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Synthesis of Asymmetric 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates with Vasodilating and Antihypertensive Activities[1)]

SACHIO OHNO,* OSAMU KOMATSU, KIYOSHI MIZUKOSHI, KENJI ICHIHARA, YOSHIKI NAKAMURA, TAKASHI MORISHIMA, and KAZUHARU SUMITA

Research Laboratories, Maruko Seiyaku Co., Ltd., 1212 Teramae, Gejo-cho, Kasugai 486, Japan

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Asymmetric 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates with a 2-ethylenedioxypropyl, 2-oxopropyl, or cyclopropylmethyl group as the ester moiety and related derivatives were synthesized and tested for vasodilating activity in anesthetized open-chest dogs and for antihypertensive activity in conscious spontaneously hypertensive rats. Cyclopropylmethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**5f**, MPC-2101) and methyl 2-oxopropyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (**8i**, MPC-1304) exhibited potent cerebral vasodilating and antihypertensive activities, respectively. The maximum increase of vertebral blood flow after intravenous administration at 3.0 μg/kg was 221.4% for **5f**, compared with 187.0 and 166.3% for nifedipine and nicardipine hydrochloride, respectively. The maximum falls of systolic blood pressure after oral administration of **8i** at 0.3 and 1.0 mg/kg were 42.2 and 54.0 mmHg, while those of nifedipine, nicardipine, and hydralazine hydrochloride at 3.0 mg/kg were 23.3, 16.8, and 24.5 mmHg, respectively. The durations of significant vasodilating and antihypertensive effects for **5f** and **8i** were longer than those of nifedipine and nicardipine.

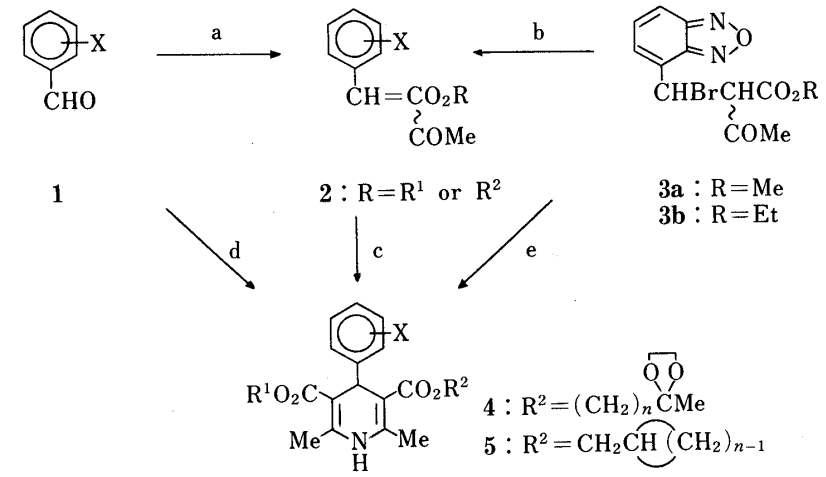
Keywords——dihydropyridine; Hantzsch reaction; calcium antagonist; antihypertensive activity; vasodilating activity; nifedipine; nicardipine; felodipine

Since nifedipine, dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate, was found to possess coronary vasodilating activity in 1969[2)] and to be a so-called calcium antagonist in 1973,[3)] much interest has centered on its structure and potent vasodilating activity.[4)] At present, nifedipine is widely used for the treatment of angina pectoris and hypertension, and nicardipine hydrochloride (**17**),[4b,5)] methyl 2-(*N*-benzyl-*N*-methylamino)ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride, is utilized for the treatment of cerebral ischemia and hypertension.

We found that cyclopropylmethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**5f**, MPC-2101), methyl 2-oxopropyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (**8i**, MPC-1304), and related compounds possess potent and long-lasting vasodilating and antihypertensive activities. In this paper we report the synthesis and biological activities of new dihydropyridines.

Chemistry

The synthesis of alkyl ethylenedioxyalkyl (**4**) and alkyl cycloalkylmethyl 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**5**) were carried out by means of a modification of the Hantzsch method.[4f,j,6)] 2-Arylmethyleneacetoacetates (**2**)[7)] were reacted with 3-aminocrotonates (**7**)[8)] in ethanol under reflux to afford the dihydropyridines (**4**, **5**) in 16—88% yields (route A). These compounds were also prepared from arylaldehydes (**1**),[9)] acetoacetates



a) $CH_3COCH_2CO_2R$ (**6**, $R=R^1$ or R^2), piperidine, $AcOH/C_6H_6$;
b) Et_3N/CH_2Cl_2; c) $MeC(NH_2)=CHCO_2R$ (**7**, $R=R^2$ or R^1)/EtOH;
d) **6**, **7**/EtOH; e) **7**/EtOH

Chart 1

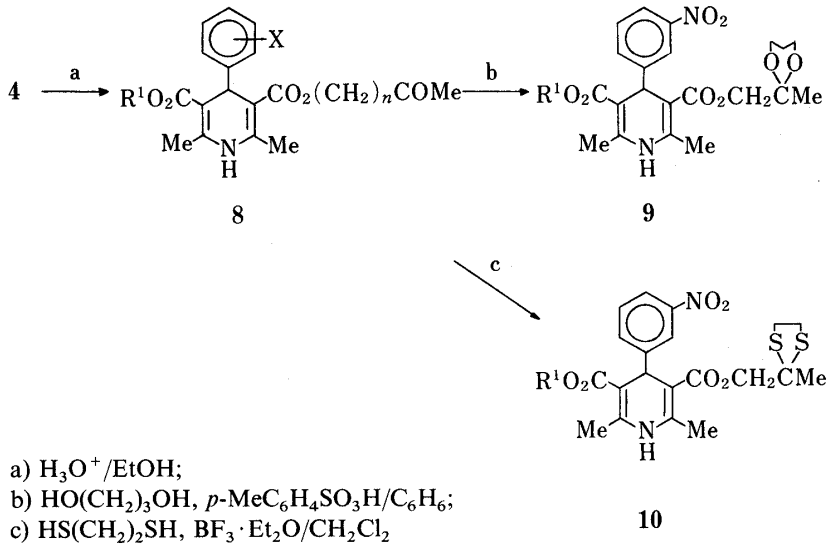


Chart 2

(**6**), and **7** in 8—64% yields (route B). Furthermore, **4p** and **5t** were also directly obtained from 2-(2,1,3-benzoxadiazol-4-ylbromomethyl)acetoacetates (**3**) and **7a** or **c** by refluxing in ethanol, respectively.

The acetates (**2a—o**)[7] were prepared from **1** and **6** by means of the Knoevenagel reaction[10] in 50—96% yields, and **2p** and **q** were obtained quantitatively from **3a** and **b** by treatment with triethylamine in dichloromethane, respectively.

The ketals (**4**) were hydrolyzed under acidic conditions to give ketones (**8**), which were reketalized with 1,3-propanediol or 1,2-ethanedithiol to afford alkyl 2,2-trimethylenedioxypropyl (**9**) or alkyl 2,2-ethylenedithiopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**10**).

The starting materials were prepared as follows. The reactions of the alcohols (**11**)[11] with diketene afforded the esters (**6**), which were treated with ammonia in methanol to give **7**. The treatment of 2,1,3-benzoxadiazol-4-ylmethyl bromide (**12**)[12] with sodium salts of the acetoacetates (**6**) gave 2-(2,1,3-benzoxadiazol-4-ylmethyl)acetoacetates (**13**) in 75—81%

TABLE I. Alkyl Ethylenedioxyalkyl 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates (**4**)

No.	X	R^1	*n*	Route[a]	Yield[b] (%)	mp (°C)	Recrystallization solvent	Formula	Analysis (%) Calcd (Found)		
									C	H	N
4a	3-NO_2	Me	1	A (**7a**)	40	141—143	EtOH	$C_{21}H_{24}N_2O_8$	58.33	5.59	6.48
									(58.02	5.57	6.72)
4b	3-NO_2	Et	1	A (**7a**)	46	151—153	EtOH	$C_{22}H_{26}N_2O_8$	59.19	5.87	6.27
									(59.11	5.97	6.11)
4c	3-NO_2	iso-Pr	1	A (**7a**)	68	125—126	AcOEt–hexane	$C_{23}H_{28}N_2O_8$	59.99	6.13	6.08
									(59.74	6.05	6.16)
4d	3-NO_2	Pr	1	A (**7a**)	58	115—119	iso-PrOH–hexane	$C_{23}H_{28}N_2O_8$	59.99	6.13	6.08
									(59.84	6.18	6.21)
4e	3-NO_2	*cyclo*-Pen	1	A (**7a**)	47	153—156	iso-PrOH	$C_{25}H_{30}N_2O_8$	61.72	6.22	5.76
									(61.42	6.35	5.76)
4f	3-NO_2	Me	2	A (**7b**)	59	156—158	EtOH–Et_2O	$C_{22}H_{26}N_2O_8$	59.19	5.87	6.27
									(59.12	5.88	6.09)
4g	3-NO_2	Et	2	A (**7b**)	59	135—136	EtOH–Et_2O	$C_{23}H_{28}N_2O_8$	59.99	6.13	6.08
									(59.92	6.25	6.01)
4h	3-NO_2	iso-Pr	2	A (**7b**)	85	126—128	iso-PrOH–iso-Pr_2O	$C_{24}H_{30}N_2O_8$	60.75	6.37	5.90
									(60.48	6.57	5.81)
4i	2-NO_2	Me	1	A (**7a**)	76	154—156	MeOH	$C_{21}H_{24}N_2O_8$	58.33	5.59	6.48
				A (**7f**)	88				(58.29	5.83	6.46)
				B (**7a**)	9						
4j	2-NO_2	Et	1	A (**7a**)	77	Oil		$C_{22}H_{26}N_2O_8$			
4k	2-NO_2	Me	2	A (**7b**)	75	Oil		$C_{22}H_{26}N_2O_8$	59.19	5.87	6.27
									(59.28	5.87	6.34)
4l	2,3-Cl_2	Me	1	B (**7a**)	27	136—138	iso-PrOH–iso-Pr_2O	$C_{21}H_{23}Cl_2NO_6$	55.27	5.08	3.07
									(54.87	5.10	2.99)
4m	2-Cl	Me	1	A (**7a**)	47	123—127	iso-PrOH–iso-Pr_2O	$C_{21}H_{24}ClNO_6$	59.79	5.73	3.32
									(59.59	5.94	3.21)
4n	2-Br	Me	1	A (**7a**)	51	133—136	iso-PrOH–iso-Pr_2O	$C_{21}H_{24}BrNO_6$	54.09	5.19	3.00
									(53.69	5.13	2.64)
4o	2-CF_3	Me	1	A (**7a**)	19	Oil		$C_{22}H_{24}F_3NO_6$			
4p	—[c]	Me	1	A (**7a**)	48	Oil		$C_{21}H_{23}N_3O_7$			
				—[d]	37						
4q	2-OMe	Me	1	A (**7a**)	33	128—132	CH_2Cl_2–hexane	$C_{22}H_{27}NO_7$	63.30	6.52	3.36
									(62.91	6.84	3.09)
4r	2-SOMe	Me	1	A (**7a**)	41	94—97	CH_2Cl_2–hexane	$C_{22}H_{27}NO_7S$	58.78	6.05	3.12
									(58.49	6.00	3.28)
4s	2-SO_2Me	Me	1	A (**7a**)	18	Oil		$C_{22}H_{27}NO_8S$	56.76	5.85	3.01
									(56.51	6.13	2.78)

a) The compound number in parentheses indicates the 3-aminocrotonate used as a starting material. *b*) The yields from the corresponding aryl compounds. *c*) 2,1,3-Benzoxadiazol-4-yl group as the 4-aryl group. *d*) From **3a**.

yields, and these products were brominated with *N*-bromosuccinimide (NBS) in carbon tetrachloride to afford **3**. 2-Methylthiobenzaldehyde (**1b**)[9c,13] was obtained from 2-chlorobenzaldehyde (**1a**) and 15% sodium methanethiolate.

