
VIg	2-F	Me	3353	1705, 1681	2.33 (3H, s), 2.35 (3H, s), 2.63 (2H, t, J=7 Hz), 3.62 (3H, s), 4.22 (2H, m), 5.22 (1H, s), 5.72 (1H, br s), 6.86—7.37 (4H, m)
VIh	3-F	Me	3344	1700	2.32 (3H, s), 2.37 (3H, s), 2.64 (2H, m), 3.64 (3H, s), 4.27 (2H, m), 5.00 (1H, s), 5.81 (1H, br s), 6.78—7.31 (4H, m)
VIi	3-CF_3	Me	3350	1698, 1685	2.32 (3H, s), 2.37 (3H, s), 2.63 (2H, t, J=6 Hz), 3.64 (3H, s), 4.25 (2H, m), 5.05 (1H, s), 5.91 (1H, br s), 7.28—7.56 (4H, m)
VIj	2,3-Cl_2	Me	3338	1708, 1677	2.30 (3H, s), 2.33 (3H, s), 2.66 (2H, t, J=6 Hz), 3.62 (3H, s), 4.23 (2H, t, J=6 Hz), 5.45 (1H, s), 6.20 (1H, br s), 7.03—7.36 (3H, m)
VIk	3-Cl	Me	3345	1687	2.36 (3H, s), 2.39 (3H, s), 2.65 (2H, t, J=6 Hz), 3.77 (3H, s), 4.28 (2H, m), 4.98 (1H, s), 5.75 (1H, br s), 7.08—7.36 (4H, m)
VII	3,4-OCH_2O–	Me	3346	1695	2.36 (3H, s), 2.38 (3H, s), 2.66 (2H, t, J=6 Hz), 3.68 (3H, s), 4.28 (2H, m), 4.92 (1H, s), 5.69 (1H, br s), 5.90 (2H, s), 6.60—6.86 (3H, m)

a) Measured in DMSO-d_6.

ratio of isomers was 10 : 1 as judged from the NMR spectrum. IR (KBr) cm^{-1}: 1725, 1697 (C=O). *Anal.* Calcd for $C_{13}H_{12}N_2O_8$: C, 48.15; H, 3.73; N, 8.64. Found: C, 48.28; H, 3.70; N, 8.39. A solution of Va (3.24 g, 10 mmol) and methyl 3-aminocrotonate (IV) (1.15 g, 10 mmol) in propanol (30 ml) was refluxed for 2 h with stirring. After removal of the solvent, the residue was purified by chromatography on silica gel hexane–AcOEt (1 : 1, v/v) to yield **1** (2.85 g, 67.7%).

Method C: A solution of the carboxylic acid (VIIa) (3.32 g, 10 mmol), 2-nitrooxyethyl bromide (1.87 g, 11 mmol), and potassium carbonate (1.66 g, 12 mmol) in *N*,*N*-dimethylformamide (DMF, 30 ml) was stirred for 12 h at room temperature. The mixture was extracted with CH_2Cl_2 (100 ml). The CH_2Cl_2 layer was washed with water and brine, and dried (Na_2SO_4), and the solvent was removed. The residue was purified by chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give the product **1** (2.11 g, 50.1%) as yellow crystals.

3-Nitrooxypropyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (13) Acetic anhydride (3.06 g, 30 mmol) was added to a suspension of the carboxylic acid (VIIa) (3.32 g, 10 mmol) in CH_2Cl_2 (30 ml) at room temperature, and the mixture was stirred for 5 h at the same temperature. A solution of 3-nitrooxypropanol (X) (1.33 g, 11 mmol) in CH_2Cl_2 containing a catalytic amount of acetyl chloride was added to the reaction mixture at the same temperature, and the mixture was stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 (20 ml), and washed with 1 N NaOH and brine. The solvent was removed, and the residue was purified by chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give the product (**13**) (2.85 g, 65.5%) as light yellow crystals,

mp 114—116 °C. MS *m/z*: 435 (M^+). *Anal.* Calcd for $C_{19}H_{21}N_3O_9$: C, 52.41; H, 4.86; N, 9.65. Found: C, 52.17; H, 4.84; N, 9.31. Spectral data of I are shown in Table IV.

