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Synthesis and Antihypertensive Activities of 1,4-Dihydropyridine-5-phosphonate Derivatives. I[1]

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A series of phosphonate derivatives, designed as analogues of 1,4-dihydropyridine-3,5-dicarboxylates in which a phosphonate group was introduced instead of the carboxylate group at the 5-position, was synthesized, and their antihypertensive activities were examined. Among the compounds examined, 5-diallyloxyphosphinyl-1,4-dihydropyridine-3-carboxylates were most effective in lowering the blood pressure in normotensive rats and spontaneously hypertensive rats (SHR). The phosphonate derivatives are considered to be close analogues of the carboxylate derivatives. The structure–activity relationships are discussed.

Keywords——1,4-dihydropyridine derivative; phosphonate derivative; calcium antagonist; antihypertensive activity; nifedipine; nicardipine; structure–activity relationship

Nifedipine[2] and nicardipine[3] are widely used clinically in the treatment of angina pectoris and hypertension, and a number of 1,4-dihydropyridine-3,5-dicarboxylate derivatives[4] have been reported to possess calcium-antagonistic activity. It has been generally recognized that the carboxylate moieties in these agents are essential for calcium-antagonistic activity.[5]

Our effort to find a new type of calcium antagonists was focused on replacing the usual carboxylate moiety with a phosphonate moiety, which was expected to be very hydrophilic, so that the bioavailability and/or pharmacokinetic parameters of the drugs coud be modulated. In this paper we describe the synthesis, pharmacological activities and structure–activity relationships of several 1,4-dihydropyridine-5-phosphonate derivatives. Although these compounds have been noted in the literature,[6] their biological activities have not been described.

Chemistry

The 1,4-dihydropyridine-5-phosphonate derivatives [I: **7**—**37**] listed in Table I were synthesized *via* the routes shown in Chart 1. The preparation of compounds I (R^1,R^2=Et; Ar=C_6H_5, 4-MeO–C_6H_5) has been described by Issleib *et al.*[6] In the same manner, the 1-

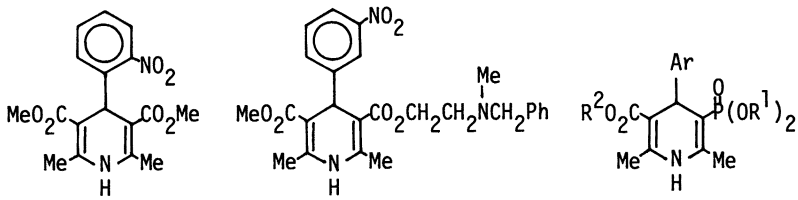


Fig. 1

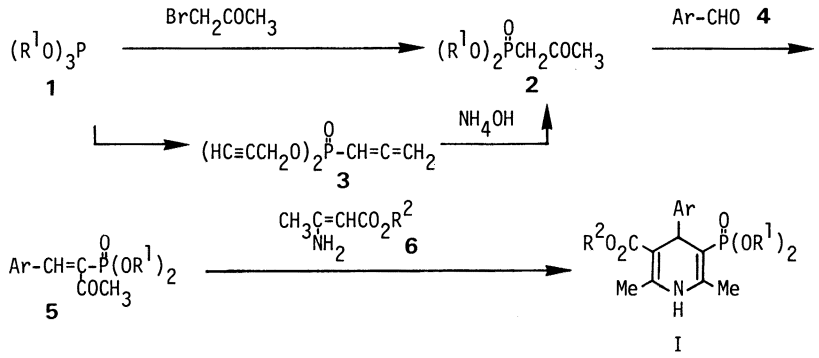


Chart 1

arylideneacetonylphosphonates **5** were allowed to react with the appropriate 3-aminocrotonates **6** in 2-propanol under reflux to afford 1,4-dihydropyridines (I) in 12—47% yields (method A). When compounds **5** were used without further purification (method B), the yields of (I) were low (2—35%, from **2**). The 1,4-dihydropyridines (I) were also prepared directly from the acetonylphosphonates **2**, the appropriate arylaldehydes **4** and **6** in the presence of piperidine–AcOH salt (method C).

In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum the values of the P–H coupling constants and the chemical shifts in the 1,4-dihydropyridines (I) were 4.7—5.1 (1H, d, J=10—11 Hz, C_4-H), 5.8—6.2 (1H, d, J=5—6 Hz, NH) and 2.25—2.35 (3H, d, J=2—3 Hz, C_6–CH_3), which clearly indicate the formation of the desired phosphonates.