PY-108-068 (**14**),[4i] diethyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, was directly prepared from **3b** and ethyl 3-aminocrotonate (**7g**). Nicardipine (**17**) was prepared as follows. Ethylene glycol was treated with diketene followed by reaction with 3-nitrobenzaldehyde and methyl 3-aminocrotonate (**7f**) to give 2-hydroxyethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**15**),[4j] which was converted to the sulfonates (**16**) by reaction with methanesulfonyl or *p*-

TABLE II. Alkyl Cycloalkylmethyl 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates (**5**)

No.	X	R^1	*n*	Route[a]	Yield[b] (%)	mp (°C)	Recrystallization solvent	Formula	Analysis (%) Calcd (Found)		
									C	H	N
5a	3-NO_2	Me	6	A (**7c**)	71	121—123	CH_2Cl_2–iso-Pr_2O	$C_{23}H_{28}N_2O_6$	64.47 (64.29	6.59 6.74	6.54 6.52)
5b	3-NO_2	Me	5	B (**7f**)	43	117—119	EtOH–iso-Pr_2O	$C_{22}H_{26}N_2O_6$	63.76 (64.14	6.32 6.45	6.76 6.84)
5c	3-NO_2	Me	4	B (**7f**)	49	130—133	EtOH–iso-Pr_2O	$C_{21}H_{24}N_2O_6$	62.99 (63.03	6.04 6.22	7.00 6.94)
5d	3-NO_2	Et	4	A (**7c**)	61	135—137	EtOH–iso-Pr_2O	$C_{22}H_{26}N_2O_6$	63.76 (63.73	6.32 6.44	6.76 6.83)
5e	3-NO_2	Pr	4	A (**7c**)	60	159—162	EtOH–iso-Pr_2O	$C_{23}H_{28}N_2O_6$	64.47 (64.15	6.59 6.61	6.54 6.36)
5f	3-NO_2	Me	3	A (**7c**)	72	160—163	CH_2Cl_2–Et_2O	$C_{20}H_{22}N_2O_6$	62.17 (62.14	5.74 5.77	7.25 7.24)
				B (**7c**)	56						
5g	3-NO_2	Et	3	A (**7c**)	59	169—170	EtOH–iso-Pr_2O	$C_{21}H_{24}N_2O_6$	62.99 (62.77	6.04 6.13	7.00 6.85)
5h	3-NO_2	Pr	3	A (**7c**)	60	167—168	EtOH–iso-Pr_2O	$C_{22}H_{26}N_2O_6$	63.76 (63.82	6.32 6.42	6.76 6.69)
5i	3-NO_2	CH_2CF_3	3	B (**7c**)	64	186—188	EtOH–iso-Pr_2O	$C_{21}H_{21}F_3N_2O_6$	55.51 (55.90	4.66 4.62	6.17 6.20)
5j	2-NO_2	Me	6	B (**7f**)	42	Oil		$C_{23}H_{28}N_2O_6$	64.47 (64.20	6.59 6.82	6.54 6.27)
5k	2-NO_2	Me	3	B (**7f**)	43	Oil		$C_{20}H_{22}N_2O_6$	62.17 (61.78	5.74 5.49	7.25 7.31)
5l	2,3-Cl_2	Me	3	A (**7c**)	39	138—142	CH_2Cl_2–hexane	$C_{20}H_{21}Cl_2NO_4$	58.55 (58.31	5.16 5.08	3.41 3.22)
				B (**7c**)	33						
5m	2,3-Cl_2	Et	3	B (**7c**)	31	76—78	EtOH–hexane	$C_{21}H_{23}Cl_2NO_4$	59.44 (59.04	5.46 5.39	3.30 3.09)
5n	2,3-Cl_2	Pr	3	B (**7c**)	30	75 103—106[c]	Et_2O–hexane	$C_{22}H_{25}Cl_2NO_4$	60.28 (60.15	5.75 5.35	3.20 3.02)
5o	2-Cl	Me	3	B (**7c**)	8	128—130	iso-Pr_2O	$C_{20}H_{22}ClNO_4$	63.91 (63.51	5.90 5.94	3.73 3.65)
5p	2-Br	Me	3	B (**7c**)	10	140—142	iso-Pr_2O	$C_{20}H_{22}BrNO_4$	57.15 (57.03	5.28 5.30	3.33 3.29)
5q	2-CF_3	Me	3	A (**7c**)	16	124—127	CH_2Cl_2–hexane	$C_{21}H_{22}F_3NO_4$	61.61 (61.21	5.42 5.09	3.42 3.13)
5r	3-Cl	Me	3	B (**7c**)	15	124—128	iso-PrOH–iso-Pr_2O	$C_{20}H_{22}ClNO_4$	63.91 (64.17	5.90 6.00	3.73 3.65)
5s	3-CF_3	Me	3	B (**7c**)	47	114—117	CH_2Cl_2–hexane	$C_{21}H_{22}F_3NO_4$	61.61 (61.33	5.42 5.41	3.42 3.31)
5t	—[d]	Me	3	A (**7c**)	38	158—160	CH_2Cl_2–iso-Pr_2O	$C_{20}H_{21}N_3O_5$	62.65 (62.35	5.52 5.64	10.96 10.80)
				—[c]	42						
5u	2-SMe	Me	3	A (**7c**)	45	137—141	iso-PrOH–iso-Pr_2O	$C_{21}H_{25}NO_4S$	65.09 (64.98	6.50 6.44	3.61 3.56)
5v[f]	2-SOMe	Me	3	A (**7c**)	19	Oil		$C_{21}H_{25}NO_5S$			
5w	2-SO_2Me	Me	3	A (**7c**)	62	158—162	iso-PrOH–iso-Pr_2O	$C_{21}H_{25}NO_6S$	60.13 (60.05	6.01 6.03	3.34 3.27)

a, *b*) See footnotes *a*, *b* in Table I. *c*) Colorless needles melted at 75 °C and solidified immediately. This solid melted again at 103—106 °C. *d*, *e*) See footnotes *c*, *d* in Table I. *f*) One of the diastereomers was isolated.

toluenesulfonyl chloride in the presence of triethylamine in tetrahydrofuran (THF). The sulfonates (**16**) were heated with *N*-benzylmethylamine followed by treatment with hydrochloric acid to give **17** in good yield.

TABLE III. Alkyl Oxoalkyl 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates (**8**)

No.	X	R^1	*n*	Acid	Yield (%)	mp (°C)	Recrystallization solvent	Formula	Analysis (%) Calcd (Found)		
									C	H	N
8a	3-NO_2	Me	1	HCl	65	138—139	AcOEt–hexane	$C_{19}H_{20}N_2O_7$	58.76	5.19	7.21
									(58.79	5.25	6.99)
8b	3-NO_2	Et	1	HCl	89	156—159	iso-PrOH	$C_{20}H_{22}N_2O_7 \cdot 1/3H_2O$	58.82	5.59	6.86
									(58.86	5.73	6.55)
8c	3-NO_2	Pr	1	$MeSO_3H$	40	101—103	CH_2Cl_2–Et_2O	$C_{21}H_{24}N_2O_7$	60.57	5.81	6.73
									(60.36	5.97	6.76)
8d	3-NO_2	iso-Pr	1	HCl	88	Oil		$C_{21}H_{24}N_2O_7$	60.57	5.81	6.73
									(60.39	5.92	6.62)
8e	3-NO_2	*cyclo*-Pen	1	HCl	85	Oil		$C_{23}H_{26}N_2O_7$	62.43	5.92	6.33
									(62.03	5.98	6.18)
8f	3-NO_2	Me	2	HCl	82	Oil		$C_{20}H_{22}N_2O_7$			
8g	3-NO_2	Et	2	HCl	83	Oil		$C_{21}H_{24}N_2O_7$	60.57	5.81	6.73
									(60.50	5.73	6.84)
8h	3-NO_2	iso-Pr	2	HCl	76	Oil		$C_{22}H_{26}N_2O_7$	61.39	6.09	6.51
									(61.21	6.00	6.48)
8i	2-NO_2	Me	1	HCl	67	154—156	EtOH	$C_{19}H_{20}N_2O_7$	58.76	5.19	7.21
				$MeSO_3H$	89				(58.77	5.34	7.20)
				AcOH	92						
8j	2,3-Cl_2	Me	1	$MeSO_3H$	89	161—164	CH_2Cl_2–hexane	$C_{19}H_{19}Cl_2NO_5$	55.35	4.65	3.40
									(55.32	4.70	3.35)
8k	2-Cl	Me	1	$MeSO_3H$	84	126—130	iso-Pr_2O–hexane	$C_{19}H_{20}ClNO_5$	60.40	5.34	3.71
									(60.24	5.53	3.58)
8l	2-Br	Me	1	$MeSO_3H$	93	102—106	iso-Pr_2O	$C_{19}H_{20}BrNO_5$	54.04	4.77	3.32
									(54.16	5.06	3.19)
8m	2-CF_3	Me	1	$MeSO_3H$	90	144—147	CH_2Cl_2–hexane	$C_{20}H_{20}F_3NO_5$	58.39	4.90	3.40
									(58.04	4.72	3.13)
8n	2-OMe	Me	1	$MeSO_3H$	85	159—162	iso-PrOH–iso-Pr_2O	$C_{20}H_{23}NO_6$	64.33	6.21	3.75
									(64.41	6.49	3.66)
8o	2-SOMe	Me	1	$MeSO_3H$	42	204—207	CH_2Cl_2–hexane	$C_{20}H_{23}NO_6S$	59.25	5.72	3.45
									(58.94	5.88	3.31)
8p	2-SO_2Me	Me	1	$MeSO_3H$	65	121—125	CH_2Cl_2–iso-Pr_2O	$C_{20}H_{23}NO_7S$	57.00	5.50	3.32
									(57.08	5.33	3.08)
8q	—[a]	Me	1	$MeSO_3H$	79	162—164	CH_2Cl_2–iso-Pr_2O	$C_{19}H_{19}N_3O_6$	59.22	4.97	10.90
									(58.83	4.82	10.52)

a) See footnote *c* in Table I.

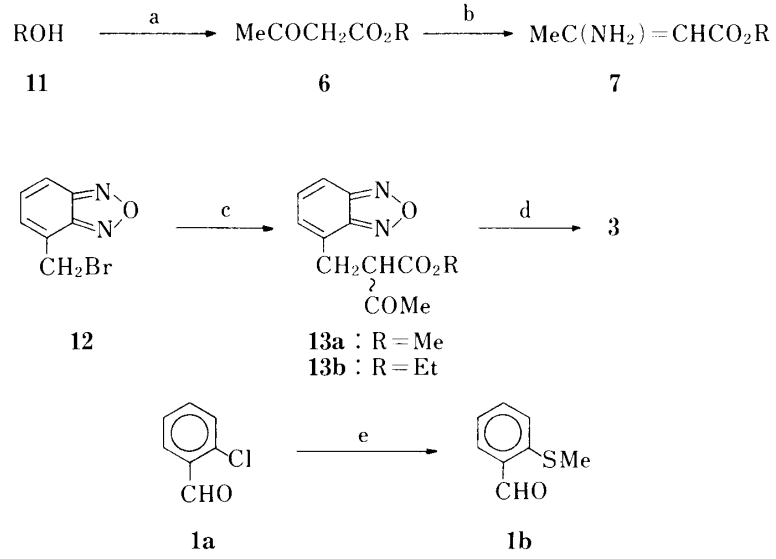
Pharmacology

The screening test for vasodilating activity was carried out by measurement of vertebral, coronary, and femoral blood flow in anesthetized open-chest dogs. The test drugs were administered intravenously. The vasodilating activity was expressed as the ratio of the potency to that of nifedipine. The potency was represented as the product of the maximum increase of blood flow and the half-maximum duration of the effect.

The results for the vasodilating activities of the ketals (**4**, **9**, **10**) and ketones (**8**) are summarized in Tables V and VI. The ketals (**4b**—**l**, **9b**, **c**, **10**) were weakly active, but **4a** showed activities comparable to nifedipine on the vertebral and coronary arteries. The activities of the 3-nitro ketones (**8a**—**h**) were low, while the 2-nitro ketone (**8i**) was slightly more active than nifedipine. The 2-nitrophenyl group of **8i** was converted into various aryl groups. The ketones (**8j**—**m**) exhibited high potency, but **8n**—**q** were inactive. In this series, the 2,3-dichlorophenyl compound (**8j**) had the highest potency.