3-(4-Diphenylmethyl-1-piperazinyl)propyl 3-Nitrooxypropyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (39) A solution of 3-nitrobenzaldehyde (II) (30.22 g, 0.2 mol), 3-nitrooxypropyl 3-aminocrotonate (IVb) (40.84 g, 0.2 mol), and 3-bromopropyl acetoacetate (VIIIb) (44.61 g, 0.2 mol) in 2-propanol (300 ml) was refluxed for 3 h with stirring. The precipitated crystals were collected, washed with Et_2O, and dried to afford IX (82.35 g, 75.9%). mp 131—132 °C (from CH_2Cl_2–iso-Pr_2O). MS *m/z*: 543 $(M+H)^+$. IR (KBr) cm^{-1}: 3380 (NH), 1698 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.07 (2H, t, J=5 Hz), 2.16 (2H, m), 2.41 (6H, s), 3.33 (2H, m), 4.15 (2H, m), 4.20 (2H, m), 4.41 (2H, t, J=5 Hz), 5.07 (1H, s), 5.99 (1H, br s), 7.35—8.17 (4H, m). *Anal.* Calcd for $C_{21}H_{24}BrN_3O_9$: C, 46.50; H, 4.46; N, 7.75. Found: C, 46.35; H, 4.20; N, 7.73.

A solution of IX (5.42 g, 10 mmol) and 1-(diphenylmethyl)piperazine (2.52 g, 10 mmol) in MeCN (30 ml) was added to a solution of K_2CO_3 (1.66 g, 12 mmol) in MeCN. The mixture was refluxed for 3 h with stirring. The solvent was removed, and the residue was extracted with CH_2Cl_2. After removal of the solvent, the extract was chromatographed on silica gel with hexane–AcOEt (1:1, v/v) to give **39** as yellow crystals (3.86 g, 53.9%). Compound **37** (Table I) was prepared similarly.

3-Nitrooxypropyl 2-Amino-3-ethoxycarbonyl-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-5-pyridinecarboxylate (40) A solution of 3-nitrooxypropyl 2-(3-nitrobenzylidene)acetoacetate (Vb) (6.77 g, 20 mmol), ethoxycarbonylacetamidine hydrochloride (3.33 g, 20 mmol) and piperidine (2.13 g, 25 mmol) in 2-propanol was refluxed for 1 h with stirring. The reaction mixture was concentrated, diluted with water and extracted with CH_2Cl_2. After removal of the solvent, the extract was chromatographed on silica gel with hexane–EtOAc (1:1, v/v) to give **40** as a yellow powder (2.40 g, 28.4%). MS *m/z*: 422 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_4O_9$: C, 50.66; H, 4.92; N, 12.44. Found: C, 50.27; H, 4.91; N, 12.36.

2-Nitrooxyethyl 2,6-Dimethyl-4-(3-nitrophenyl)-5-(*N*-methylcarbamoyl)-1,4-dihydropyridine-3-carboxylate (41) A solution of VIIa (4.07 g, 10 mmol), *N*,*N*-dicyclohexylcarbodiimide (2.06 g, 10 mmol) and methylamine (in 40% methanol) (0.78 g, 10 mmol) in CH_2Cl_2 was stirred for 2 h under ice cooling, and then the mixture was stirred at room temperature for 8 h. The precipitate was filtered off. The filtrate was evaporated at reduced pressure, and the residue was purified by chromatography on silica

