Studies on Nilvadipine. II. Synthesis and Structure–Activity Relationships of 2-Hydroxymethyl- and 2-Cyano-1,4-dihydropyridines Containing Heteroatom-Substituted Ester at the 5-Position

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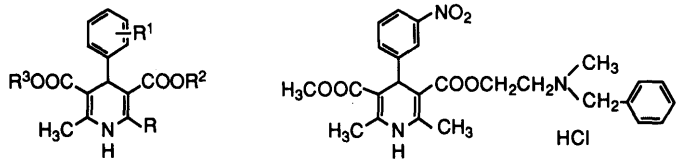
The synthesis of new 2-hydroxymethyl- and 2-cyano-1,4-dihydropyridines possessing a heteroatom-substituted alkyl ester group at the 5-position of the nucleus is described. The esters were introduced *via* a suitable method selected from the modified Hantzsch method (method A), the hydrolysis of a chloroethyl ester obtained by method A (method B) or the replacement of the chlorine atom with various kinds of amino groups (method C). Hydroxymethyl and cyano groups at the 2-position were prepared in a similar manner to that described in a previous paper.[1]

The hypotensive activities of the compounds prepared in this paper were compared with the corresponding alkyl ester at the 5-position reported previously. It was found that *N*-benzylmethylaminoethyl esters, especially *N*-(4-chlorobenzyl)- and *N*-(3,4-dichlorobenzyl)-*N*-methylaminoethyl esters, were suitable substituents at the 5-position of the 1,4-dihydropyridine nucleus and that these substituents were somewhat more effective for hypotensive activity than simple alkyl esters in a series of 2-hydroxymethyl-1,4-dihydropyridine derivatives. But it was found that the effect was reversed in a series of 2-cyano-1,4-dihydropyridine derivatives. Both of them were found to be inferior to nilvadipine (1c), accepted in clinical use for the treatment of hypertension.

Keywords 2-hydroxymethyl-1,4-dihydropyridine; 2-cyano-1,4-dihydropyridine; nilvadipine; calcium antagonist; antihypertension; structure–activity relationship

In a previous paper,[1] we described the synthesis and structure–activity relationships of 1,4-dihydropyridines containing a novel substituent at the 2-position of the nucleus. It was found in the study that 2-hydroxymethyl- (Ia) and 2-cyano-1,4-dihydropyridines (Ib) possessed potent activities both in increasing coronary blood flow and in hypotensive effect, and Ib was slightly superior to Ia. This finding indicates that a hydroxymethyl or a cyano group seems to be a useful substituent at the 2-position for creating a novel 1,4-dihydropyridine system as a calcium antagonist. It was also found that unsymmetrical esters at the 3- and the 5-positions were somewhat effective to symmetrical esters in the 2-hydroxymethyl and the 2-cyano series. In fact, from the compounds we synthesized, nilvadipine (Ic) was selected for further biological evaluations and consequently it has been accepted in clinical use for the treatment of hypertension.

In order to find more potent 1,4-dihydropyridine as a calcium antagonist, we next focused on the modification of its ester moieties. When we initiated this study, it was known that nicardipine (II) haing a novel ester moiety containing an amino group was under going clinical trials, although its synthesis and the structure–activity relationships[2] had remained unpublished. We assumed that the potent activities of nicardipine (II) might be due not only to the unsymmetrical feature of its structure, but also to good bioavailability owing to its physicochemical properties. We intended to combine the novel ester moiety of nicardipine (II) and our novel substituents at the 2-position of the 1,4-dihydropyridine nucleus, namely hydroxymethyl and cyano groups. Thus we synthesized 2-hydroxymethyl- and 2-cyano-1,4-dihydropyridine derivatives containing a heteroatom-substituted alkyl ester at the 5-position, whereas the alkyl part of the ester at the 3-position remained as an ethyl group. Studies[1] on the substituent effect of the phenyl ring at the 4-position showed that an electron-withdrawing substituent such as 3-nidro, 2-trifluoromethyl or 2-cyano could be adoped in efficient achievement of our objective to find more potent 1,4-dihydropyridine derivatives. The 2-nitro group was excluded from the outset because a 1,4-dihydropyridine derivative having a 2-nitrophenyl group at the 4-position is unstable to sunlight which causes the intramolecular oxidation–reduction reaction as reported by Berson.[3]



I

a: R=CH_2OH
b: R=CN
c: R=CN, R^1=3-NO_2, R^2=CH_3, R^3=$CH(CH_3)_2$ (nilvadipine)

II

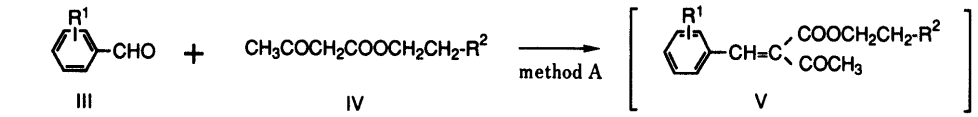
nicardipine

Fig. 1

Among the heteroatom-substituted alkyl esters in this study, 5-(*N*-benzyl-*N*-methyl)aminoethyl ester, particularly substituted by either one or two chlorines at the benzyl moiety exhibited potent hypotensive activity. This finding coincides with the results on nicardipine related compounds.[2] The compounds possessing ethoxyethyl ester, phenoxyethyl ester, benzyloxyethyl ester or their sulfur analogues at the 5-position, however, exhibited only a moderate hypotensive effect.

Some compounds having a cyano group at the 2-position of the 1,4-dihydropyridine nucleus, *e.g.* [*N*-(4-chlorobenzyl)-*N*-methyl]aminoethyl 4-(3-nitrophenyl)-(Xq), [*N*-(4-chlorobenzyl)-*N*-methyl]aminoethyl 4-(2-cyanophenyl)-(Xs), and [*N*-(3,4-dichlorobenzyl)-*N*-methyl]aminoethyl 4-(3-nitrophenyl)-2-cyano-3-ethoxycarbonyl-6-methyl-1,4-dihydropyridine-5-carboxylate (Xt), were found to show comparable activities to that of nilvadipine (Ic) in hypotensive effect at the dose of 10 mg/kg, but to be inferior to Ic at the dose of 1 mg/kg.