Table IV. Alkyl 2,2-Trimethylenedioxypropyl (**9**) and Alkyl 2,2-Ethylenedithiopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylates (**10**)

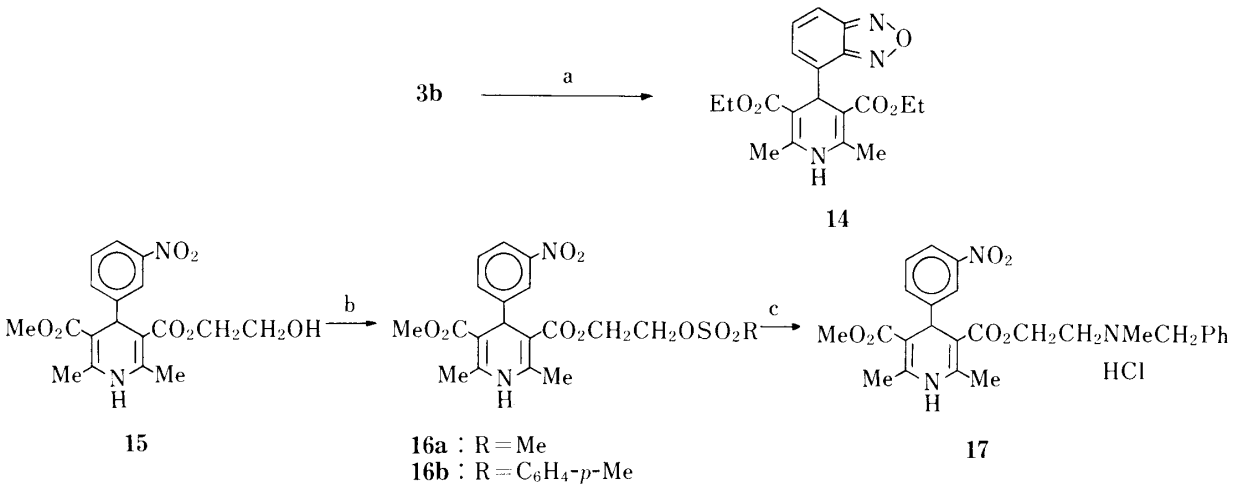
No.	R^1	Yield (%)	mp (°C)	Recrystallization solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
9a	Me	74	131—134	EtOH–iso-Pr_2O	$C_{22}H_{26}N_2O_8$	59.19 (58.95	5.87 6.01	6.27 6.27)
9b	Et	88	120—122	iso-PrOH–hexane	$C_{23}H_{28}N_2O_8$	59.99 (59.68	6.13 6.26	6.08 6.05)
9c	Pr	56	Oil		$C_{24}H_{30}N_2O_8$	60.75 (60.65	6.37 6.39	5.90 5.93)
10a	Me	35	140 144	EtOH–Et_2O	$C_{21}H_{24}N_2O_6S_2$	54.29 (53.89	5.21 5.14	6.03 5.93)
10b	Et	52	143—145	CH_2Cl_2–Et_2O	$C_{22}H_{26}N_2O_6S_2$	55.21 (55.10	5.48 5.50	5.89 5.66)
10c	Pr	19	124—127	CH_2Cl_2–Et_2O	$C_{23}H_{28}N_2O_6S_2$	56.08 (56.11	5.73 5.84	5.69 5.50)



a) diketene, NaH/C_6H_6; b) NH_3/MeOH; c) $NaCH(COMe)CO_2R$/DMF; d) NBS, $(PhCO)_2O_2/CCl_4$; e) NaSMe/HMPA

Chart 3

On the other hand, the activity of **4a**, with a 2-methyl-1,3-dioxolan-2-ylmethyl group, led us to prepare the cyclopentylmethyl analogue (**5b**), which was as active as nifedipine, as shown in Table VII. The cyclopentylmethyl group was converted into other cycloalkylmethyl groups. The cyclohexylmethyl compound (**5a**) was weakly active, but the cyclobutylmethyl (**5c**) and cyclopropylmethyl compounds (**5f**) showed high activities. Various aryl groups were introduced into the 4-position instead of the 3-nitrophenyl group. The dihydropyridines (**5l**, **o**—**r**, **t**), with 2,3-dichloro-, 2-chloro-, 2-bromo-, 2-trifluoromethyl-, and 3-chlorophenyl and 2,1,3-benzoxadiazol-4-yl groups also exhibited high activities. Compared with **5f** and **q**, the 2-nitro (**5k**) and 3-trifluoromethyl compounds (**5s**) unexpectedly showed low activity. The dihydropyridines (**5u**—**w**) were inactive. The conversion of the methyl ester into ethyl and



a) **7g**/EtOH; b) $MeSO_2Cl$ or p-$MeC_6H_4SO_2Cl$, Et_3N/THF; c) 1) $MeNHCH_2Ph$, 2) HCl

Chart 4

TABLE V. Vasodilating Activities of Dihydropyridines (**4**, **9**, **10**)

Compd.	Vasodilating activity[a]			Compd.	Vasodilating activity[a]		
	Ver	Cor	Fem		Ver	Cor	Fem
4a	1.5	1.5	1.2	**4k**	0.2	0.1	0.5
4b	0.7	0.6	0.9	**4l**	0.5	0.4	0.6
4c	0.0	—[b]	0.0	**9a**	0.8	1.9	1.0
4d	0.7	0.3	0.5	**9b**	0.6	0.1	0.7
4e	0.6	—	0.6	**9c**	0.2	0.1	0.4
4f	0.1	—	0.4	**10a**	0.7	0.6	0.5
4g	0.0	—	0.9	**10b**	0.5	—	0.3
4h	0.1	—	0.1	**10c**	0.2	0.2	0.6
4i	0.2	0.3	0.1	Nicardipine	1.3	0.7	0.6
4j	0.2	—	0.4	Nifedipine	1.0	1.0	1.0

a) The test drugs were administered at 3.0 μg/kg intravenously in anesthetized open-chest dogs. Vasodilating activity was expressed as the ratio of the potency to that of nifedipine. The potency was represented as the product of the maximum increase of blood flow and the half-maximum duration of the effect. The initial values of vertebral, coronary, and femoral blood flow were 21.57±0.80 ml/min (n=150), 29.04±1.23 ml/min (n=137), and 48.00±2.24 ml/min (n=127), respectively. Ver, vertebral; Cor, coronary; Fem, femoral. *b*) Not tested.

propyl esters tended to decrease the activities (**5d**, **e**, **g**, **h**, **m**, **n**).

Antihypertensive activity was evaluated in conscious spontaneously hypertensive rats by measurement of systolic blood pressure of tail arteries after oral administration of the test drugs. The heart rate was measured simultaneously.

The dihydropyridines (**5l**, **o**—**q**, **t**, **8k**—**m**), which possessed high vasodilating activities on the vertebral and coronary arteries, showed potent and long-lasting antihypertensive activity. The ketone (**8i**), which was slightly more active than nifedipine in terms of vasodilating activity, showed excellent antihypertensive activity. The ketones (**8n**, **o**) exhibited moderate activity in spite of their weak vasodilating activity.

The results for **5f**, **l**, **8i**, and reference drugs are summarized in Tables VIII, IX, and X.

The maximum increases of vertebral and coronary blood flow after intravenous administration of 3.0 μg/kg were 221.4 and 93.6% for **5f**, 175.3 and 86.7% for **5l**, and 98.2 and

TABLE VI. Vasodilating and Antihypertensive Activities of Dihydropyridines (**8**)

Compd.	Vasodilating activity[a]			Antihypertensive activity[b]				
				Systolic blood pressure			Heart rate	
	Ver	Cor	Fem	Initial value (mmHg)	Maximum change (mmHg)	Duration[c] (h)	Initial value (beats/min)	Maximum change (beats/min)
8a	0.2		0.0					
8b	0.6	0.2	1.3					
8c	0.6	0.5	0.5					
8d	0.5	0.3	0.8					
8e	0.6	0.9	0.6					
8f	0.7	0.1	0.6					
8g	0.7	0.7	0.6					
8h	0.6	0.6	0.8					
8i	1.4	1.5	0.3	183	−92	>6	418	+51, −12
8j	3.7	3.1	6.6	198	−92[d]	>6	391	+98
8k	2.4	2.7	2.6	192	−71	>6	417	−22
8l	2.6	2.8	3.7	194	−72	>6	401	+35
8m	1.2	5.9	0.7	199	−98	>6	407	+53
8n	0.0	0.2	0.2	205	−45	>6	420	−25
8o	0.4	0.5	0.3	194	−43	4—6	420	−35
8p	0.0	0.0	0.3	190	−13		406	−30
8q	0.0	0.0	0.0	201	−8		407	−27
Nicardipine	1.3	0.7	0.6	184	−17		393	+16
Nifedipine	1.0	1.0	1.0	184	−23	2—4	404	+25

a) See footnote *a* in Table V. *b*) The test drugs were administered at 3 mg/kg orally in conscious spontaneously hypertensive rats. *c*) The time at which blood pressure recovered to within 10% of the initial value. *d*) 10 mg/kg, *p.o.*

48.4% for **8i**, compared with 187.0 and 107.0% for nifedipine, 166.3 and 66.8% for nicardipine, and 144.6 and 166.9% for PY-108-068. The half-maximum durations of action of **5f**, **l**, and **8i** were longer than those of the reference drugs. The dihydropyridine (**5f**) acted selectively on the cerebral artery compared with nifedipine.

The maximum falls of systolic blood pressure after oral administration of **5f** and **5l** at 3.0 mg/kg and of **8i** at 1.0 mg/kg were 33.7, 50.4, and 54.0 mmHg, while those of nifedipine, nicardipine, felodipine[4e] and hydralazine hydrochloride[14] at 3.0 mg/kg were 23.3, 16.8, 39.6, and 24.5 mmHg, respectively. The antihypertensive response of **8i** even at 0.3 mg/kg was greater than those of the reference drugs at 3.0 mg/kg. Significant effects of **8i** at 1.0 mg/kg and **5l** and felodipine at 3.0 mg/kg were observed for more than 6 h, while nifedipine, nicardipine, and hydralazine at 3.0 mg/kg were effective for 4 h. On the other hand, hydralazine increased the heart rate significantly, but **5f**, **l**, and **8i** did not affect the heart rate significantly in spite of their potent antihypertensive activity.

The *Rm* values,[15,16] which were determined by reversed-phase thin-layer chromatography (TLC), are lipophilic parameters. The drugs with higher *Rm* values are more lipophilic than those with lower values.[15,16] The *Rm* values of the dihydropyridines were determined using 60% aqueous acetone as the mobile phase, and are summarized in Table XI. Nicardipine and **5l** displayed extreamly high lipophilicity, and **5f** and felodipine moderate lipophilicity compared with nifedipine. On the other hand, **8i** was less lipophilic than nifedipine. Some correlations for calcium antagonists between the lipophilicity and the biological activity *in vitro* were reported,[16] but little is known about the relationship *in vivo*. Our results suggest that there is no significant direct correlation between vasodilating and

TABLE VII. Vasodilating and Antihypertensive Activities of Dihydropyridines (**5**)

Compd.	Vasodilating activity[a]			Antihypertensive activity[b]				
				Systolic blood pressure			Heart rate	
	Ver	Cor	Fem	Initial value (mmHg)	Maximum change (mmHg)	Duration[c] (h)	Initial value (beats/min)	Maximum change (beats/min)
5a	0.1	0.2	0.1					
5b	1.0	1.0	—					
5c	2.8	2.9	—					
5d	1.9	2.4	—					
5e	1.0	0.9	—					
5f	3.2	2.3	3.4	183	−33	4—6	415	+10
5g	1.5	2.4	2.0	189	−12	>6	390	+12
5h	2.0	1.0	2.4					
5i	0.3	1.0	0.6					
5j	0.3	0.3	0.3					
5k	1.1	1.7	4.0					
5l	5.5	8.7	1.9	194	−50	>6	457	+10, −17
5m	1.9	2.0	1.2	190	−23	>6	432	−13
5n	1.0	1.0	0.9	195	−37	>6	434	−27
5o	2.1	2.1	0.6	192	−40	>6	391	+8
5p	2.2	2.6	1.4	200	−48	>6	407	−38
5q	4.0	3.7	1.9	211	−68	>6	416	−18
5r	2.0	1.8	0.4	193	−24	1—2	412	−32
5s	0.7	0.4	0.3	208	−13		413	−36
5t	3.1	3.3	0.3	187	−52	>6	404	−21
5u	0.0	0.0	0.0	198	−11		431	−24
5v	0.1	0.1	0.0	189	−9		414	−47
5w	0.0	0.0	0.1	194	−29	>6	415	−26
Nicardipine	1.3	0.7	0.6	184	−17		393	+16
Nifedipine	1.0	1.0	1.0	184	−23	2—4	404	+25

a—*c*) See footnotes *a*—*c* in Table VI.

antihypertensive activities and the lipophilicity.