TABLE VI. Physical Data for VI

Compd. No.	X	R^1	Yield[a] (%)	mp (°C)	Recryst. solvent[b]	Formula[c]	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	MS (*m/z*) (M^+)
VIa	3-NO_2	$CH_2CH_2ONO_2$	69.7	150—152	D–E	$C_{20}H_{20}N_4O_9$	52.17	4.38	12.17	52.07	4.56	12.38	460
VIb	3-NO_2	Et	72.1	127—129	D–IPE	$C_{20}H_{21}N_3O_6$	60.14	5.30	10.52	59.80	5.24	10.40	399
VIc	3-NO_2	iso-Pr	75.6	120—122	D–IPE	$C_{21}H_{23}N_3O_6$	61.01	5.61	10.16	60.78	5.55	10.16	413
VId	3-NO_2	iso-Bu	72.3	138—140	D–IPE	$C_{22}H_{25}N_3O_6$	61.81	5.90	9.83	61.60	5.90	9.95	427
VIe	3-NO_2	iso-Amyl	74.9	114—116	D–IPE	$C_{23}H_{27}N_3O_6$	62.57	6.16	9.52	62.36	6.09	9.30	441
VIf	3-NO_2	CH_2CH_2OMe	69.4	118—120	D–IPE	$C_{21}H_{23}N_3O_7$	58.73	5.40	9.79	58.39	5.36	9.75	429
VIg	2-F	Me	76.1	95—97	E–H	$C_{19}H_{19}FN_2O_4$	63.68	5.34	7.82	63.37	5.34	7.72	358
VIh	3-F	Me	75.7	102—104	D–IPE	$C_{19}H_{19}FN_2O_4$	63.68	5.34	7.82	63.40	5.30	7.75	358
VIi	3-CF_3	Me	74.2	105—106	D–IPE	$C_{20}H_{19}F_3N_2O_4$	58.82	4.69	6.86	58.68	4.54	6.81	408
VIj	2,3-Cl_2	Me	70.8	99—101	E–H	$C_{18}H_{18}Cl_2N_2O_4$	54.42	4.56	7.05	54.70	4.59	7.09	395
VIk	3-Cl	Me	77.2	105—107	E–H	$C_{18}H_{19}ClN_2O_4$	59.59	5.28	7.72	59.92	5.31	7.77	362
VIl	3,4-OCH_2O–	Me	71.3	118—119	D–H	$C_{20}H_{20}N_2O_6$	62.49	5.24	7.29	62.33	5.11	6.98	384

a) Overall yield from V. *b*) See footnotes *b*, *c*) in Table I.

TABLE VII. Spectral Data for 1,4-Dihydropyridines (VII)