In the present paper we describe the synthesis and the structure–activity relationships of these novel 1,4-dihydro-



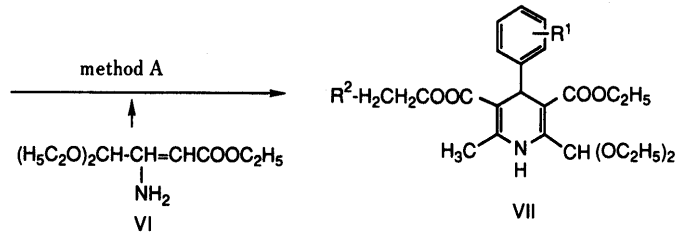


Chart 1

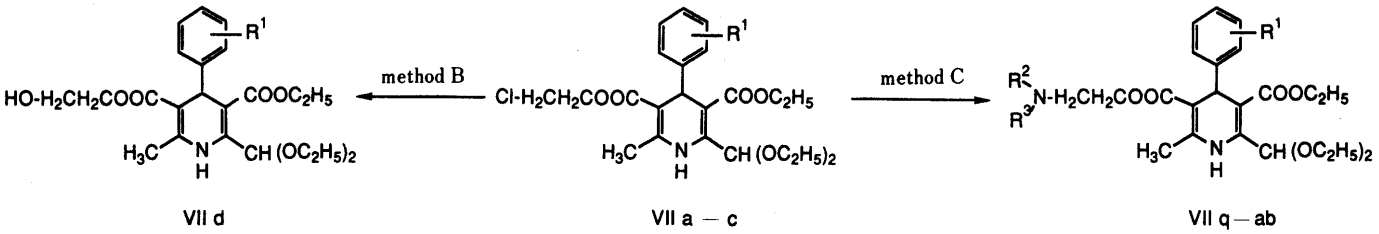


Chart 2

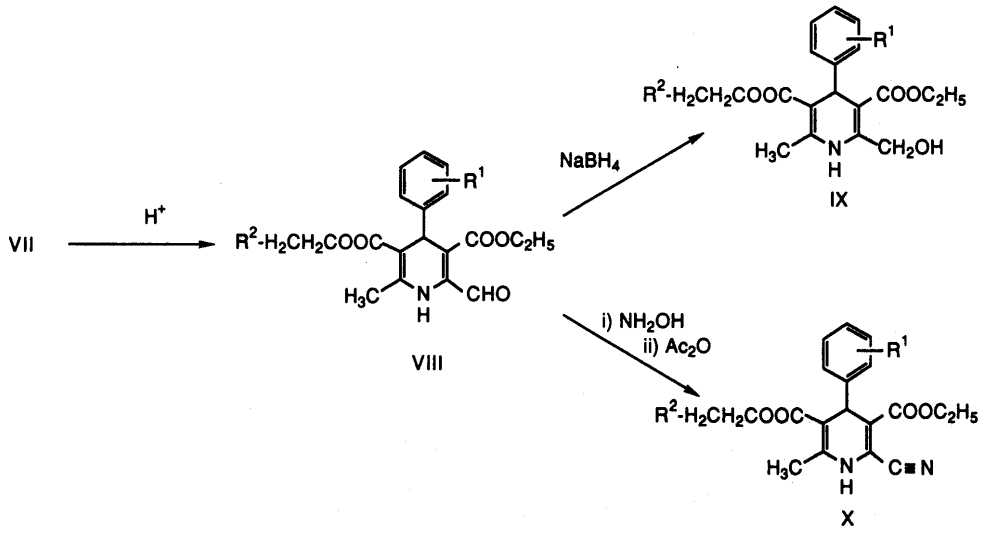
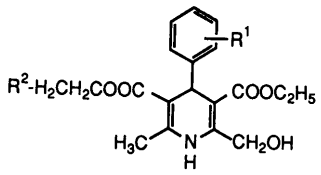


Chart 3

pyridines possessing a heteroatom-substituted alkyl ester at the 5-position of 2-hydroxymethyl- and 2-cyano-1,4-dihydropyridines.

Chemistry As shown in Chart 1, the 1,4-dihydropyridine nucleus was synthesized according to the modified Hantzsch method[4] which has been described in a previous paper.[1] Aryl aldehyde (III) reacted with heteroatom-substituted ethyl acetoacetate (IV) under the Knoevenagel reaction conditions to afford a benzylidene derivative (V), which comprises a mixture of *E*- and *Z*-forms observed as two separable spots on thin layer chromatography. V was subsequently treated with ethyl 4,4-diethoxy-3-aminocrotonate (VI) to give the intermediate 2-diethoxymethyl-1,4-dihydropyridine (VII) (method A). 2-Chloroethyl esters (VIIa—c, $R^2 = Cl$) were also obtained *via* a simple modification of method A. Namely in the process to prepare V, acetic acid was added to prevent the displacement of the chlorine in the ester part with piperidine as a catalyst (method A'). This chlorine atom in VIIa—c appears to be highly reactive to nucleophile such as a hydroxide ion or an amine. Thus, 2-diethoxymethyl-1,4-dihydropyridines having 2-hydroxyethyl (VIId), substituted or unsubstituted benzylmethylaminoethyl esters (VIIq—ab) were prepared from the 2-chloroethyl esters (VIIa—c) as depicted in Chart 2. VIId and VIIq—ab were obtained by hydrolysis with potassium carbonate in aqueous ethanol (method B) and by substitution with the corresponding amines (method C), respectively. 2-Formyl derivatives (VIII), precursors of the desired 2-hydroxymethyl- and 2-cyano-1,4-dihydropyridines, were easily obtained by acid hydrolysis of the acetals (VII) with 6 N HCl in acetone at room temperature. 2-Hydroxymethyl-1,4-dihydropyridines (IX) were prepared

TABLE I. 2-Hydroxymethyl-1,4-dihydropyridines (IX)



Compd. No.	R^1	R^2	Yields (%)	mp (°C) (Recryst. solv.)	NMR δ value ($CDCl_3$)			Formula	*Anal.* Calcd (Found)		
					C_4-H	C_6-CH_3	C_2-CH_2		C	H	N
IXa	3-NO_2	OC_2H_5	79.4	99—100 (Et_2O–*n*-Hex)	5.14	2.42	4.81	$C_{21}H_{26}N_2O_8$	58.05 (58.20)	6.03 (6.08)	6.45 (6.34)
IXb	3-NO_2	OC_6H_5	65.3	136—138 (MeOH–IPE)	5.11	2.41	4.82	$C_{25}H_{26}N_2O_8$	62.23 (62.54)	5.43 (5.52)	5.81 (5.79)
IXc	3-NO_2	$OCH_2C_6H_5$	80.6	118—119 (MeOH–IPE)	5.13	2.39	4.52	$C_{26}H_{28}N_2O_8$	62.90 (63.08)	5.68 (5.78)	5.64 (5.63)
IXd	2-CN	OC_2H_5	97.1	127—128.5 (MeOH)	5.34	2.42	4.81	$C_{22}H_{26}N_2O_6$	63.75 (63.81)	6.32 (6.25)	6.76 (6.89)
IXe	2-CN	OC_6H_5	87.6	116—117 (MeOH)	5.35	2.40	4.82	$C_{26}H_{26}N_2O_6$	67.51 (67.68)	5.67 (5.54)	6.06 (5.92)
IXf	2-CN	$OCH_2C_6H_5$	87.4	109—110 (MeOH)	5.35	2.41	4.80	$C_{27}H_{28}N_2O_6$	68.05 (67.92)	5.92 (6.11)	5.88 (5.76)
IXg	2-CN	SC_2H_5	91.4	85—87 (IPE)	5.35	2.41	4.83	$C_{22}H_{26}N_2O_5S$	61.37 (61.53)	6.09 (6.08)	6.51 (6.61)
IXh	2-CN	SC_6H_5	76.6	114—116 (IPE–C_6H_6)	5.31	2.35	4.78	$C_{26}H_{26}N_2O_5S$	65.25 (65.11)	5.48 (5.35)	5.85 (5.88)
IXi	2-CN	$SCH_2C_6H_5$	88.9	121—122 (IPE–C_6H_6)	5.32	2.38	4.80	$C_{27}H_{28}N_2O_5S$	75.49 (75.51)	6.57 (6.51)	6.52 (6.48)
IXj	3-NO_2	$N(CH_3)CH_2C_6H_5 \cdot HCl$	90.2	133—135 (EtOH)	5.14	2.20	[a]	$C_{27}H_{31}N_3O_7 \cdot HCl \cdot 1/2H_2O$	58.42 (58.17)	5.99 (5.96)	7.57 (7.23)
IXk	2-CN	$N(CH_3)CH_2C_6H_4Cl(4)$	75.6	158—159 (EtOH)	5.31	2.33	4.78	$C_{28}H_{30}ClN_3O_5$	64.18 (64.33)	5.77 (5.76)	8.02 (8.12)
IXl	2-CN	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	77.7	167—169 (aq. EtOH)	5.43	2.36	4.79	$C_{28}H_{29}ClN_3O_5$	60.22 (59.92)	5.23 (5.26)	7.52 (7.38)
IXm	2-CN	$N(CH_3)CH_2C_6H_4CH_3(4)$	85.3	174—176 (EtOH–AcOEt)	5.34	2.38	4.79	$C_{29}H_{33}N_3O_5$	69.17 (69.28)	6.60 (6.62)	8.34 (8.36)
IXn	2-CN	$N(CH_3)CH_2C_6H_4OCH_3(4)$	63.4	161—163 (aq. EtOH)	5.33	2.38	4.79	$C_{29}H_{33}N_3O_6$	67.04 (66.56)	6.40 (6.37)	8.09 (8.09)