We have selected **5f** (MPC-2101) and **8i** (MPC-1304) for clinical evaluation, and further investigation is in progress.

Experimental

All melting points were determined on a Yanagimoto MP-S3 and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 260-10 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Hitachi R-90H or JEOL PMX-60 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS D-300 spectrometer. Column chromatography was carried out on Wakogel C-200.

Alkyl Ethylenedioxyalkyl (4) and Alkyl Cycloalkylmethyl 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (5)——a) 2,2-Ethylenedioxypropyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (**4i**) (Route A): A solution of **2o** (10 g) and methyl 3-aminocrotonate (**7f**, 4.1 g) in EtOH (30 ml) was refluxed for 10 h and then cooled on an ice bath. The precipitate was filtered off, and washed with Et_2O to give **4i** (11 g), which was recrystallized from MeOH to give yellow prisms.

b) Cyclopropylmethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**5f**) (Route A): A solution of **2a** (13.9 g) and **7c** (8.7 g) in EtOH (50 ml) was refluxed for 4 h, and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **5f** (15.4 g) as pale yellow prisms. MS *m/e* (relative intensity, %): 388 (19), 331 (29), 315 (16), 287 (27), 265 (62), 264 (100), 211 (49), 210 (100), 168 (31), 165 (18), 150 (34).

TABLE VIII. Vasodilating Activities of Dihydropyridines Administered Intravenously at 3.0 μg/kg on Vertebral, Coronary, and Femoral Blood Flow in Open-Chest Dogs[a]

Compd.	n[d]	Vertebral			Coronary			Femoral		
		Initial value (ml/min)	Maximum[b] increase (%)	Half-max.[c] duration (min)	Initial value (ml/min)	Maximum[b] increase (%)	Half-max.[c] duration (min)	Initial value (ml/min)	Maximum[b] increase (%)	Half-max.[c] duration (min)
5f	4	20.9±1.7	221.4±28.0[e]	9.2±1.4[e]	29.3± 8.8	93.6±17.2[f]	6.1±1.0[e]	40.3±0.8	75.3±23.4[f]	9.2±3.8
5l	4	23.1±6.1	175.3±43.3[f]	19.8±4.6[e]	34.0±11.5	86.7±4.9[e]	24.8±3.2[g]	43.8±2.2	42.4±14.7	9.2±2.9
8i	4	25.1±1.7	98.2±40.1	9.1±3.8	26.9± 2.2	48.4±8.7[f]	7.5±2.8[f]	51.5±5.9	23.7±10.4	2.8±0.4
Nif[h]	5	21.1±1.0	187.0±27.9[e]	3.4±0.7	28.5± 3.7	107.0±14.9[e]	2.3±0.4	45.4±4.5	67.3±24.6	3.0±0.9
Nic[i]	4	21.6±2.3	166.3±43.1[f]	3.5±0.6	22.5± 3.0	66.8± 9.1[e]	1.9±0.3	37.4±4.5	42.2±11.4	3.0±1.5
PY[j]	4	20.8±2.6	144.6±19.7[e]	3.6±1.0	26.0± 3.5	166.9±50.9[f]	4.2±0.5[f]	45.8±4.6	26.2±18.3	4.5±1.7

a) The values represent the means ± standard error. *b*) Statistical analysis was performed using paired Student's *t*-test. *c*) Statistical analysis was performed using unpaired Student's *t*-test in comparison with nifedipine. *d*) Number of animals. *e*) $p<0.01$. *f*) $p<0.05$. *g*) $p<0.001$. *h*) Nifedipine. *i*) Nicardipine. *j*) PY-108-068.

TABLE IX. Effects of Dihydropyridines and Hydralazine on Systolic Blood Pressure in Spontaneously Hypertensive Rats[a]

Compd.	Dose mg/kg (*p.o.*)	n[b]	Initial value (mmHg)	Changes in blood pressure (mmHg) 1	2	4	6	24 h
Control	—	7	186.6±2.9	−1.9±2.5	−1.4± 2.6	−5.7± 2.6	−7.7± 2.9	−2.6± 2.1
5f	3.0	6	183.2±6.4	−21.7±5.6[c]	−25.8± 7.1[d]	−33.7± 7.2[d]	−13.7± 6.2	2.3± 4.2
5l	3.0	5	194.8±4.6	−47.2±5.9[e]	−42.6± 5.8[e]	−50.4± 7.6[e]	−49.0±10.4[d]	−5.0± 5.8
8i	0.3	5	210.2±5.4	−42.2±3.4[e]	−39.6±10.5[d]	−22.6± 9.5	−23.0± 8.0[c]	−12.8± 4.6
8i	1.0	4	188.8±3.6	−48.5±4.2[e]	−54.0± 2.9[e]	−46.8± 5.4[e]	−42.0± 4.3[e]	−4.0± 5.1
Nif[f]	3.0	6	184.2±4.1	−23.3±6.0[d]	−19.2± 5.5[c]	−15.7± 5.6[c]	−16.0± 7.8	3.5± 2.6
Nic[g]	3.0	5	183.6±5.5	−10.4±2.6	−7.4± 2.6	−16.8± 4.8[c]	−16.0± 5.0	−0.8± 4.1
Fel[h]	3.0	5	197.2±8.6	−31.0±6.7[c]	−27.6± 8.2[c]	−31.4±11.8	−39.6± 9.1[c]	−10.6±10.3
Hyd[i]	3.0	4	183.3±6.7	−7.5±6.0	−14.5± 8.7	−24.5± 6.3[c]	−14.8± 6.4	3.5± 9.1

a) The values represent the means±standard error; paired Student's *t*-test. *b*) Number of animals. *c*) $p<0.05$. *d*) $p<0.01$. *e*) $p<0.001$. *f*) Nifedipine. *g*) Nicardipine. *h*) Felodipine. *i*) Hydralazine.

TABLE X. Effects of Dihydropyridines and Hydralazine on Heart Rate in Spontaneously Hypertensive Rats[a]

Compd.	Dose mg/kg (*p.o.*)	n[b]	Initial value (beats/min)	Changes in heart rate (beats/min) 1	2	4	6	24 h
Control	—	7	398.1± 1.9	−7.4± 4.1	−3.7± 3.5	6.6± 5.7	2.6± 8.9	−2.6±10.0
5f	3.0	6	410.3± 7.6	5.7±10.7	6.2±10.5	−18.3± 7.6	−10.5±11.8	−7.5± 9.2
5l	3.0	5	457.2± 5.3	10.2±13.0	−16.4± 9.5	−10.4± 6.3	−17.2± 5.4	−22.8±13.6
8i	0.3	5	447.0± 4.3	6.4± 9.9	−7.4±10.5	−2.2± 6.5	−16.0± 9.8	−15.6±11.3
8i	1.0	4	449.5± 9.9	12.3± 8.9	−14.8± 8.2	−7.8± 6.0	−13.5± 6.5	−21.3±10.6
Nif[c]	3.0	6	403.7±10.1	25.5±13.3	8.5±11.9	15.8±10.2	12.2±17.9	5.8±10.3
Nic[d]	3.0	5	393.0± 9.1	14.8±10.2	14.2±10.6	16.2± 6.3	16.4± 8.8	1.0± 3.6
Fel[e]	3.0	5	445.8± 9.9	−10.2± 5.2	−25.0± 7.3	−10.0± 7.6	1.6±11.3	−17.2± 8.2
Hyd[f]	3.0	4	389.3± 2.6	21.7± 6.4[g]	29.5± 5.9[h]	42.0± 8.6[h]	23.2± 8.2[g]	1.7± 3.6

a, *b*) See footnotes *a*, *b* in Table IX. *c*—*f*) See footnotes *f*—*i* in Table IX. *g*) $p<0.05$. *h*) $p<0.01$.

TABLE XI. *Rf* and *Rm* Values of Dihydropyridines

Compd.	*Rf*[a]	*Rm*[a]	Compd.	*Rf*	*Rm*
5f	0.35	0.26	Felodipine	0.36	0.25
5l	0.31	0.35	Nicardipine[b]	0.28	0.42
8i	0.55	−0.08	PY-108-068	0.41	0.16
Nifedipine	0.50	0.00			

a) The values were determined by reversed-phase TLC on silica gel in acetone-H_2O (60:40), and represent the mean of 6 or 7 determinations. The *Rm* value was calculated by means of the formula $Rm=\log(1/Rf-1)$. *b*) The free base was used.

c) Cyclopropylmethyl Methyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**5l**) (Route B): A solution of 2,3-dichlorobenzaldehyde[9b] (8.6 g), **7c** (7.7 g), and methyl acetoacetate (5.7 g) in EtOH (50 ml) was refluxed for 8 h, and evaporated *in vacuo*. The residual oil was purified by column chromatography with isopropyl ether to give **5l** (6.7 g), which was recrystallized from CH_2Cl_2–hexane to afford colorless needles.

d) 2,2-Ethylenedioxypropyl Methyl 4-(2,1,3-Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**4p**): A solution of **3a** (4.9 g) and **7a** in EtOH (60 ml) was refluxed for 1 h, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, and the organic layer was washed with H_2O and dried over $MgSO_4$. After removal

TABLE XII. NMR Data for Dihydropyridines (**4**, **5**, **8**—**10**)