Compd. No.	X	R^1	IR (KBr) cm^{-1} (NH)	IR (KBr) cm^{-1} (CO)	^{1}H-NMR (DMSO-d_6) δ (ppm)
VIIa	3-NO_2	$CH_2CH_2ONO_2$	3326	1658	2.28 (3H, s), 2.30 (3H, s), 4.28 (2H, m), 4.71 (2H, m), 4.98 (1H, s), 7.47—8.08 (4H, m), 9.03 (1H, br s), 11.89 (1H, br s)
VIIb	3-NO_2	Et	3363	1657	1.16 (3H, t, J=7 Hz), 2.28 (6H, s), 4.01 (2H, m), 4.98 (1H, s), 7.49—8.06 (4H, m), 8.93 (1H, br s), 11.86 (1H, br s)
VIIc	3-NO_2	iso-Pr	3362	1677, 1655	1.04 (3H, d, J=7 Hz), 1.20 (3H, d, J=7 Hz), 2.27 (3H, s), 2.30 (3H, s), 4.83 (1H, m), 4.96 (1H, s), 7.47—8.06 (4H, m), 8.89 (1H, br s), 11.72 (1H, br s)
VIId	3-NO_2	iso-Bu	3367	1703, 1687	0.78 (3H, d, J=6 Hz), 0.82 (3H, d, J=6 Hz), 1.82 (1H, m), 2.27 (3H, s), 2.33 (3H, s), 3.76 (2H, m), 5.01 (1H, 7.48—8.07 (4H, m), 8.96 (1H, br s), 11.75 (1H, br s)
VIIe	3-NO_2	iso-Amyl	3355	1663	0.76 (3H, d, J=5 Hz), 0.83 (3H, d, J=5 Hz), 1.41 (2H, m), 2.28 (3H, s), 2.32 (3H, s), 3.81 (1H, m), 4.00 (2H, m), 4.97 (1H, s), 7.45—8.09 (4H, m), 8.92 (1H, br s), 11.75 (1H, br s)
VIIf	3-NO_2	CH_2CH_2OMe	3412	1678	2.29 (3H, s), 2.32 (3H, s), 3.22 (3H, s), 3.49 (2H, m), 4.08 (2H, m), 5.00 (1H, s), 7.47—8.04 (4H, m), 8.97 (1H, br s), 11.12 (1H, br s)
VIIg	2-F	Me	3342	1657	2.24 (3H, s), 2.26 (3H, s), 3.50 (3H, s), 5.11 (1H, s), 6.90—7.27 (4H, m), 8.76 (1H, br s), 11.50 (1H, br s)
VIIh	3-F	Me	3343	1695	2.27 (3H, s), 2.28 (3H, s), 3.58 (3H, s), 4.92 (1H, s), 6.80—7.34 (4H, m), 8.85 (1H, br s), 11.17 (1H, br s)
VIIi	3-CF_3	Me	3351	1676	2.28 (3H, s), 2.29 (3H, s), 3.56 (3H, s), 4.98 (1H, s), 7.38—7.51 (4H, m), 8.89 (1H, br s), 11.77 (1H, br s)
VIIj	2,3-Cl_2	Me	3333	1699	2.23 (3H, s), 2.26 (3H, s), 3.50 (3H, s), 5.32 (1H, s), 7.26—7.58 (3H, m), 8.83 (1H, br s), 11.46 (1H, br s)
VIIk	3-Cl	Me	3402	1698	2.29 (3H, s), 2.31 (3H, s), 3.57 (3H, s), 4.89 (1H, s), 7.06—7.31 (4H, m), 8.84 (1H, br s), 11.70 (1H, br s)
VIIl	3,4-OCH_2O–	Me	3344	1655	2.25 (3H, s), 2.27 (3H, s), 3.56 (3H, s), 4.80 (1H, s), 5.92 (2H, s), 6.55—6.83 (3H, m), 8.75 (1H, br s), 11.58 (1H, br s)

TABLE VIII. Physical Data for VII

Compd. No.	X	R^1	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	MS (m/z) (M^+)
VIIa	3-NO_2	$CH_2CH_2ONO_2$	80.0	167—168	E–Et	$C_{17}H_{17}N_3O_9$	50.12	4.21	10.32	50.51	4.43	9.87	408[b]
VIIb	3-NO_2	Et	70.2	177—179	E–M	$C_{17}H_{18}N_2O_6$	58.95	5.24	8.09	58.86	5.24	7.79	346
VIIc	3-NO_2	iso-Pr	58.3	172—174	E–Et	$C_{18}H_{20}N_2O_6$	59.99	5.59	7.77	59.61	5.57	7.42	360
VIId	3-NO_2	iso-Bu	68.7	180—181	E–T	$C_{19}H_{22}N_2O_6$	60.95	5.92	7.48	60.63	5.93	7.26	374
VIIe	3-NO_2	iso-Amyl	78.6	161—163	E–T	$C_{20}H_{24}N_2O_6$	61.84	6.23	7.21	61.53	6.22	6.97	388
VIIf	3-NO_2	MeO	79.8	165—166	E–T	$C_{18}H_{20}N_2O_7$	57.44	5.35	7.44	57.15	5.11	7.08	376
VIIg	2-F	Me	78.3	215—216	E–M	$C_{16}H_{16}FNO_4$	62.94	5.28	4.59	62.63	5.29	4.59	305
VIIh	3-F	Me	77.3	216—218	E–T	$C_{16}H_{16}FNO_4$	62.94	5.28	4.59	62.66	5.01	4.23	305
VIIi	3-CF_3	Me	75.6	200—201	E–M	$C_{17}H_{16}F_3NO_4$	57.46	4.54	3.94	57.32	4.52	3.78	355
VIIj	2,3-Cl_2	Me	72.0	199—200	E–M	$C_{16}H_{15}Cl_2NO_4$	53.95	4.24	3.93	53.68	4.24	3.73	357[b]
VIIk	3-Cl	Me	75.6	211—212	E–M	$C_{16}H_{16}ClNO_4$	59.76	5.02	4.36	59.74	4.99	4.27	321
VIIl	3,4-OCH_2O–	Me	55.6	204—206	E–M	$C_{17}H_{17}NO_6$	61.63	5.17	4.23	61.57	5.15	3.97	331