a) Overlapped with other signals. IPE, diisopropyl ether.

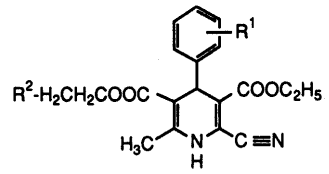
by reduction of VIII using sodium borohydride. This reaction was carried out under cooling in an ice-bath to avoid the formation of a lactone by-product as reported in the previous paper.[1] 2-Cyano-1,4-dihydropyridines (X) were obtained by hydroxyimination of VIII, followed by dehydration with acetic anhydride as illustrated in Chart 3. When these reactions were employed to the 2-hydroxyethyl ester (VIIIa, $R^2 = OH$), the 2-cyano derivative (Xj) possessing a 2-acetoxyethyl ester at the 5-position was obtained by reaction with an excess of acetic anhydride. Xj was able to be converted to 2-hydroxyethyl 2-cyano-1,4-dihydropyridine-5-carboxylate (Xa) by refluxing with potassium carbonate in an aqueous ethanolic solution.

2-Hydroxymethyl- and 2-cyano-1,4-dihydropyridines (IX, X) prepared in this study are summarized in Tables I and II.

Structure–Activity Relationships and Discussion The biological activities of the compounds prepared in this paper were evaluated *via* the following test, *i.e.* hypotensive effect in normotensive rats after oral administration at the doses of 1 and 10 mg/kg. The evaluation results of 2-hydroxymethyl- and 2-cyano-1,4-dihydropyridines are summarized in Tables III and IV, respectively.

In the 2-hydroxymethyl-4-(3-nitrophenyl)-1,4-dihydropyridine series, the introduction of the ethoxy (IXa), the phenoxy (IXb), the benzyloxy (IXc) or the *N*-benzyl-*N*-methylamino (IXj) group instead of the hydrogen of the ethyl group at the 5-position of IXaa, which was reported in the previous paper,[1] decreased the hypotensive effect slightly. Nevertheless the benzyloxy group was found to be effective at the dose of 10 mg/kg. But in the case of 2-cyanophenyl substituent at the 4-position, the introduction of the ethoxy (IXd), the phenoxy (IXe) and the benzyloxy (IXf) slightly strengthen the hypotensive activities when comparing them to their 3,5-dimethyl ester (IXac). Benzyloxyethyl ester was slightly superior to ethoxyethyl esters in both series of 3-nitrophenyl and 2-cyanophenyl substituents in comparison with each pair of IXc *vs.* IXa, b and IXf *vs.* IXd, e. This might be due to an increase in lipophilicity. The introduction of a sulfur atom instead of an oxygen atom results in a decrease of its potency as exemplified by IXd *vs.* IXg, IXe *vs.* IXh and IXf *vs.* IXi, respectively. *N*-Benzyl-*N*-methylaminoethyl esters showed high potency in general and the substituent on the phenyl ring of the benzyl group was found to have a profound effect, *i.e.* when the benzyl group was substituted with an electron-withdrawing substituent such as chlorine (IXk, IXl), the activity was increased whereas with an electron-

TABLE II. 2-Cyano-1,4-dihydropyridines (X)