4a	1.31 (3H, s), 2.37 (6H, s), 3.65 (3H, s), 3.93 (4H, s), 4.01 (2H, s), 5.16 (1H, s), 6.27 (1H, br s), 7.38 (1H, t, J=7.6 Hz), 7.56—8.23 (3H, m)
4b	1.20 (3H, t, J=7.0 Hz), 1.28 (3H, s), 2.33 (6H, s), 3.90 (4H, s), 3.99 (2H, s), 4.12 (2H, q, J=7.0 Hz), 5.13 (1H, s), 6.60 (1H, br s), 7.38 (1H, t, J=7.4 Hz), 7.57—7.65 (1H, m), 7.87—8.27 (2H, m)
4c	1.18 (3H, d, J=6.0 Hz), 1.29 (3H, d, J=6.0 Hz), 1.35 (3H, s), 2.39 (6H, s), 3.94 (4H, s), 4.01 (2H, s), 4.97 (1H, hept., J=6.0 Hz), 5.15 (1H, s), 6.62 (1H, br s), 7.40 (1H, t, J=7.3 Hz), 7.60—7.83 (1H, m), 7.88—8.40 (2H, m)
4d	0.89 (3H, t, J=7.0 Hz), 1.33 (3H, s), 1.40—1.83 (2H, m), 2.37 (6H, s), 3.94 (4H, s), 3.99 (2H, t, J=6.5 Hz), 4.00 (2H, s), 5.16 (1H, s), 5.82 (1H, br s), 7.37 (1H, t, J=8.0 Hz), 7.57—7.77 (1H, m), 7.90—8.20 (2H, m)
4e	1.12—2.92 (8H, m), 1.31 (3H, s), 2.34 (6H, s), 3.93 (4H, s), 4.00 (2H, s), 5.00—5.33 (1H, m), 5.15 (1H, s), 6.65 (1H, br s), 7.41 (1H, t, J=7.7 Hz), 7.62—7.87 (1H, m), 7.91—8.29 (2H, m)
4f	1.39 (3H, s), 2.06 (2H, t, J=7.1 Hz), 2.43 (6H, s), 3.70 (3H, s), 3.96 (4H, s), 4.21 (2H, t, J=7.1 Hz), 5.16 (1H, s), 6.13 (1H, br s), 7.21—8.23 (4H, m)
4g	1.23 (3H, t, J=7.0 Hz), 1.30 (3H, s), 1.98 (2H, t, J=7.0 Hz), 2.33 (6H, s), 3.91 (4H, s), 4.17 (4H, t, J=7.0 Hz), 5.11 (1H, s), 6.15 (1H, br s), 7.13—8.23 (4H, m)
4h	1.11 (3H, d, J=6.0 Hz), 1.25 (3H, d, J=6.0 Hz), 1.30 (3H, s), 1.97 (2H, t, J=7.2 Hz), 2.34 (6H, s), 3.90 (4H, s), 4.16 (2H, t, J=7.2 Hz), 4.94 (1H, hept., J=6.0 Hz), 5.08 (1H, s), 6.02 (1H, br s), 7.16—8.20 (4H, m)
4i	1.24 (3H, s), 2.28 (3H, s), 2.43 (3H, s), 3.58 (3H, s), 3.88 (4H, s), 4.02 (2H, AB q, J=11.0 Hz, $\Delta\nu$=6.9 Hz), 5.78 (1H, s), 6.26 (1H, br s), 7.10—7.76 (4H, m)
4j	1.15 (3H, t, J=6.8 Hz), 1.26 (3H, s), 2.30 (6H, s), 3.77—4.35 (4H, m), 3.88 (4H, s), 5.81 (1H, s), 6.26 (1H, br s), 7.00—7.80 (4H, m)
4k	1.27 (3H, s), 1.82—2.20 (2H, m), 2.28 (3H, s), 2.33 (3H, s), 3.59 (3H, s), 3.84—4.40 [6H, m, 3.87 (4H, s)], 5.77 (1H, s), 6.22 (1H, br s), 7.06—7.85 (4H, m)
4l	1.30 (3H, s), 2.29 (3H, s), 2.32 (3H, s), 3.63 (3H, s), 3.91 (4H, s), 4.04 (2H, AB q, J=11.7 Hz, $\Delta\nu$=8.4 Hz), 5.50 (1H, s), 5.97 (1H, br s), 6.94—7.45 (3H, m)
4m	1.33 (3H, s), 2.30 (3H, s), 2.33 (3H, s), 3.63 (3H, s), 3.92 (4H, s), 4.05 (2H, AB q, J=12.0 Hz, $\Delta\nu$=13.4 Hz), 5.44 (1H, s), 5.92 (1H, br s), 6.92—7.50 (4H, m)
4n	1.31 (3H, s), 2.30 (3H, s), 2.32 (3H, s), 3.63 (3H, s), 3.89 (4H, s), 4.06 (2H, AB q, J=12.0 Hz, $\Delta\nu$=10.6 Hz), 5.39 (1H, s), 5.69 (1H, br s), 6.82—7.53 (4H, m)
4o	1.27 (3H, s), 2.27 (6H, s), 3.57 (3H, s), 3.87 (4H, s), 4.02 (2H, AB q, J=11.6 Hz, $\Delta\nu$=24.4 Hz), 5.56 (1H, s), 5.93 (1H, br s), 6.97—7.73 (4H, m)
4p	1.29 (3H, s), 2.31 (3H, s), 2.34 (3H, s), 3.61 (3H, s), 3.80—4.03 [6H, m, 3.96 (2H, s)], 5.48 (1H, s), 6.17 (1H, br s), 7.20—7.38 (2H, m), 7.50—7.72 (1H, m)
4q	1.33 (3H, s), 2.29 (3H, s), 2.32 (3H, s), 3.64 (3H, s), 3.80 (3H, s), 3.92 (4H, s), 4.02 (2H, AB q, J=11.7 Hz, $\Delta\nu$=8.1 Hz), 5.33 (1H, s), 5.80 (1H, br s), 6.69—6.92 (2H, m), 7.00—7.30 (2H, m)
4r	1.33 (3H, s), 2.28 (6H, s), 2.77 (3H, s), 3.58 (3H, s), 3.90 (4H, s), 4.02 (2H, AB q, J=12.0 Hz, $\Delta\nu$=21.9 Hz), 5.45 (1H, s), 6.35 (1H, br s), 7.20—7.50 (3H, m), 7.80—8.10 (1H, m)
4s	1.28 (3H, s), 2.23 (3H, s), 2.26 (3H, s), 3.29 (3H, s), 3.58 (3H, s), 3.86 (4H, mc), 3.99 (2H, AB q, J=11.7 Hz, $\Delta\nu$=4.7 Hz), 5.77 (1H, s), 6.18 (1H, br s), 7.15—7.93 (4H, m)
5a	0.57—1.93 (11H, m), 2.34 (3H, s), 2.37 (3H, s), 3.67 (3H, s), 3.80—4.07 (2H, m), 5.14 (1H, s), 6.44 (1H, br s), 7.40 (1H, t, J=7.5 Hz), 7.57—7.80 (1H, m), 7.87—8.23 (2H, m)
5b	0.98—1.89 (8H, m), 1.99—2.47 [7H, m, 2.36 (3H, s), 2.38 (3H, s)], 3.66 (3H, s), 3.93 (1H, dd, J=10.8, 6.6 Hz), 3.94 (1H, dd, J=11.1, 7.3 Hz), 5.11 (1H, s), 5.76 (1H, br s), 7.36 (1H, t, J=8.0 Hz), 7.55—7.73 (1H, m), 7.87—8.15 (2H, m)
5c	1.52—2.54 [13H, m, 2.34 (6H, s)], 3.64 (3H, s), 4.00 (2H, d, J=7.2 Hz), 5.08 (1H, s), 6.37 (1H, br s), 7.37 (1H, t, J=7.5 Hz), 7.51—7.84 (1H, m), 7.85—8.20 (2H, m)
5d	1.25 (3H, t, J=7.0 Hz), 1.50—2.17 (7H, m), 2.35 (3H, s), 2.37 (3H, s), 4.08 (2H, d, J=6.5 Hz), 4.11 (2H, q, J=7.0 Hz), 5.12 (1H, s), 5.90 (1H, br s), 7.36 (1H, t, J=8.0 Hz), 7.56—7.74 (1H, m), 7.92—8.20 (2H, m)
5e	0.93 (3H, t, J=7.0 Hz), 1.37—2.60 [15H, m, 2.37 (6H, s)], 4.02 (2H, t, J=6.4 Hz), 4.08 (2H, d, J=6.8 Hz), 5.13 (1H, s), 6.55 (1H, br s), 7.37 (1H, t, J=7.5 Hz), 7.57—7.81 (1H, m), 7.88—8.30 (2H, m)
5f	0.05—0.69 (4H, m), 0.89—1.29 (1H, m), 2.36 (6H, s), 3.63 (3H, s), 3.85 (2H, d, J=7.2 Hz), 5.10 (1H, s), 5.80 (1H, br s), 7.35 (1H, t, J=7.8 Hz), 7.54—7.72 (1H, m), 7.88—8.16 (2H, m)

TABLE XII. (continued)

5g	0.10—0.63 (4H, m), 0.81—1.40 [4H, m, 1.20 (3H, t, J=6.9 Hz)], 2.33 (6H, s), 3.85 (2H, d, J=6.5 Hz), 4.08 (2H, q, J=6.9 Hz), 5.12 (1H, s), 6.24 (1H, br s), 7.37 (1H, t, J=7.4 Hz), 7.55—7.81 (1H, m), 7.87—8.23 (2H, m)
5h	0.11—1.97 (7H, m), 0.87 (3H, t, J=7.0 Hz), 2.34 (6H, s), 3.87 (2H, d, J=6.6 Hz), 4.00 (2H, t, J=6.4 Hz), 5.14 (1H, s), 6.37 (1H, br s), 7.37 (1H, t, J=7.5 Hz), 7.55—8.30 (3H, m)
5i	0.10—0.87 (4H, m), 0.82—1.38 (1H, m), 2.36 (6H, s), 3.88 (2H, d, J=6.8 Hz), 4.43 (2H, q, J=8.2 Hz), 5.11 (1H, s), 6.33 (1H, br s), 7.37 (1H, t, J=7.8 Hz), 7.55—7.82 (1H, m), 7.87—8.23 (2H, m)
5j	0.47—1.90 (11H, m), 2.30 (3H, s), 2.36 (3H, s), 3.60 (3H, s), 3.87 (2H, d, J=6.0 Hz), 5.79 (1H, s), 6.46 (1H, br s), 7.05—7.86 (4H, m)
5k	0.02—0.70 (4H, m), 0.87—1.40 (1H, m), 2.33 (3H, s), 2.38 (3H, s), 3.58 (3H, s), 3.75 (1H, dd, J=11.0, 7.3 Hz), 3.93 (1H, dd, J=11.0, 7.5 Hz), 5.82 (1H, s), 6.01 (1H, br s), 7.13—7.78 (4H, m)
5l	0.00—0.59 (4H, m), 0.86—1.27 (1H, m), 2.30 (3H, s), 2.32 (3H, s), 3.62 (3H, s), 3.85 (2H, d, J=6.9 Hz), 5.48 (1H, s), 5.71 (1H, br s), 6.95—7.40 (3H, m)
5m	0.00—0.59 (4H, m), 0.76—1.47 [4H, m, 1.20 (3H, t, J=7.1 Hz)], 2.31 (6H, s), 3.83 (2H, d, J=7.3 Hz), 4.08 (2H, q, J=7.1 Hz), 5.50 (1H, s), 5.76 (1H, br s), 6.95—7.42 (3H, m)
5n	0.03—0.59 (4H, m), 0.69—1.80 [6H, m, 0.81 (3H, t, J=7.5 Hz)], 2.30 (6H, s), 3.81 (2H, d, J=6.9 Hz), 3.90 (2H, t, J=6.8 Hz), 5.49 (1H, s), 5.67 (1H, br s), 6.94—7.42 (3H, m)
5o	0.07—0.60 (4H, m), 0.87—1.36 (1H, m), 2.31 (3H, s), 2.33 (3H, s), 3.63 (3H, s), 3.83 (2H, d, J=7.0 Hz), 5.43 (1H, s), 6.90—7.47 (4H, m)
5p	0.08—0.59 (4H, m), 0.95—1.31 (1H, m), 2.29 (3H, s), 2.30 (3H, s), 3.63 (3H, s), 3.88 (2H, d, J=7.0 Hz), 5.38 (1H, s), 5.77 (1H, br s), 6.80—7.51 (4H, m)
5q	0.02—0.59 (4H, m), 0.78—1.33 (1H, m), 2.29 (3H, s), 2.30 (3H, s), 3.59 (3H, s), 3.73 (1H, dd, J=11.5, 7.5 Hz), 3.94 (1H, dd, J=11.5, 7.5 Hz), 5.58 (1H, s), 5.82 (1H, br s), 7.07—7.85 (4H, m)
5r	0.12—0.67 (4H, m), 0.73—1.37 (1H, m), 2.34 (6H, s), 3.63 (3H, s), 3.87 (2H, d, J=7.0 Hz), 5.00 (1H, s), 5.69 (1H, br s), 7.00—7.33 (4H, m)
5s	0.07—0.63 (4H, m), 0.83—1.32 (1H, m), 2.34 (6H, s), 3.64 (3H, s), 3.87 (2H, d, J=7.0 Hz), 5.08 (1H, s), 5.83 (1H, br s), 7.20—7.62 (4H, m)
5t	0.03—0.56 (4H, m), 0.81—1.35 (1H, m), 2.33 (6H, s), 3.59 (3H, s), 3.78 (2H, d, J=6.9 Hz), 5.51 (1H, s), 6.04 (1H, br s), 7.20—7.41 (2H, m), 7.49—7.73 (1H, m)
5u	0.07—0.58 (4H, m), 0.88—1.39 (1H, m), 2.26 (3H, s), 2.28 (3H, s), 2.80 (3H, s), 3.59 (3H, s), 3.83 (1H, dd, J=11.5, 7.5 Hz), 3.89 (1H, dd, J=11.5, 7.7 Hz), 5.46 (1H, s), 6.83 (1H, br s), 7.22—7.68 (3H, m), 7.82—8.17 (1H, m)
5v	0.11—0.59 (4H, m), 0.80—1.36 (1H, m), 2.28 (6H, s), 2.46 (3H, s), 3.60 (3H, s), 3.85 (2H, d, J=7.2 Hz), 5.47 (1H, s), 5.72 (1H, br s), 6.97—7.43 (4H, m)
5w	0.07—0.59 (4H, m), 0.83—1.33 (1H, m), 2.23 (3H, s), 2.26 (3H, s), 3.30 (3H, s), 3.59 (3H, s), 3.86 (2H, d, J=7.0 Hz), 6.05 (1H, br s), 6.21 (1H, s), 7.14—7.97 (4H, m)
8a	2.10 (3H, s), 2.37 (6H, s), 3.67 (3H, s), 4.67 (2H, s), 5.17 (1H, s), 6.46 (1H, br s), 7.40 (1H, t, J=7.8 Hz), 7.60—7.79 (1H, m), 7.90—8.21 (2H, m)
8b	1.23 (3H, t, J=6.8 Hz), 2.07 (3H, s), 2.35 (6H, s), 4.09 (2H, q, J=6.8 Hz), 4.60 (2H, s), 5.13 (1H, s), 6.63 (1H, br s), 7.40 (1H, t, J=7.2 Hz), 7.57—7.84 (1H, m), 7.87—8.24 (2H, m)
8c	0.86 (3H, t, J=6.5 Hz), 1.40—1.83 (2H, m), 2.06 (3H, s), 2.38 (3H, s), 4.03 (2H, t, J=6.5 Hz), 4.62 (2H, s), 5.17 (1H, s), 6.04 (1H, br s), 7.37 (1H, t, J=8.0 Hz), 7.61—7.79 (1H, m), 7.91—8.20 (2H, m)
8d	1.11 (3H, d, J=6.1 Hz), 1.27 (3H, d, J=6.1 Hz), 2.05 (3H, s), 2.33 (6H, s), 4.61 (2H, s), 4.93 (1H, hept., J=6.1 Hz), 5.13 (1H, s), 6.83 (1H, br s), 7.40 (1H, t, J=7.4 Hz), 7.59—7.82 (1H, m), 7.88—8.29 (2H, m)
8e	1.43—1.95 (8H, m), 2.10 (3H, s), 2.38 (6H, s), 4.67 (2H, s), 5.02—5.27 (1H, m), 5.15 (1H, s), 6.63 (1H, br s), 7.40 (1H, t, J=7.5 Hz), 7.59—7.83 (1H, m), 7.88—8.22 (2H, m)
8f	2.13 (3H, s), 2.32 (6H, s), 2.73 (2H, t, J=6.5 Hz), 3.66 (3H, s), 4.33 (2H, t, J=6.5 Hz), 5.06 (1H, s), 6.50 (1H, br s), 7.15—8.18 (4H, m)
8g	1.25 (3H, t, J=7.0 Hz), 2.15 (3H, s), 2.34 (6H, s), 2.73 (2H, t, J=6.0 Hz), 4.11 (2H, q, J=7.0 Hz), 4.32 (2H, t, J=6.0 Hz), 5.05 (1H, s), 6.48 (1H, br s), 7.23—8.20 (4H, m)
8h	1.11 (3H, d, J=6.0 Hz), 1.25 (3H, d, J=6.0 Hz), 2.15 (3H, s), 2.35 (6H, s), 2.71 (2H, t, J=6.0 Hz), 4.31 (2H, t, J=6.0 Hz), 4.95 (1H, hept., J=6.0 Hz), 5.03 (1H, s), 6.24 (1H, br s), 7.18—8.20 (4H, m)
8i	1.99 (3H, s), 2.30 (6H, s), 3.53 (3H, s), 4.57 (2H, AB q, J=17.1 Hz, $\Delta\nu$=10.6 Hz), 5.73 (1H, s), 6.63 (1H, br s), 7.13—7.78 (4H, m)
8j	1.99 (3H, s), 2.30 (3H, s), 2.32 (3H, s), 3.60 (3H, s), 4.58 (2H, AB q, J=16.5 Hz, $\Delta\nu$=7.2 Hz), 5.52 (1H, s), 6.16 (1H, br s), 5.98—7.40 (3H, m)