The intermediates **5** were prepared by condensation of **2** and **4** in the presence of a catalyst in benzene by means of the Knoevenagel reaction, in 15—70% yield. The intermediates **2** and **6** were prepared as follows. The Arbuzov reaction[7] of the phosphites **1** with bromoacetone afforded **2** in 33—69% yields. However, the propargyl ester of **2** (not obtained under the Arbuzov reaction conditions) was prepared by reaction of ammonia with the allene intermediate[8] **3** obtained by the thermal rearrangement of tripropargyl phosphite. The reaction of the appropriate acetoacetates with ammonia in methanol gave the 3-aminocrotonates **6** in good yields.

Pharmacology

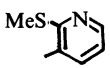
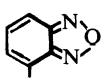
The compounds listed in Table I were examined for antihypertensive activities. Blood pressure was measured in unanesthetized rats with normal blood pressure (normotensive rats).[9] Some of the compounds were examined for antihypertensive activity in spontaneously hypertensive rats (SHR)[9] and the dose in mg/kg which produced a 30% drop in blood pressure was calculated from the regression line as the ED_{30} value (Table II).

Results and Discussion

The antihypertensive activities of the new dihydropyridine derivatives (I) are shown in Table I. In general, the 1,4-dihydropyridines (I), in which one carboxylate group of the 1,4-dihydropyridine-3,5-dicarboxylates was replaced by a phosphonate moiety, showed weaker antihypertensive activity than the corresponding carboxylate compounds. Among the phosphonate substituents, the diallyl phosphonate was most effective, and the activities are assumed to decrease in the following order: (R^1); allyl, crotyl, cyclopropylmethyl, iso-Pr, propargyl, 2-methoxyethyl, methyl, phenyl. Highly potent and long-lasting effects were observed with compounds bearing diallyl phosphonate in combination with the 2-(*N*-benzyl-

TABLE I. Physical and Biological Properties of 1,4-Dihydropyridine-5-phosphonates (I)

Compd. No.	R^1	R^2	R^3	Method[a]	Yield (%)	mp (°C)	Crystn.[b] solvent	Formula[c]	Antihypertensive[d] potency
Ar = R^3–C_6H_4									
7	Me	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	A	15	101—103	a	$C_{26}H_{32}N_3O_7P$	2
8	iso-Pr	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	A	25	113—115	b	$C_{30}H_{40}N_3O_7P$	3—4
9	C_6H_5	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	A	18	130—135	a	$C_{36}H_{36}N_3O_7P$	1
10	CH_2CH_2OMe	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	A	21	55—58	c	$C_{30}H_{40}N_3O_9P$	3
11	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	B	17	80—82	a	$C_{30}H_{36}N_3O_7P$	4
12	$CH_2CH=CHCH_3$	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	B	2	102—104	d	$C_{32}H_{40}N_3O_7P$	3—4
13	$CH_2C\equiv CH$	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	A	36	102—103	a	$C_{30}H_{32}N_3O_7P$	3
14	CH_2–◁	$CH_2CH_2N(Me)CH_2C_6H_5$	3-NO_2	B	31	101—103[e]	c	$C_{32}H_{40}N_3O_7P$[e]	3—4
15	Me	Me	3-NO_2	B	35	221—223	d	$C_{17}H_{21}N_2O_7P$	1
16	iso-Pr	Me	3-NO_2	A	34	205—207	d	$C_{21}H_{29}N_2O_7P$	1
17	$CH_2CH=CH_2$	Me	3-NO_2	A	28	164—166	d	$C_{21}H_{25}N_2O_7P$	3
18	$CH_2CH=CH_2$	iso-Bu	3-NO_2	A	38	114—115	c	$C_{24}H_{31}N_2O_7P$	1
19	$CH_2CH=CH_2$	$CH_2CH_2NMe_2$	3-NO_2	A	12	94—96	a	$C_{24}H_{32}N_3O_7P$	2
20	$CH_2CH=CH_2$	CH_2CH_2OPr	3-NO_2	A	32	91—92	c	$C_{25}H_{33}N_2O_8P$	2
21	$CH_2CH=CH_2$	$CH_2CH_2OCH_2C_6H_5$	3-NO_2	A	37	Oil	—	$C_{29}H_{33}N_2O_8P \cdot 1/2\,H_2O$	4
22	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$	2-NO_2	A	27	Oil	—	$C_{30}H_{36}N_3O_7P$	3
23	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$	3-CF_3	B	24	Oil	—	$C_{31}H_{36}F_3N_2O_5P \cdot 1/2\,H_2O$	3
24	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$	2-CF_3	B	7	Oil	—	$C_{31}H_{36}F_3N_2O_5P$	4
25	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$	2,3-Cl_2	B	20	Oil	—	$C_{30}H_{35}Cl_2N_2O_5P \cdot 1/2\,H_2O$	4