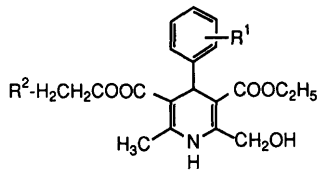
Compd. No.	R^1	R^2	Yields (%)	mp (°C) (Recryst. solv.)	IR (Nujol) $\nu_{C\equiv N}$ (cm^{-1})	NMR δ value[a]		Formula	*Anal.* Calcd (Found)		
						C_4-H	C_6-CH_3		C	H	N
Xa	3-NO_2	OH	93.1[b]	150—152 (C_6H_6)	2230	5.80	2.38	$C_{19}H_{19}N_3O_7$	56.85 (56.98)	4.77 4.66	10.47 10.51)
Xb	3-NO_2	OC_2H_5	50.3	115—116 (Et_2O–*n*-Hex)	2260	5.23	2.40	$C_{21}H_{23}N_3O_7$	58.74 (58.69)	5.40 5.38	9.79 9.61)
Xc	3-NO_2	OC_6H_5	73.1	133—135 (IPE–Et_2O)	2300	5.20	2.42	$C_{25}H_{23}N_3O_7$	62.89 (63.21)	4.86 4.77	8.80 8.70)
Xd	3-NO_2	$OCH_2C_6H_5$	46.8	117—119 (IPE–Et_2O)	2300	5.21	2.38	$C_{26}H_{25}N_3O_7$	63.54 (63.62)	5.13 5.10	8.55 8.48)
Xe	2-CF_3	OC_2H_5	72.6	104—105 (IPE)	2300	5.71	2.29	$C_{21}H_{23}F_3N_2O_5$	58.40 (58.53)	5.12 5.24	6.19 6.29)
Xf	2-CF_3	OC_6H_5	53.6	118—119 (IPE)	2250	5.70	2.32	$C_{27}H_{25}F_3N_2O_5$	62.32 (62.40)	4.68 4.63	5.59 5.60)
Xg	2-CF_3	$OCH_2C_6H_5$	67.4	146—147.5 (*n*-Hex–C_6H_6)	2250	5.6—5.7	2.23	$C_{28}H_{27}F_3N_2O_5$	63.03 (63.10	4.90 4.96	5.45 5.45)
Xh	2-CN	OC_2H_5	75.1	135—136 (IPE–C_6H_6)	2225	5.43	2.37	$C_{22}H_{21}N_3O_5$	64.54 (64.43	5.66 5.61	10.26 10.51)
Xi	2-CN	OC_6H_5	58.6	170—172 (AcOEt)	2245	5.34	2.33	$C_{26}H_{21}N_3O_5$	68.26 (67.99	5.08 5.14	9.19 9.08)
Xj	3-NO_2	$OCOCH_3$	44.1	114—116 (Et_2O)	2230	5.17	2.41	$C_{21}H_{21}N_3O_8$	56.88 (56.90	4.77 4.70	9.48 9.40)
Xk	2-CF_3	SC_2H_5	53.4	81—82 (IPE–PE)	2240	5.6—5.7	2.32	$C_{22}H_{23}F_3N_2O_4S$	56.40 (56.39	4.95 4.65	5.98 6.09)
Xl	2-CN	SC_2H_5	35.7	125—127 (IPE–AcOEt)	2220	5.44	2.42	$C_{22}H_{23}N_3O_4S$	62.10 (62.32	5.45 5.40	9.88 9.68)
Xm	2-CN	SC_6H_5	67.5	126—128.5 (IPE–C_6H_6)	2250	5.36	2.34	$C_{26}H_{23}N_3O_4S$	65.94 (65.81	4.90 5.11	8.87 8.74)
Xn	3-NO_2	$N(CH_3)CH_2C_6H_5 \cdot HCl$	47.5	228—229 (dec.) (aq. EtOH)	2240	5.26[c]	2.39[c]	$C_{27}H_{29}ClN_4O_6$	59.95 (60.02	5.40 5.29	10.36 10.17)
Xo	2-CF_3	$N(CH_3)CH_2C_6H_5 \cdot HCl$	28.5	203—204 (dec.) (EtOH–Et_2O)	2260	5.35—5.6[c]	2.50[c]	$C_{28}H_{29}ClF_3N_3O_4$	59.63 (59.31	5.18 5.24	7.45 7.18)
Xp	2-CN	$N(CH_3)CH_2C_6H_5 \cdot HCl$	48.7	230 (dec.) (aq. EtOH)	2250	5.25[c]	2.33[c]	$C_{28}H_{29}ClN_4O_4$	64.55 (64.39	5.61 5.72	10.75 10.71)
Xq	3-NO_2	$N(CH_3)CH_2C_6H_4Cl(4) \cdot HCl$	39.1	223—225 (dec.) (aq. EtOH)	[d]	5.26	2.40	$C_{27}H_{28}Cl_2N_4O_6$	56.35 (56.50	4.90 4.79	9.74 9.71)
Xr	2-CF_3	$N(CH_3)CH_2C_6H_4Cl(4) \cdot HCl$	47.1	226—227 (dec.) (EtOH–Et_2O)	2270	5.45—5.6[c]	2.55[c]	$C_{28}H_{28}Cl_2F_3N_3O_4$	56.20 (55.98	4.72 4.76	7.02 7.13)
Xs	2-CN	$N(CH_3)CH_2C_6H_4Cl(4) \cdot HCl$	59.2	232—233 (dec.) (aq. EtOH)	2250	5.25[c]	2.32[c]	$C_{28}H_{28}Cl_2N_4O_4$	60.55 (60.29	5.08 5.03	10.09 9.95)
Xt	3-NO_2	$N(CH_3)CH_2C_6H_3Cl_2(3,4) \cdot HCl$	41.3	233.5—234 (dec.) (aq. EtOH)	[d]	5.24	2.43	$C_{27}H_{27}Cl_3N_4O_6$	53.17 (53.22	4.46 4.40	9.17 9.07)
Xu	2-CF_3	$N(CH_3)CH_2C_6H_3Cl_2(3,4) \cdot HCl$	36.4	228—229 (dec.) (EtOH–Et_2O)	2260	5.35—5.4[c]	2.33[c]	$C_{28}H_{27}Cl_3F_3N_3O_4$	53.14 (52.74	4.30 4.43	6.64 6.58)
Xv	2-CN	$N(CH_3)CH_2C_6H_3Cl_2(3,4) \cdot HCl$	55.0	240 (dec.) (aq. EtOH)	2250	5.24[c]	2.31[c]	$C_{28}H_{27}Cl_3N_4O_4$	57.01 (56.68	4.61 4.54	9.50 9.36)
Xw	2-CN	$N(CH_3)CH_2C_6H_4CH_3(4) \cdot HCl$	58.1	230 (dec.) (aq. EtOH)	2240	5.33[c]	2.38[c]	$C_{29}H_{31}ClN_4O_4$	65.10 (64.97	5.84 5.82	10.47 10.32)
Xx	2-CN	$N(CH_3)CH_2C_6H_4OCH_3(4) \cdot HCl$	38.1	213—214 (dec.) (EtOH)	2250	5.25[c]	2.33[c]	$C_{29}H_{31}ClN_4O_5$	63.21 (62.68	5.67 5.73	10.17 9.95)

a) ppm from $Si(CH_3)_4$ as an internal standard in $CDCl_3$. *b*) Yield from Xj. *c*) Measured in DMSO-d_6 as a solvent. *d*) Not detected. IPE, diisopropyl ether; PE, petroleum ether.

donating group such as methyl or methoxy (IXm, n), the activity was relatively diminished. The most potent IXk and IXl in this 2-hydroxymethyl series were somewhat superior to IXab and IXad, which were prepared previously[1] and contained a hydroxymethyl group at the 2-position and unsymmetrical lower alkyl esters at the 3- and the 5-positions but they were found to be inferior to nilvadipine (Ic).

It was found that the introduction of an *N*-benzyl-*N*-methylaminoethyl ester instead of a lower alkyl ester at the 5-position of the 2-hydroxymethyl-1,4-dihydropyridine potentiated the activities, but it was not as effective as that

TABLE III. Biological Activities of 2-Hydroxymethyl-1,4-dihydropyridines (IX)



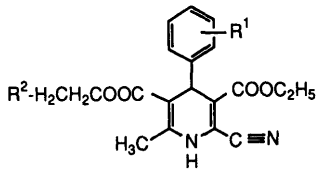
Compd. No.	R^1	R^2	Hypotensive effect[a] Δ_{max} (mmHg) 1 mg/kg	10 mg/kg
IXa	3-NO_2	OC_2H_5	−2.8	−20.2
IXb	3-NO_2	OC_6H_5	NE	−20.0
IXc	3-NO_2	$OCH_2C_6H_5$	−5.8	−43.8
IXd	2-CN	OC_2H_5	−6.7	−33.8
IXe	2-CN	OC_6H_5	−4.0	−30.4
IXf	2-CN	$OCH_2C_6H_5$	−9.0	−40.2
IXg	2-CN	SC_2H_5	NT	−7.4
IXh	2-CN	SC_6H_5	NT	−5.5
IXi	2-CN	$SCH_2C_6H_5$	−5.4	−30.4
IXj	3-NO_2	$N(CH_3)CH_2C_6H_5 \cdot HCl$	−4.6	−29.0
IXk	2-CN	$N(CH_3)CH_2C_6H_4Cl(4)$	−20.4	−49.8
IXl	2-CN	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	−20.6	−39.2
IXm	2-CN	$N(CH_3)CH_2C_6H_4CH_3(4)$	NT	−11.6
IXn	2-CN	$N(CH_3)CH_2C_6H_4OCH_3(4)$	−9.2	−22.6
IXaa[b]	3-NO_2	(3-, 5-diC_2H_5 ester)	−20.7	−38.2
IXab[b]	3-NO_2	(3-CH_3, 5-iso-C_3H_7 ester)	−12.2	−41.2
IXac[b]	2-CN	(3-, 5-diCH_3 ester)	−6.2	−31.8
IXad[b]	2-CN	(3-CH_3, 5-iso-C_3H_7 ester)	−19.2	−46.8

a) Δ_{max} (mmHg) on blood pressure in normotensive rats after *p.o.* administration. NE, no effect; NT, not tested. *b*) Prepared in the previous paper.[1]

observed in the case of 2,6-dimethyl-1,4-dihydropyridines.[2]