Table XII. (continued)

8k	1.94 (3H, s), 2.33 (6H, s), 3.60 (3H, s), 4.55 (2H, s), 5.55 (1H, s), 6.04 (1H, br s), 6.90—7.45 (4H, m)
8l	1.93 (3H, s), 2.33 (6H, s), 3.63 (3H, s), 4.57 (2H, s), 5.42 (1H, s), 5.92 (1H, br s), 6.83—7.53 (4H, m)
8m	1.93 (3H, s), 2.30 (6H, s), 3.56 (3H, s), 4.52 (2H, AB q, $J=17.0$ Hz, $\Delta\nu=14.0$ Hz), 5.59 (1H, br s), 6.11 (1H, br s), 7.08—7.67 (4H, m)
8n	1.93 (3H, s), 2.27 (3H, s), 2.32 (3H, s), 3.61 (3H, s), 3.77 (3H, s), 4.51 (2H, s), 5.33 (1H, s), 5.82 (1H, br s), 6.67—6.93 (2H, m), 6.98—7.33 (2H, m)
8o	1.97 (3H, s), 2.30 (6H, s), 2.83 (3H, s), 3.58 (3H, s), 4.70 (2H, s), 5.54 (1H, s), 6.78 (1H, br s), 7.20—7.47 (3H, m), 7.75—8.03 (1H, m)
8p	1.98 (3H, s), 2.28 (3H, s), 2.30 (3H, s), 3.25 (3H, s), 3.62 (3H, s), 4.60 (2H, s), 6.03 (1H, br s), 6.32 (1H, s), 7.15—7.95 (4H, m)
8q	2.02 (3H, s), 2.34 (6H, s), 3.60 (3H, s), 4.56 (2H, s), 5.54 (1H, s), 6.20 (1H, br s), 7.22—7.43 (2H, m), 7.51—7.63 (1H, m)
9a	1.32 (3H, s), 1.53—1.83 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 3.63 (3H, s), 3.69—4.02 (4H, m), 4.13 (2H, AB q, $J=12.3$ Hz, $\Delta\nu=4.3$ Hz), 5.10 (1H, s), 5.99 (1H, br s), 7.31 (1H, t, $J=7.4$ Hz), 7.54—7.74 (1H, m), 7.81—8.11 (2H, m)
9b	1.26 (3H, t, $J=7.0$ Hz), 1.37 (3H, s), 1.49—2.00 (2H, m), 2.35 (3H, s), 2.37 (3H, s), 3.62—4.35 (6H, m), 4.15 (2H, s), 5.19 (1H, s), 6.57 (1H, br s), 7.39 (1H, t, $J=7.8$ Hz), 7.61—8.27 (3H, m)
9c	0.90 (3H, t, $J=6.8$ Hz), 1.19—1.97 (4H, m), 1.34 (3H, s), 2.36 (6H, s), 3.65—4.26 [8H, m, 4.13 (2H, s)], 5.14 (1H, s), 6.10 (1H, br s), 7.39 (1H, t, $J=7.7$ Hz), 7.59—8.27 (3H, m)
10a	1.63 (3H, s), 2.33 (3H, s), 2.38 (3H, s), 3.25 (4H, s), 3.63 (3H, s), 4.13 (2H, s), 5.14 (1H, s), 6.36 (1H, br s), 7.36 (1H, t, $J=7.5$ Hz), 7.58—8.23 (3H, m)
10b	1.28 (3H, t, $J=7.1$ Hz), 1.66 (3H, s), 2.36 (3H, s), 2.42 (3H, s), 3.31 (4H, s), 4.12 (2H, q, $J=7.1$ Hz), 4.22 (2H, s), 5.21 (1H, s), 5.95 (1H, br s), 7.19—8.32 (4H, m)
10c	0.91 (3H, t, $J=6.8$ Hz), 1.43—1.99 (2H, m), 1.64 (3H, s), 2.33 (3H, s), 2.37 (3H, s), 3.32 (4H, s), 4.04 (2H, t, $J=6.2$ Hz), 4.19 (2H, s), 5.18 (1H, s), 6.04 (1H, br s), 7.39 (1H, t, $J=7.7$ Hz), 7.56—8.29 (3H, m)

of the solvent, the residue was purified by column chromatography with AcOEt–hexane to give **4p** (2.5 g) as a pale yellow oil.

The dihydropyridines (**4a—h, j—o, q—s, 5a—e, g—k, m—w**) were prepared in the same manner as described for **4i, p, 5f,** and **l**. Data for **4** and **5** are given in Tables I, II, and XII.

2-Arylmethyleneacetoacetates (2)——a) Methyl 2-(3-Nitrophenylmethylene)acetoacetate (**2a**)[4f]: A soluton of 3-nitrobenzaldehyde (10 g), methyl acetoacetate (11 g), AcOH (1 ml), and piperidine (1 ml) in benzene (60 ml) was stirred at room temperature for 4 h. The reaction mixture was washed with 10% NaOH and then with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The residual oil was crystallized with hexane to give **2a** (22 g, 80%), which was recrystallized from acetone to afford colorless prisms. The ratio of isomers was 1.5 as judged from the nuclear magnetic resonance (NMR) spectrum. NMR ($CDCl_3$) δ: 2.38 (3H, s, minor[17]), 2.43 (3H, s), 3.88 (3H, s), 7.40—7.84 (3H, m), 7.58 (1H, s), 7.67 (1H, s, minor), 8.08—8.34 (1H, m).

b) Methyl 2-(2,1,3-Benzoxadiazol-4-ylmethylene)acetoacetate (**2p**): A solution of **3a** (5.0 g) and triethylamine (1 ml) in CH_2Cl_2 (20 ml) was stirred at room temperature for 1 h. The reaction mixture was washed with H_2O, dried over $MgSO_4$, and then evaporated *in vacuo*. The residual oil was crystallized with isopropyl ether to give **2p** (3.6 g, 98%). The ratio of isomers was 1.3. NMR ($CDCl_3$) δ: 2.48 (3H, s, minor), 2.50 (3H, s), 3.82 (3H, s), 3.92 (3H, s, minor), 7.22—7.70 (2H, m), 7.74—8.00 (1H, m).

The acetates (**2b—o, q**) were prepared in the same manner as described for **2a** and **p**.

Ethyl 2-(3-Nitrophenylmethylene)acetoacetate (**2b**)[4f]: 75% yield. The ratio of isomers was 1.8. NMR ($CDCl_3$) δ: 1.00 (3H, t, $J=6.6$ Hz), 1.33 (3H, t, $J=7.2$ Hz, minor), 2.20 (3H, s, minor), 2.47 (3H, s), 4.09 (2H, q, $J=6.6$ Hz), 4.34 (2H, q, $J=7.2$ Hz), 7.27—8.41 (5H, m).

Propyl 2-(3-Nitrophenylmethylene)acetoacetate (**2c**)[4f]: 58% yield. The ratio of isomers was 3.1. NMR ($CDCl_3$) δ: 0.96 (3H, t, $J=7.0$ Hz, minor), 1.05 (3H, t, $J=7.0$ Hz), 1.33—2.13 (2H, m), 2.39 (3H, s, minor), 2.43 (3H, s), 4.27 (2H, t, $J=7.0$ Hz), 7.39—7.98 (3H, m), 8.13—8.43 (2H, m).

Isopropyl 2-(3-Nitrophenylmethylene)acetoacetate (**2d**)[4f]: 62% yield. The ratio of isomers was 2.0. NMR ($CDCl_3$) δ: 1.31 (6H, d, $J=6.5$ Hz), 1.35 (6H, d, $J=6.5$ Hz, minor), 2.40 (3H, s, minor), 2.45 (3H, s), 5.28 (1H, hept., $J=6.5$ Hz), 7.23—8.40 (5H, m).

Cyclopentyl 2-(3-Nitrophenylmethylene)acetoacetate (**2e**): 78% yield. The ratio of isomers was 2.0. NMR ($CDCl_3$) δ: 1.07—2.13 (8H, m), 2.37 (3H, s, minor), 2.43 (3H, s), 5.22—5.51 (1H, m), 7.40—7.82 (3H, m), 8.17—8.34 (2H, m).