a) Solvents for recrystallization: E, ether; Et, ethanol; M, methanol; T, THF. *b*) $(M+H)^+$.

gel with hexane–AcOEt (1 : 1, v/v) to give yellow crystals (1.83 g, 43.5%). MS *m/z*: 420 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_4O_8$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.39; H, 4.70; N, 13.10.

2-Nitrooxyethyl 5-Cyano-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3-carboxylate (42) A solution of 2-nitrooxyethyl 2-(3-nitrobenzylidene)acetoacetate (Va) (3.24 g, 10 mmol) and 3-aminocrotonitrile (0.62 g, 10 mmol) in 2-propanol (30 ml) was refluxed for 1 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 **42** (1.50 g, 38.7%). Recrystallization from CH_2Cl_2–iso-Pr_2O gave white crystals. MS *m/z*: 388 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.52; H, 4.02; N, 14.53.

2-Nitrooxyethyl 2-Cyanoethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (VIa) A solution of Va (64.85 g, 0.2 mol), and 2-cyanoethyl 3-aminocrotonate (30.83 g, 0.2 mol) in 2-propanol (500 ml) was refluxed for 3 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 VIa (75.80 g, 82.3%), which was recrystallized from CH_2Cl_2–Et_2O to give light yellow crystals.

Other 1,4-dihydropyridines (VI) were prepared similarly and their spectral and physical data are listed in Tables V and VI.

2,6-Dimethyl-4-(3-nitrophenyl)-3-(2-nitrooxyethoxy)carbonyl-1,4-dihydropyridine-5-carboxylic Acid (VIIa) A suspension of VIa (46.04 g, 0.1 mol) in acetone (400 ml) and 5 N NaOH (200 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with water, and extracted with CH_2Cl_2. The aqueous layer was acidified with phosphoric acid (24.5 g, 0.25 mol) under ice cooling. The precipitated product was filtered off, washed with water, and then dried *in vacuo*. Recrystallization from ethanol gave VIIa (32.60 g, 80.0%) as yellow crystals. Other carboxylic acid (VII) were prepared similarly and their spectral and physical data are listed in Tables VII and VIII.

Biological Evalution Procedures

Male and female mongrel dogs weighing 8—15 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v. supplemented with additional dose as necessary). Femoral arterial blood pressure was measured with a pressure transducer (Nihon Kohden MPV-0.5, Tokyo, Japan) connected to a rigid polyethylene tube introduced into the femoral artery. Heart rate was measured by using a heart rate counter (Nihon Kohden T-600G, Japan) driven by arterial pulse pressure. An extracorporeal path was contructed in the femoral or vertebral arteries. The heparinized blood was perfused from the proximal sites of the femoral and vertebral arteries to the distal sites through the extracorporeal path. A test compound or nifedipine (Bayer, Germany) was dissolved in 50% ethanol solution at concentrations of 100—500 μg/ml. A dose of 0.1, 0.3 or 1 μg was administered intra-arterially *via* the extracorporeal path. The flow meter probe was also interposed in the extracorporeal path. The femoral and vertebral blood flow was measured by means of electromagnetic blood flow meters (Nihon Kohden MF-27 and MFV-1200, Japan). The maximum increase in blood flow induced by each compound was represented as the ratio to the maximum increase in blood flow induced by nifedipine. Half-maximum duration of increased blood flow induced by each compound was represented in minutes; half-maximum duration means period for which the increase in blood flow level was maintained at over half the level of the maximum increase in blood flow.

References and Notes

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