In the series of 2-cyano-1,4-dihydropyridine derivatives, the activities of the compounds prepared in this paper were compared with 3-methyl 5-isopropyl esters (Xaa, Xab) and nilvadipine (Ic) prepared in the previous paper.[1] Contrary to our expectations 5-hydroxyethyl ester (Xa) was found to have only weak activity possibly due to the presence of a hydrophilic hydroxy group. 5-Ethoxyethyl esters (Xb, Xe, Xh) were found to be somewhat inferior to Xaa and Xab at the dose of 10 mg/kg. But the activities at the dose of 1 mg/kg resulted in more decrease than those of Xaa and Xab. Amongst these three compounds, 3-nitrophenyl group was the most effective with a substituent at the 4-position and 2-cyanophenyl and 2-trifluoromethylphenyl groups followed in this order. But in the 5-phenoxyethyl esters (Xc, Xf, Xi), 2-trifluoromethylphenyl was a more effective substituent than the others. The 2-trifluoromethylphenyl group was also effective in 5-benzyloxyethyl ester (Xg), which was just as potent as Xaa and Xab at the dose of 10 mg/kg. Introduction of a sulfur atom instead of oxygen in the ester part decreased its potency in this 2-cyano-1,4-dihydropyridine series also when comparing with each pair of Xk *vs.* Xe, Xl *vs.* Xh, and Xm *vs.* Xi. Acetoxyethyl ester (Xj) was found to be as weak as Xa, because it is possible for Xj to deacetylate to form Xa after oral administration. *N*-Benzyl-*N*-methylaminoethyl esters (Xn—x) were relatively potent as shown in Table IV. In comparison with each trio of (Xn, Xq, Xt), (Xo, Xr, Xu) and (Xp, Xs, Xv), monochloro- or dichloro-substituted benzyl group was very effective in terms of the increase

TABLE IV. Biological Activities of 2-Cyano-1,4-dihydropyridines (X)



Compd. No.	R^1	R^2	Hypotensive effect[a] Δ_{max} (mmHg) 1 mg/kg	10 mg/kg
Xa	3-NO_2	OH	−4.5	NT
Xb	3-NO_2	OC_2H_5	−9.4	−45.0
Xc	3-NO_2	OC_6H_5	NE	−23.0
Xd	3-NO_2	$OCH_2C_6H_5$	−3.7	−27.1
Xe	2-CF_3	OC_2H_5	−8.8	−27.4
Xf	2-CF_3	OC_6H_5	−22.8	−44.2
Xg	2-CF_3	$OCH_2C_6H_5$	−11.6	−48.2
Xh	2-CN	OC_2H_5	−8.0	−34.2
Xi	2-CN	OC_6H_5	−6.9	−17.2
Xj	3-NO_2	$OCOCH_3$	−5.1	NT
Xk	2-CF_3	SC_2H_5	−0.2	−21.8
Xl	2-CN	SC_2H_5	−7.3	−28.8
Xm	2-CN	SC_6H_5	−8.7	−14.0
Xn	3-NO_2	$N(CH_3)CH_2C_6H_5 \cdot HCl$	−11.0	−42.4
Xo	2-CF_3	$N(CH_3)CH_2C_6H_5 \cdot HCl$	−8.6	−43.4
Xp	2-CN	$N(CH_3)CH_2C_6H_5 \cdot HCl$	−4.0	−33.1
Xq	3-NO_2	$N(CH_3)CH_2C_6H_4Cl(4) \cdot HCl$	−29.2	−63.6
Xr	2-CF_3	$N(CH_3)CH_2C_6H_4Cl(4) \cdot HCl$	−35.2	−45.2
Xs	2-CN	$N(CH_3)CH_2C_6H_4Cl(4) \cdot HCl$	−13.0	−50.8
Xt	3-NO_2	$N(CH_3)CH_2C_6H_3Cl_2(3,4) \cdot HCl$	−25.6	−56.4
Xu	2-CF_3	$N(CH_3)CH_2C_6H_3Cl_2(3,4) \cdot HCl$	−23.0	−47.1
Xv	2-CN	$N(CH_3)CH_2C_6H_3Cl_2(3,4) \cdot HCl$	−2.6	−40.0
Xw	2-CN	$N(CH_3)CH_2C_6H_4CH_3(4) \cdot HCl$	−7.0	−36.8
Xx	2-CN	$N(CH_3)CH_2C_6H_4OCH_3(4) \cdot HCl$	−5.1	−29.2
Ic[b]	3-NO_2	(3-CH_3, 5-iso-C_3H_7 ester)	−44.6	−50.0
Xaa[b]	2-CF_3	(3-CH_3, 5-iso-C_3H_7 ester)	−34.6	−47.4
Xab[b]	2-CN	(3-CH_3, 5-iso-C_3H_7 ester)	−39.6	−50.2

a) Δ_{max} (mmHg) on blood pressure in normotensive rats after *p.o.* administration. NE, no effect; NT, not tested. *b*) Prepared in the previous paper.[1]

of potency, and 3-nitrophenyl or 2-trifluoromethylphenyl substituent at the 4-position was superior to the 2-cyanophenyl group. An electron-donating substituent such as methyl or methoxy on the benzyl group (Xw, Xx) decreased the activity in comparison with Xs and Xv. Three derivatives (Xq, Xs, Xt) were found to be more potent than nilvadipine (Ic), Xaa and Xab at the dose of 10 mg/kg but were inferior at the dose of 1 mg/kg.

It was also found that the heteroatom-substituted alkyl ester was not so suitable for potentiating the hypotensive effect of the 2-cyano-1,4-dihydropyridine derivatives, although it was a success in the 2,6-dimethyl-1,4-dihydropyridine series as nicardipine (II).[2]

Comparing with each pair of 2-hydroxymethyl-1,4-dihydropyridines (IX) and 2-cyano-1,4-dihydropyridines (X) possessing the same esters at the 5-positions respectively, 2-cyano derivatives were somewhat superior to 2-hydroxymethyl derivatives in their hypotensive effect, and the same tendency was observed in the series of 3,5-dialkyl esters reported previously.[1]

Experimental

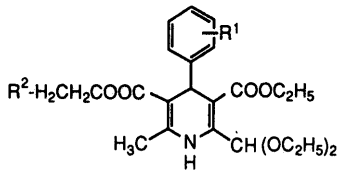
Melting points were determined using a Thomas–Hoover capillary melting point apparatus and uncorrected. Nuclear magnetic resonance

(NMR) spectra were recorded on a JNN-PMR spectrometer using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on either a Hitachi 260-10 spectrophotometer or a Shimadzu IR-420 spectrophotometer. Column chromatography was performed on silica gel (Merck Kieselgel 60, 230—400 mesh).