Methyl 2-(2-Nitrophenylmethylene)acetoacetate (**2f**): 89% yield. The ratio of isomers was 1.7. NMR ($CDCl_3$) δ:

2.20 (3H, s, minor), 2.47 (3H, s), 3.60 (3H, s), 3.87 (3H, s, minor), 7.27—8.43 (5H, m).

Ethyl 2-(2-Nitrophenylmethylene)acetoacetate (**2g**): 85% yield. The ratio of isomers was 2.0. NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.0 Hz), 1.37 (3H, t, J=7.0 Hz, minor), 2.20 (3H, s, minor), 2.47 (3H, s), 4.08 (2H, q, J=7.0 Hz), 4.35 (2H, q, J=7.0 Hz, minor), 7.27—7.85 (3H, m), 7.99—8.37 (2H, m).

Methyl 2-(2-Chlorophenylmethylene)acetoacetate (**2h**): 84% yield. The ratio of isomers was 1.3. NMR ($CDCl_3$) δ: 2.25 (3H, s, minor), 2.48 (3H, s), 3.77 (3H, s), 3.88 (3H, s, minor), 7.10—7.59 (4H, m), 7.91 (1H, s), 7.98 (1H, s, minor).

Methyl 2-(2-Bromophenylmethylene)acetoacetate (**2i**): 85% yield. The ratio of isomers was 1.5. NMR ($CDCl_3$) δ: 2.20 (3H, s, minor), 2.47 (3H, s), 3.73 (3H, s), 3.86 (3H, s, minor), 7.00—7.70 (4H, m), 7.80 (1H, s), 7.87 (1H, s, minor).

Methyl 2-(2-Trifluoromethylphenylmethylene)acetoacetate (**2j**): 84% yield. The ratio of isomers was 1.1. NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.42 (3H, s, minor), 3.71 (3H, s), 3.83 (3H, s, minor), 7.10—8.03 (5H, m).

Methyl 2-(2-Methoxyphenylmethylene)acetoacetate (**2k**): 77% yield. The ratio of isomers was 4.6. NMR ($CDCl_3$) δ: 2.28 (3H, s, minor), 2.42 (3H, s), 3.78 (3H, s), 3.82 (3H, s, minor), 3.86 (3H, s, minor), 3.87 (3H, s), 6.78—7.02 (2H, m), 7.20—7.50 (2H, m), 7.93 (1H, s), 7.97 (1H, s, minor).

Methyl 2-(2-Methylthiophenylmethylene)acetoacetate (**2l**): 85% yield. The ratio of isomers was 3.0. NMR ($CDCl_3$) δ: 2.46 (3H, s, minor), 2.50 (3H, s), 3.72 (3H, s), 3.85 (3H, s, minor), 6.90—7.80 (4H, m), 8.00 (1H, s), 8.05 (1H, s, minor).

Methyl 2-(2-Methylsulfinylphenylmethylene)acetoacetate (**2m**): 96% yield. The ratio of isomers was 2.0. NMR ($CDCl_3$) δ: 2.31 (3H, s, minor), 2.43 (3H, s), 2.68 (3H, s), 2.82 (3H, s, minor), 3.69 (3H, s), 3.88 (3H, s, minor), 7.32—7.70 (4H, m), 7.86—8.13 (2H, m).

Methyl 2-(2-Methanesulfonylphenylmethylene)acetoacetate (**2n**): 84% yield. The ratio of isomers was 2.0. NMR ($CDCl_3$) δ: 2.32 (3H, s, minor), 2.49 (3H, s), 3.03 (3H, s), 3.10 (3H, s, minor), 3.63 (3H, s), 3.88 (3H, s, minor), 7.30—7.70 (4H, m), 8.00—8.43 (2H, m).

2,2-Ethylenedioxypropyl 2-(2-Nitrophenylmethylene)acetoacetate (**2o**): 83% yield from **3b**. The ratio of isomers was 1.5. NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.43 (3H, s, minor), 2.20 (3H, s, minor), 2.49 (3H, s), 3.80 (4H, mc), 3.93 (2H, s), 4.00 (4H, s, minor), 4.22 (2H, s, minor), 7.22—7.73 (3H, m), 7.95—8.15 (2H, m).

Ethyl 2-(2,1,3-Benzoxadiazol-4-ylmethylene)acetoacetate (**2q**): 99% yield. The ratio of isomers was 1.7. NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz), 1.38 (3H, t, J=7.0 Hz, minor), 2.47 (3H, s, minor), 2.52 (3H, s), 4.32 (2H, q, J=7.0 Hz), 4.36 (2H, q, J=7.0 Hz, minor), 7.26—8.03 (5H, m).

Alkyl Oxoalkyl-4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (8)——a) Methyl 2-Oxopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**8a**): A mixture of **4a** (8.2 g) and 10% HCl (5 ml) in EtOH (30 ml) was refluxed for 3 h, and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, and the organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–hexane gave **8a** (4.8 g) as pale yellow prisms.

b) Methyl 2-Oxopropyl 1,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (**8i**): A mixture of **4i** (11 g), AcOH (33 ml), and H_2O (66 ml) was stirred at 85 °C for 10 h and then allowed to cool. The precipitate was filtered off, washed with Et_2O, and recrystallized from EtOH–H_2O to give **8i** (9.3 g) as yellow prisms. MS *m/e* (relative intensity, %): 388 (23), 372 (53), 371 (100), 326 (69), 310 (32), 284 (70).

c) Methyl 2-Oxopropyl 4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**8j**): A mixture of **4l** (1.5 g), methanesulfonic acid (0.5 ml), H_2O (10 ml), and EtOH (100 ml) was refluxed for 6 h, and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, and the organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized from CH_2Cl_2–hexane to give **8j** (1.4 g) as pale yellow needles.

The ketones (**8b—h, k—q**) were prepared in the same manner as described for **8a, i,** and **j**. Data for **8** are given in Tables III and XII.

Alkyl 2,2-Trimethylenedioxypropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (9)——Methyl 2,2-Trimethylenedioxypropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**9a**): A solution of **8a** (5.0 g), 1,3-propanediol (3.0 g) and *p*-toluenesulfonic acid hydrate (0.1 g) in benzene (30 ml) was refluxed for 4 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2. The organic layer was washed with 10% K_2CO_3 and then H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The residual oil was crystallized with isopropyl ether to give **9a** (2.1 g), which was recrystallized from EtOH–isopropyl ether to afford pale yellow prisms.

The ketals (**9b, c**) were prepared in the same manner as described above. Data for **9** are given in Tables IV and XII.

Alkyl 2,2-Ethylenedithiopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (10)——Methyl 2,2-Ethylenedithiopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**10a**): Boron trifluoride etherate (0.1 g) was added dropwise to a solution of **8a** (6.0 g) and 1,2-ethanedithiol (5.0 g) in $CHCl_3$ (50 ml) at 0 °C. After being stirred at 0 °C for 5 h, the reaction mixture was washed with 10% K_2CO_3 and then H_2O. The organic layer was dried over $MgSO_4$, and evaporated *in vacuo*. The residual oil was purified by column chromatography with Et_2O to give **10a** (2.5 g), which was recrystallized from EtOH–Et_2O to afford pale yellow

prisms.

The ketals (**10b, c**) were prepared in the same manner as described above. Data for **10** are given in Tables IV and XII.

Acetoacetates (6)——Cyclopropylmethyl Acetoacetate (**6c**): First 60% NaH in oil (0.1 g) and then diketene (29 g) were added dropwise to cyclopropylmethanol (25 g) with stirring at 50—60 °C. After being stirred for 2 h at 70—80 °C, the reaction mixture was distilled *in vacuo* to give **6c** (50 g, 93%) as a colorless oil, bp 78 °C (4 mmHg). NMR ($CDCl_3$) δ: 0.17—0.74 (4H, m), 0.91—1.33 (1H, m), 2.28 (3H, s), 3.47 (2H, s), 3.95 (2H, d, J=7.2 Hz).

The acetates (**6a, b, d—h**) were prepared in the same manner as above.

2,2-Ethylenedioxypropyl Acetoacetate (**6a**): 70% yield, bp 90 °C (6 mmHg). NMR ($CDCl_3$) δ: 1.36 (3H, s), 2.25 (3H, s), 3.46 (2H, s), 3.95 (4H, s), 4.06 (2H, s).

3,3-Ethylenedioxybutyl Acetoacetate (**6b**): 76% yield, bp 120 °C (5 mmHg). NMR ($CDCl_3$) δ: 1.31 (3H, s), 2.00 (2H, t, J=7.0 Hz), 2.22 (3H, s), 3.40 (2H, s), 3.88 (4H, s), 4.20 (2H, t, J=7.0 Hz).

Cyclobutylmethyl Acetoacetate (**6d**): 88% yield, bp 82 °C (6 mmHg). NMR ($CDCl_3$) δ: 1.56—2.40 [10H, m, 2.27 (3H, s)], 3.40 (2H, s), 4.10 (2H, d, J=6.4 Hz).

Cyclopentylmethyl Acetoacetate (**6e**): 56% yield, bp 93 °C (6 mmHg). NMR ($CDCl_3$) δ: 1.07—2.03 (9H, m), 2.30 (3H, s), 3.48 (2H, s), 4.06 (2H, d, J=7.0 Hz).

Cyclohexylmethyl Acetoacetate (**6f**): 79% yield, bp 105 °C (4 mmHg). NMR ($CDCl_3$) δ: 0.50—2.06 (11H, m), 2.11 (3H, s), 3.47 (2H, s), 3.95 (2H, d, J=5.8 Hz).

2,2,2-Trifluoroethyl Acetoacetate (**6g**): 58% yield, bp 64 °C (12 mmHg). NMR ($CDCl_3$) δ: 2.27 (3H, s), 3.59 (2H, s), 4.53 (2H, q, J=8.0 Hz).

Cyclopentyl Acetoacetate (**6h**): 56% yield, bp 93 °C (6 mmHg). NMR ($CDCl_3$) δ: 1.49—2.16 (8H, m), 2.28 (3H, s), 3.42 (2H, s), 5.06—5.32 (1H, m).

3-Aminocrotonates (7)——a) 2,2-Ethylenedioxypropyl 3-Aminocrotonate (**7a**): Ammonia gas was bubbled into a solution of **6a** (20 g) in MeOH (100 ml) at 0—5 °C for 2.5 h. The reaction mixture was evaporated under reduced pressure and then the residual oil was distilled *in vacuo* to yield **7a** (17 g, 84%) as a pale yellow oil, bp 20 °C (5 mmHg). NMR ($CDCl_3$) δ: 1.41 (3H, s), 1.94 (3H, s), 3.97 (4H, s), 4.00 (2H, s), 4.57 (1H, s), 6.50 (2H, br).

b) Cyclopropylmethyl 3-Aminocrotonate (**7c**): Ammonia gas was bubbled into a solution of **6c** (21 g) in MeOH (100 ml) at 0—5 °C for 4 h. The reaction mixture was evaporated under reduced pressure and the residue was recrystallized from hexane to give **7c** (18 g, 85%) as colorless needles, mp 55—58 °C. NMR ($CDCl_3$) δ: 0.13—0.68 (4H, m), 0.87—1.36 (1H, m), 1.90 (3H, s), 3.87 (2H, d, J=7.2 Hz), 4.53 (1H, s).

The crotonates (**7b, d, e**) were prepared in the same manner as described for **7a** and **c**.

3,3-Ethylenedioxybutyl 3-Aminocrotonate (**7b**): 87% yield, bp 144 °C (4 mmHg). NMR ($CDCl_3$) δ: 1.33 (3H, s), 1.87 (3H, s), 1.96 (2H, t, J=6.6 Hz), 3.90 (4H, s), 4.11 (2H, t, J=6.6 Hz), 4.43 (1H, s), 6.50 (2H, br s).

Cyclobutylmethyl 3-Aminocrotonate (**7d**): 85% yield, mp 37—40 °C. NMR ($CDCl_3$) δ: 1.60—2.30 (7H, m), 1.86 (3H, s), 4.07 (2H, d, J=6.4 Hz), 4.50 (1H, s), 6.55 (2H, br).