2-Ethoxyethyl 2-Diethoxymethyl-3-ethoxycarbonyl-6-methyl-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate (VIIe) (Method A) To a solution of 3-nitrobenzaldehyde (4.54 g, 0.03 mol) and 2-ethoxyethyl acetoacetate (5.23 g, 0.03 mol), prepared from ethylene glycol monoethylether and diketene in the presence of NaOAc, in dried C_6H_6 (15 ml) was added piperidine (85.2 mg, 1 mmol) and the mixture was refluxed under azeotropic dehydration for 3 h. The reaction mixture was washed with H_2O and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure to afford a red oil, which was a mixture of *E*- and *Z*-forms of 2-ethoxyethyl 2-(3-nitrobenzylidene)-acetoacetate. To the oil was added ethyl 4,4-diethoxy-3-aminocrotonate (6.52 g, 0.03 mol), which was prepared from 4,4-diethoxyacetoacetate[5] and NH_3, and the mixture was heated at 110 °C in neat with stirring for 3 h. The obtained viscous oil was dissoved in AcOEt, washed with H_2O twice and dried. Removal of the solvent afforded a brown oil, which was subjected to column chromatography on silica gel with (C_6H_6 : AcOEt = 10 : 1) as an eluent. The fractions containing the desired compound were combined and evaporated to afford VIIe, which crystallized by triturating in *n*-hexane and was collected by filtration (8.09 g, 53.2%). An analytical sample was obtained by recrystallization from a mixture of Et_2O and *n*-hexane (1 : 5), mp 99—100 °C. *Anal.* Calcd for $C_{25}H_{34}N_2O_9$: C, 59.28; H, 6.77; N, 5.53. Found: C, 59.46; H, 6.84; N, 5.57. IR (Nujol) cm^{-1}: 3400 (NH), 1700 (COOR), 1650, 1610 (C=C). NMR ($CDCl_3$) δ: 1.0—1.5 (12H, m, $COOCH_2CH_3$, $OCH_2CH_3 \times 3$), 2.40 (3H, s, C_6-CH_3), 3.4—4.3 (12H, m, $COOCH_2CH_3$, $COOCH_2CH_2OCH_2$, $OCH_2CH_3 \times 2$), 5.16 (1H, s, C_4-H), 6.22 (1H, s, $CH(OR)_2$), 6.85 (1H, br s, NH), 7.2—8.2 (4H, m, aromatic protons).

2-Chloroethyl 2-Diethoxymethyl-3-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate (VIIa) (Method A′) To a solution of 3-nitrobenzaldehyde (30.22 g, 0.2 mol) and 2-chloroethyl acetoacetate (36.21 g, 0.22 mol), prepared from 2-chloroethanol and diketene in the presence of a catalytic amount of AcONa, in C_6H_6 (150 ml) were added AcOH (0.73 g) and piperidine (0.68 g) and the mixture was refluxed under azeotropic dehydration for 9.5 h. After cooling, the reaction mixture was washed with H_2O, aq. solution of $NaHCO_3$ and H_2O in turn and dried over $MgSO_4$. Removal of solvent afforded a viscous oil, which was chromatographed on silica gel with C_6H_6 as an eluent to give a mixture of *E*- and *Z*-forms of 2-chloroethyl 2-(3-nitrobenzylidene)-acetoacetate as an oil (35.64 g). A mixtue of the oil (16.0 g, 0.05 mol) obtained above and ethyl 4,4-diethoxy-3-aminocrotonate (10.85 g, 1.0 eq mol), prepared from ethyl 4,4-diethoxyacetoacetate[5] and NH_3, was heated in neat at 100 °C for 3 h. After cooling, the oily reaction mixture (26.8 g) crystallized on standing. This was subjected to column chromatography on silica gel with (C_6H_6 : AcOEt = 20 : 1) as an eluent. The fractions containing the desired compound were combined and evaporated to afford an oil (14.42 g), which crystallized on standing in *n*-hexane containing a small amount of Et_2O. Collection by filtration afforded the titled compound as yellow crystals (10.62 g, 42.8%) and an analytical sample was obtained by recrystallization from a mixture of *n*-hexane and Et_2O (10 : 1), mp 96—97 °C. *Anal.* Calcd for $C_{24}H_{29}ClN_2O_8$: C, 55.59; H, 5.88; Cl, 7.14; N, 5.64. Found: C, 56.19; H, 5.96; Cl, 7.22;

TABLE V. 2-Diethoxymethyl-1,4-dihydropyridines (VII)



Compound No.	R^1	R^2	Synthetic method	Yields (%)	mp (°C) (Recryst. solv.)	NMR δ value ($CDCl_3$) C_4-H
VIIa	3-NO_2	Cl	A′	a)		
VIIb	2-CN	Cl	A′	51.6	Oil	5.39
VIIc	2-CF_3	Cl	A′	60.4	Oil	5.5—5.7
VIId	3-NO_2	OH	B	a)		
VIIe	3-NO_2	OC_2H_5	A	a)		
VIIf	2-CF_3	OC_2H_5	A	44.4	110 (IPE)	5.5—5.7
VIIg	2-CN	OC_2H_5	A	61.3	Oil	5.45
VIIh	3-NO_2	OC_6H_5	A	93.3	Oil	5.15
VIIi	2-CF_3	OC_6H_5	A	67.0	Oil	5.67
VIIj	2-CN	OC_6H_5	A	69.3	94—95 (*n*-Hex–EtOAc)	5.43
VIIk	3-NO_2	$OCH_2C_6H_5$	A	54.0	Oil	5.18
VIIl	2-CF_3	$OCH_2C_6H_5$	A	51.9	Oil	5.6—5.7
VIIm	2-CN	$OCH_2C_6H_5$	A	58.6	97.5—98.5 (*n*-Hex–EtOAc)	5.48
VIIn	2-CF_3	SC_2H_5	A	43.3	Oil	5.5—5.6
VIIo	2-CN	SC_2H_5	A	72.5	Oil	5.37
VIIp	2-CN	SC_6H_5	A	89.5	Oil	5.33
VIIq	2-CN	$SCH_2C_6H_5$	A	58.4	83—84 (IPE)	5.39
VIIr	3-NO_2	$N(CH_3)CH_2C_6H_5$	C	a)		
VIIs	2-CF_3	$N(CH_3)CH_2C_6H_5$	C	60.4	Oil	5.63
VIIt	2-CN	$N(CH_3)CH_2C_6H_5$	C	74.5	Oil	5.44
VIIu	3-NO_2	$N(CH_3)CH_2C_6H_4Cl(4)$	C	96.8	Oil	(2.36)b)
VIIv	2-CF_3	$N(CH_3)CH_2C_6H_4Cl(4)$	C	66.9	Oil	5.55—5.65
VIIw	2-CN	$N(CH_3)CH_2C_6H_4Cl(4)$	C	88.4	Oil	5.41
VIIx	3-NO_2	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	C	78.6	Oil	(2.41)b)
VIIy	2-CF_3	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	C	84.6	Oil	5.62
VIIz	2-CN	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	C	92.7	Oil	5.38
VIIaa	2-CN	$N(CH_3)CH_2C_6H_4CH_3(4)$	C	84.8	Oil	5.38
VIIab	2-CN	$N(CH_3)CH_2C_6H_4OCH_3(4)$	C	98.5	Oil	5.38

a) See experimental. b) Chemical shift of C_6-CH_3. IPE, diisopropyl ether.

N, 5.73. IR (Nujol) cm^{-1}: 3360 (NH), 3100, 1700 (COOR), 1645, 1605 (C=C). NMR ($CDCl_3$) δ: 1.22 (9H, t, J=7.0 Hz, $OCH_2C\underline{H}_3 \times 3$), 2.37 (3H, s, C_6-CH_3), 3.4—3.8 (6H, m, $COOC\underline{H}_2CH_2Cl$, $OC\underline{H}_2CH_3 \times 2$), 4.09 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 4.30 (2H, t, J=7 Hz, CH_2Cl), 5.14 (1H, s, C_4-H), 6.17 (1H, s, $C\underline{H}(OR)_2$), 6.88 (1H, s, NH), 7.2—8.12 (4H, m, aromatic protons).

VIIb, c and VIIf—q were obtained in a similar manner to that of VIIe (method A) or VIIa (method A') and their physical data are listed in Table V.

2-Hydroxyethyl 2-Diethoxymethyl-3-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate (VIId) (Method B) To a solution of VIIa (1.24 g, 2.5 mmol) in EtOH (20 ml) was added dropwise an aq. solution of K_2CO_3 (0.35 g/5 ml) under refluxing and stirring, which were continued for 2 h. After cooling, EtOH was removed by evaporation. The residual aq. solution was neutralized with AcOH and extracted twice with AcOEt. The combined extract was washed with an aq. solution of $NaHCO_3$ and H_2O successively and dried over $MgSO_4$. Removal of the solvent afforded a yellow oil (0.82 g, 68.5%). IR (neat) cm^{-1}: 3530 (OH), 3410 (NH), 1707 (sh, COOR), 1698 (COOR'). This was used in the following reaction without further purification.

2-(*N*-Benzyl-*N*-methyl)aminoethyl 2-Diethoxymethyl-3-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate(VIIr) (Method C) A mixture of VIIa (8.5 g, 17.1 mmol), *N*-benzyl-*N*-methylamine (2.70 g, 22.2 mmol, 1.2 eq mol) and Et_3N (2.60 g, 25.6 mmol, 1.5 eq mol) were stirred under refluxing for 56 h. EtOH was removed under reduced pressure and the residue was extracted with AcOEt. The extract was successively washed with H_2O and brine and dried over $MgSO_4$. Removal of the solvent gave an oil, which was subjected to column chromatography on silica gel with (C_6H_6 : Et_2O = 10 : 1) as an eluent. The fractions containing the desired compound were combined and evaporated under reduced pressure to afford a yellow oil (8.15 g, 82.0%). This oil was used in the following reaction without further purification. IR (neat) cm^{-1}: 3400 (NH), 1700 (COOR), 1690 (COOR'), 1610 (C=C). NMR ($CDCl_3$) δ: 1.21 (9H, t, J=7 Hz, $COOCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3 \times 2$), 2.21 (3H, s, C_6-CH_3), 2.36 (3H, s, NCH_3), 2.63 (2H, t, J=6 Hz, $NC\underline{H}_2CH_2O$), 3.50 (2H, s, NCH_2Ph), 3.65, 3.66 (4H, each q, J=7 Hz, $OC\underline{H}_2CH_3 \times 2$), 4.10 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 4.18 (2H, t, J=7 Hz, $COOCH_2C\underline{H}_2N$), 5.18 (1H, s, C_4-H), 6.2 (1H, s, $C\underline{H}(OR)_2$), 6.86 (1H, s, NH), 7.16—8.16 (9H, m, aromatic protons).

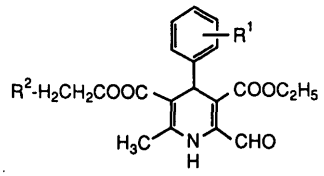
VIIs—ab were obtained in a similar manner to that of VIIr and their yields and physical data are summarized in Table V.

2-Ethoxyethyl 3-Ethoxycarbonyl-2-formyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate (VIIIb) To a solution of VIIe (5.85 g, 11.5 mmol) in acetone (60 ml) was added 6 N HCl under stirring at room temperature and maintained at that temperature for 1.5 h. Acetone was evaporated under reduced pressure and the residue was diluted with H_2O. The resultant mixture was extracted twice with AcOEt. The extract was washed with aq. solution of $NaHCO_3$ and H_2O sucessively. The solvent was dried over $MgSO_4$ and removed to give a red oil, which crystallized on standing and was washed with *n*-hexane. Collection by filtration afforded a yellowish orange powder (4.81 g, 96.4%). An analytical sample was obtained by recrystallization from a mixture of Et_2O and AcOEt, mp 100—101 °C. *Anal.* Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48. Found: C, 58.58; H, 5.63; N, 6.46. IR (Nujol) cm^{-1}: 3400 (NH), 1707 (COOR), 1688 (CHO), 1650, 1612 (C=C). NMR ($CDCl_3$) δ: 1.23, 1.33 (6H, each t, J=7 Hz, $COOCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 2.53 (3H, s, C_6-CH_3), 3.2—3.8, 4.0—4.4 (8H, each m, $COOC\underline{H}_2CH_3$, $COOC\underline{H}_2C\underline{H}_2OC\underline{H}_2CH_3$), 5.30 (1H, s, C_4-H), 7.13 (1H, brs, NH), 7.3—8.3 (4H, m, aromatic protons), 10.67 (1H, s, CHO).

The other 2-formyl-1,4-dihydropyridines (VIII) were prepared in a similar manner to that of VIIIb and their yields and physical data are listed in Table VI.

2-Ethoxyethyl 3-Ethoxycarbonyl-2-hydroxymethyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate(IXa) To a suspension of VIIIb (1.13 g, 26.2 mmol) in EtOH (15 ml) was added $NaBH_4$ (80 mg, 21.0 mmol) portionwise under stirring and cooling at 0—5 °C in an ice-bath. After the addition was completed, the mixture was stirred for 1 h under the same conditions. The reaction mixture was adjusted to pH 6

TABLE VI. 2-Formyl-1,4-dihydropyridines (VIII)