Cyclohexylmethyl 3-Aminocrotonate (**7e**): 61% yield, mp 57—59 °C. NMR ($CDCl_3$) δ: 0.53—2.10 [14H, m, 1.91 (3H, s)], 3.87 (2H, d, J=7.0 Hz), 4.53 (1H, s), 6.20 (2H, br).

2-(2,1,3-Benzoxadiazol-4-ylmethyl)acetoacetates (**13**)——Ethyl 2-(2,1,3-Benzoxadiazol-4-ylmethyl)acetoacetate (**13b**): Ethyl acetoacetate (9.4 g) was added dropwise to a solution prepared from Na (1.5 g) and EtOH (150 ml), and then 2,1,3-benzoxadiazol-4-ylmethylbromide (**12**,[12] 13 g) was added portionwise with stirring at room temperature. After being stirred at 40—50 °C for 1.5 h, the reaction mixture was acidified with AcOH, and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the organic layer was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residual oil was purified by column chromatography with Et_2O–petroleum ether (1 : 4) to give **13b** (12 g, 75%) as a pale yellow oil. NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.0 Hz), 2.28 (3H, s), 3.52 (1H, dd, J=14.5, 7.8 Hz), 3.53 (1H, dd, J=14.5, 6.2 Hz), 4.00—4.37 [3H, m, 4.15 (2H, q, J=7.0 Hz)], 7.07—7.43 (2H, m), 7.60—7.73 (1H, m).

In the same manner as described above, **13a** was obtained as a pale yellow oil in 81% yield. NMR ($CDCl_3$) δ: 2.27 (3H, s), 3.52 (2H, d like, J=7.6 Hz), 3.71 (3H, s), 4.29 (1H, dd, J=7.7, 7.5 Hz), 7.13—7.43 (2H, m), 7.57—7.77 (1H, m).

2-(2,1,3-Benzoxadiazol-4-ylbromomethyl)acetoacetates (3)——Methyl 2-(2,1,3-Benzoxadiazol-4-ylbromomethyl)acetoacetate (**3a**): A mixture of **13a** (11.5 g), NBS (10 g), benzoyl peroxide (2.0 g), and CCl_4 (150 ml) was refluxed for 8 h. After cooling, the reaction mixture was filtered, and the filtrate was washed with H_2O, and dried over $MgSO_4$. The solvent was evaporated off *in vacuo* to give **3a** (11 g) as a crude pale yellow oil. The NMR spectrum showed **3a** to be a mixture (*ca.* 1.7 : 1) of diastereomers. NMR ($CDCl_3$–CCl_4) δ: 2.45 (3H, s, minor), 2.68 (3H, s), 3.40 (3H, s, minor), 3.82 (3H, s), 5.18 (1H, d, J=11.4 Hz, minor), 5.25 (1H, d, J=11.4 Hz), 5.74 (1H, d, J=11.4 Hz, minor), 5.80 (1H, d, J=11.4 Hz), 7.17—7.51 (2H, m), 7.63—7.83 (1H, m).

In the same manner as described above, **3b** was prepared as a crude pale yellow oil in 72% yield. The NMR spectrum showed **3b** to be a mixture (*ca.* 2 : 1) of diastereomers. NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.1 Hz, minor), 1.39 (3H, t, J=7.1 Hz), 2.13 (3H, s), 2.53 (3H, s, minor), 3.92 (2H, q, J=7.1 Hz, minor), 4.36 (2H, q, J=7.1 Hz), 5.23 (1H, d, J=11.4 Hz, minor), 5.32 (1H, d, J=10.7 Hz), 5.80 (1H, d, J=11.4 Hz, minor), 5.88 (1H, d, J=10.7 Hz), 7.20—7.90

(3H, m).

2-Methylthiobenzaldehyde (1b)[9c,13]——A solution of 2-chlorobenzaldehyde (**1a**, 67 g) and 15% sodium methanethiolate (300 g) in hexamethyl phosphoramide (200 ml) was heated on a steam bath for 5 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was distilled *in vacuo* to give **1b** (62 g, 86%) as a pale yellow oil, bp 149—150 °C (19 mmHg) [lit.[13] bp 97—101 °C (0.7 mmHg)]. NMR ($CDCl_3$) δ: 2.52 (3H, s), 7.17—7.67 (3H, m), 7.72—7.92 (1H, m), 10.30 (1H, s).

Diethyl 4-(2,1,3-Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (14, PY-108-068)[4i]——A solution of **3b** (5.0 g) and ethyl 3-aminocrotonate (**7g**, 2.0 g) in EtOH (40 ml) was refluxed for 60 h, and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt. The organic layer was washed with H_2O, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography with AcOEt–petroleum ether (1 : 1) to give **14** (2.7 g, 50%), which was recrystallized from CH_2Cl_2–Et_2O to give yellow needles, mp 153—155 °C.

PY-108-068 (**14**) was also prepared from **2q** and **7g** in the same manner as described for **5f**. The yield was 55%.

2-Hydroxyethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (15)[4j]——To ethylene glycol (120 ml) was added 60% NaH in oil (50 mg) and then diketene (20 g) was added dropwise. The mixture was heated at 90—95 °C for 3 h. After the addition of 3-nitrobenzaldehyde (32 g) and **7f** (24 g), and the whole was heated at 90—95 °C for 5 h. The reaction mixture was stored overnight in a refrigerator. The precipitate was filtered off, and washed with isopropyl alcohol to give **15** (45 g, 57%), which was recrystallized from MeOH–isopropyl alcohol gave pale yellow needles, mp 175—178 °C (lit.[4j] 174—176 °C). *Anal.* Calcd for $C_{18}H_{20}N_2O_7$: C, 57.09; H, 5.23; N, 7.40. Found: C, 57.44; H, 5.36; N, 7.44. NMR ($CDCl_3$) δ: 2.03 (1H, br s), 2.36 (6H, s), 3.56—3.95 [5H, m, 3.64 (3H, s)], 4.06—4.30 (2H, m), 5.09 (1H, s), 5.98 (1H, br s), 7.37 (1H, t, J=7.8 Hz), 7.53—7.70 (1H, m), 7.96—8.14 (2H, m). NMR (CD_3OD) δ: 2.40 (6H, s), 3.63—3.95 [5H, m, 3.68 (3H, s)], 4.07—4.33 (2H, m), 5.16 (1H, s), 7.30—8.23 (4H, m).

Methyl Sulfonyloxyethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylates (16)——2-Methanesulfonyloxyethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**16a**): A solution of methanesulfonyl chloride (3.0 g) in THF (50 ml) was added dropwise to a solution of **15** (5.0 g) and triethylamine (5 ml) in THF (50 ml) on an ice bath. The reaction mixture was stirred for 1 h, and then H_2O (5 ml) was added. After being stirred for 0.5 h, the reaction mixture was poured into ice-cold dilute hydrochloric acid at below 5 °C, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give **16a** (6.0 g, 100%) as a crude pale yellow oil. NMR ($CDCl_3$) δ: 2.30 (6H, s), 2.92 (3H, s), 3.57 (3H, s), 4.26 (4H, mc), 5.03 (4H, s), 5.88 (1H, br s), 7.32 (1H, t, J=7.7 Hz), 7.56 (1H, dt, J=7.7, 1.6 Hz), 7.82—8.04 (2H, m).

The sulfonate (**16b**) was synthesized in the same manner as above. The yield was about 100%. Pale yellow oil. NMR ($CDCl_3$) δ: 1.65 (3H, s), 2.25 (3H, s), 2.29 (3H, s), 2.36 (3H, s), 3.57 (3H, s), 4.11 (4H, mc), 4.98 (1H, s), 5.80 (1H, br s), 7.12—7.40 (3H, m), 7.45—7.76 (3H, m), 7.82—8.07 (2H, m).

Methyl 2-(*N*-Benzyl-*N*-methylamino)ethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate Hydrochloride (17, Nicardipine Hydrochloride)[4b]——a) A mixture of **16b** (6.0 g) and *N*-benzylmethylamine (25 ml) was heated on a steam bath for 8 h. Then excess *N*-benzylmethylamine was evaporated off *in vacuo*, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with 5% NaOH and then H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The residual oil was purified by column chromatography with Et_2O to give a pale yellow oil, which was crystallized with isopropyl ether to afford the free base of **17** (4.9 g, 77%) as pale yellow needles, mp 76—78 °C. NMR ($CDCl_3$) δ: 2.19 (3H, s), 2.35 (6H, s), 2.63 (2H, t, J=6.1 Hz), 3.49 (2H, s), 3.63 (3H, s), 4.16 (2H, t, J=6.1 Hz), 5.12 (1H, s), 5.97 (1H, br s), 7.24 (5H, s), 7.30 (1H, t, J=7.5 Hz), 7.63 (1H, dt, J=7.5, 1.5 Hz), 7.87—8.13 (2H, m).

Hydrochloride (**17**): Pale yellow needles (Me_2CO), mp 168—170 °C (lit.[4b] 168—170 °C).

b) A mixture of **16a** (6.0 g) and *N*-benzylmethylamine (20 ml) was heated at 95 °C for 8 h. After cooling, the reaction mixture was dissolved in CH_2Cl_2. The organic layer was washed with dilute hydrochloric acid and then H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give a residual oil, which was dissolved in AcOEt. The solution was kept at 5 °C overnight. The precipitate was filtered off to give **17** (4.5 g, 66%), which was recrystallized with Me_2CO to give pale yellow needles, mp 168—170 °C.

Vasodilating Activity——Mongrel dogs of either sex weighing 12—16 kg were used. The animals were anesthetized with pentobarbital-Na (30 mg/kg, *i.v.*) and were respired with room air (25 ml/kg, 12 strokes/min) by the use of a dog respirator (SN-480-3, Shinano, Japan). The chest was opened at the left 4th or 5th intercostal space, and the left circumflex coronary artery was exposed. The right vertebral, left common carotid, and left femoral arteries were isolated from the surrounding tissues. Electromagnetic flow probes were connected around each artery and the blood flow rates were monitored with an electromagnetic flow meter (MF-27, MFV-120, Nihon Kohden, Japan). Drugs were given into the right femoral vein *via* a polyethylene tube. Drugs were dissolved in EtOH in a concentration of 1% (w/v), and the solutions were diluted 10 times with 80% aqueous polyethylene glycol 400 and then with saline. The volume injected intravenously was 0.05 ml/kg. Statistical analysis of maximum increase of blood flow was performed using paired Student's *t*-test, and that of half-maximum duration was performed using unpaired

Student's *t*-test in comparison with nifedipine.

Antihypertensive Activity——Male spontaneously hypertensive rats (Hoshino Laboratory Animal Center), 21—25 weeks of age, weighing 300—350 g, were used. Systolic blood pressure was measured by a tail-cuff method with an electrosphygmomanometer (PE-300, Narco, U.S.A.). Heart rate was measured simultaneously with pulse rate tachometer (DT-200, Takuma Giken, Japan) by counting the pulses of blood pressure. Drugs dissolved in 70% aqueous polyethylene glycol 400 were administered orally in a volume of 0.5 ml/100 g. The values obtained at each time after administration of drugs were compared with the initial values. Statistical analysis was performed using paired Student's *t*-test.

Determination of *Rf* and *Rm* Values of Dihydropyridines——Pre-coated TLC plates of Silica gel 60 F_{254} silanized (layer thickness 0.25 mm, E. Merck) were used as the stationary phase, and a mixture of acetone–H_2O (60 : 40) as the mobile phase. The drugs (8 mg) were dissolved in EtOAc (20 ml) and the solutions (2 μl) were spotted on the plates. Nicardipine was used as the free base. The *Rm* values were calculated by means of the formula $Rm = \log(1/Rf - 1)$. The *Rf* and *Rm* values are each the mean of 6 or 7 determinations. Standard errors of both *Rf* and *Rm* values are less than 0.01. The results are given in Table XI.

References and Notes

1) A part of this work was presented previously: S. Ohno, O. Komatsu, K. Mizukoshi, K. Ichihara, Y. Nakamura, T. Morishima, and K. Sumita, Abstracts of Papers, 5th Symposium on Medicinal Chemistry of Japan, Kyoto, December 1983, p. 60; *idem, J. Pharmacobio-Dyn.*, **7**, s-94 (1984).
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