Compound No.	R^1	R^2	Yields (%)	mp (°C) (Recryst. solv.)	NMR δ value ($CDCl_3$)	
					C_4-H	CHO
VIIIa	3-NO_2	OH	96.7	Oil	5.25	10.50
VIIIb	3-NO_2	OC_2H_5	a)			
VIIIc	2-CF_3	OC_2H_5	Quant.	Oil	5.7—5.8	10.27
VIIId	2-CN	OC_2H_5	63.1	115—116 (aq. MeOH)	5.46	10.58
VIIIe	3-NO_2	OC_6H_5	62.9	Oil	5.26	10.51
VIIIf	2-CF_3	OC_6H_5	98.1	Oil	5.71	10.26
VIIIg	2-CN	OC_6H_5	69.2	104—105 (aq. MeOH)	5.49	10.53
VIIIh	3-NO_2	$OCH_2C_6H_5$	95.8	97—99 (EtOH)	5.27	10.52
VIIIi	2-CF_3	$OCH_2C_6H_5$	98.3	Oil	5.7—5.8	10.28
VIIIj	2-CN	$OCH_2C_6H_5$	Quant.	Oil	5.48	10.51
VIIIk	2-CF_3	SC_2H_5	Quant.	Oil	5.5—5.65	10.22
VIIIl	2-CN	SC_2H_5	79.4	98—100 (IPE)	5.50	10.53
VIIIm	2-CN	SC_6H_5	37.3	108—110 (IPE)	5.49	10.56
VIIIn	2-CN	$SCH_2C_6H_5$	Quant.	Oil	5.48	10.51
VIIIo	3-NO_2	$N(CH_3)CH_2C_6H_5$	91.8	Oil	5.28	10.54
VIIIp	2-CF_3	$N(CH_3)CH_2C_6H_5$	96.2	Oil	5.71 (br)	10.28
VIIIq	2-CN	$N(CH_3)CH_2C_6H_5$	80.4	Oil	5.51	10.57
VIIIr	3-NO_2	$N(CH_3)CH_2C_6H_4Cl(4)$	87.2	84—85.5 (IPE)	5.26	10.45
VIIIs	2-CF_3	$N(CH_3)CH_2C_6H_4Cl(4)$	93.3	Oil	5.70 (br)	10.26
VIIIt	2-CN	$N(CH_3)CH_2C_6H_4Cl(4)$	92.0	Oil	5.48	10.52
VIIIu	3-NO_2	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	77.5	104—105 (IPE)	5.32	10.55
VIIIv	2-CF_3	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	97.4	Oil	5.71 (br)	10.29
VIIIw	2-CN	$N(CH_3)CH_2C_6H_3Cl_2(3,4)$	Quant.	Oil	5.47	10.53
VIIIx	2-CN	$N(CH_3)CH_2C_6H_3CH_3(4)$	96.8	Oil	5.49	10.52
VIIIy	2-CN	$N(CH_3)CH_2C_6H_3OCH_3(4)$	84.6	Oil	5.50	10.53

a) See experimental. IPE, diisopropyl ether.

with diluted HCl under cooling. EtOH was removed and the resultant mixture was diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O and brine successively and dried over $MgSO_4$. Removal of the solvent afforded a crude crystalline material, which was triturated in *n*-hexane and collected by filtration to give a yellow powder. Recrystallization from a mixture of Et_2O and *n*-hexane afforded light yellow granules, mp 99—100 °C. *Anal.* Calcd for $C_{21}H_{26}N_2O_8$: C, 58.05; H, 6.03; N, 6.45. Found: C, 58.20; H, 6.08; N, 6.34. IR (Nujol) cm^{-1}: 3200 (OH, NH), 1705 (COOR), 1670. NMR ($CDCl_3$) δ: 1.20 (6H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 2.42 (3H, s, C_6-CH_3), 3.35—3.9 (4H, m, $COOCH_2CH_2O$), 4.18 (4H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$), 4.81 (2H, br d, $C\underline{H}_2OH$), 5.14 (1H, s, C_4-H), 7.3—8.2 (6H, m, aromatic protons, NH, OH).

The other 2-hydroxymethyl-1,4-dihydropyridines (IX) were prepared in a similar manner to that of IXa and their yields and physical data are summarized in Table I.

2-Ethoxyethyl 2-Cyano-3-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate(Xb) A mixture of VIIIb (3.0 g, 6.94 mmol), $NH_2OH \cdot HCl$ (0.55 g, 7.98 mmol) and AcONa (1.14 g, 13.9 mmol) in AcOH (10 ml) was stirred for 0.5 h at an ambient temperature. And then to the reaction mixture was added Ac_2O (1.40 ml). The mixture was stirred for a further 0.5 h at room temperature and gently refluxed for 1 h. After removal of AcOH, the mixture was diluted with H_2O and made alkaline with an aq. solution of $NaHCO_3$. The aq. mixture was extracted twice with AcOEt and the extract was washed with H_2O and brine and dried over $MgSO_4$. Removal of the solvent gave a viscous oil, which was subjected to column chromatography on silica gel with (C_6H_6: AcOEt = 5 : 1) as an eluent. The fractions containing the desired compound were combined and evaporated *in vacuo* to give a yellow oil (1.56 g), which crystallized on standing. Recrystallization from a mixture of Et_2O and *n*-hexane afforded colorless needles (1.50 g, 50.3%), mp 115—116 °C. *Anal.* Calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79. Found: C, 58.69; H, 5.38; N, 9.61. IR (Nujol) cm^{-1}: 3340 (NH), 2260 (CN), 1710 (COOR), 1680 (COOR'). NMR ($CDCl_3$) δ: 1.17, 1.28 (6H, each t, $J=7$ Hz, $COOCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 2.40 (3H, s, C_6-CH_3), 3.4—3.8, 4.0—4.5 (8H, each m, $COOC\underline{H}_2C\underline{H}_2OC\underline{H}_2$, $COOC\underline{H}_2CH_3$), 5.23 (1H, s, C_4-H), 7.15 (1H, br s, NH), 7.2—8.2 (4H, m, aromatic protons).

The other 2-cyano-1,4-dihydropyridines (Xc—x) were prepared in a similar manner to that of Xb and their yields and physical data are summarized in Table II.

2-Hydroxyethyl 2-Cyano-3-ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-5-carboxylate(Xa) To a solution of Xj (1.12 g, 2.53 mmol) in EtOH (20 ml) was added dropwise an aq. solution of K_2CO_3 (0.35 g/5 ml) under stirring and refluxing. After the addition was completed, refluxing was continued for a further 2 h and then allowed to stand at room temperature. EtOH was removed and the resultant aq. residue was diluted with H_2O, made acidic with AcOH and extracted twice with AcOEt. The extracts were combined and washed successively with dil. aq. solution of $NaHCO_3$, H_2O and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo* to afford an oil, which crystallized on standing. The crystals were triturated in a mixture of Et_2O and *n*-hexane and collected by filtration to afford a yellow powder (0.94 g, 93.1%). An analytical sample was obtained by recrystallization from C_6H_6, mp 150—152 °C. *Anal.* Calcd for $C_{19}H_{19}N_3O_7$: C, 56.85; H, 4.77; N, 10.47. Found: C, 56.98; H, 4.66; N, 10.51. IR (Nujol) cm^{-1}: 3480 (OH), 3180 (NH), 2230 (CN), 1708 (COOR), 1700 (sh, COOR'), 1636 (C=C). NMR ($CDCl_3$): 1.29 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 2.27 (1H, t, $J=5$ Hz, OH), 2.38 (3H, s, C_6-CH_3), 3.77 (2H, br q, $J=5$ Hz, $C\underline{H}_2OH$), 4.0—4.4 (4H, m, $COOC\underline{H}_2CH_3$, $COOC\underline{H}_2CH_2$), 5.18 (1H, s, C_4-H), 7.2—8.2 (5H, m, aromatic protons and NH).

Biological evaluation of the hypotensive effect was performed according to the procedure described in the previous paper.[1]

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