26	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$	2-$OCHF_2$	A	35	Oil	—	$C_{31}H_{37}F_2N_2O_5P$	3
27	Me	Me	2-NO_2	A	39	210—211	e	$C_{17}H_{21}N_2O_7P$	4
28	$CH_2CH=CH_2$	Me	2-NO_2	A	31	132—133	c	$C_{21}H_{25}N_2O_7P$	4
29	$CH_2CH=CH_2$	Me	3-CF_3	B	28	122—124	b	$C_{22}H_{25}F_3NO_5P$	1
30	$CH_2CH=CH_2$	Me	2-CF_3	B	13	105—107	f	$C_{22}H_{25}F_3NO_5P \cdot 1/4\,H_2O$	4
31	$CH_2CH=CH_2$	Me	2,3-Cl_2	B	15	181—182	b	$C_{21}H_{24}Cl_2NO_5P$	1
32	$CH_2CH=CH_2$	Me	2-$OCHF_2$	A	47	129—130	f	$C_{22}H_{26}F_2NO_6P \cdot 1/2\,H_2O$	2
Ar = heterocycles									
33	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$		A	46	Oil	—	$C_{28}H_{35}N_2O_6P$	2
34	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$		A	27	142 (dec.)	g	$C_{29}H_{36}N_3O_5P \cdot 2HCl \cdot 5H_2O$	2
35	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$		A	47	104—105	f	$C_{30}H_{38}N_3O_5PS$	3
36	$CH_2CH=CH_2$	$CH_2CH_2N(Me)CH_2C_6H_5$		A	41	103—104	c	$C_{30}H_{35}N_4O_6P$	3
37	$CH_2CH=CH_2$	Me		A	53	115—117	b	$C_{19}H_{24}NO_6P$	1

a) See the experimental section. *b*) Solvents for recrystallization: a, AcOEt–ether; b, AcOEt–hexane; c, ether; d, AcOEt; e, AcOEt–$CHCl_3$; f, ether–hexane; g, Me_2CO. *c*) All compounds were analyzed for C, H and N; the analytical results were within ±0.4% of the calculated values. *d*) Numbers have the following meanings: 1, little or no effect at 30 mg/kg; 2, effective at 30 mg/kg; 3, effective at 10 mg/kg; 4, effective at 3 mg/kg (nicardipine is effective at 1 mg/kg). The effective dose causes 25% lowering of blood pressure. *e*) Picrate ($C_6H_3N_3O_7$), for analytical sample.

TABLE II. Antihypertensive Activity of the Most Active Compounds, **11**, **24** and **25**, in SHR Compared with That of Nifedipine and Nicardipine

Compound	ED_{30} (mg/kg)[a]	Relative potency[b]
11	4.60	2.56
24	6.58	3.66
25	5.21	2.89
Nifedipine	1.50	
Nicardipine	1.80	1.00

a) See pharmacological methods. *b*) Potency relative to that of nicardipine.

N-methylamino)ethyl ester group at the 3-position and a 3-nitrophenyl, 2-trifluoromethylphenyl or 2,3-dichlorophenyl substituent at the 4-position.

Among the carboxylate substituents, the basic carboxylates mentioned above were most effective, and the 2-benzyloxyethyl ester also showed good activity. However, the methyl ester showed marked activity only when the dimethyl (**27**) or the allyl (**28**) phosphonate group was combined with a 2-nitrophenyl substituent.

Among the variations in the aryl groups at the 4-position, the compounds possessing electron-attracting groups at the 2- or 3-position showed greater activity than the corresponding heterocyclic compounds.

Some of the effective 1,4-dihydropyridines (I) were selected from those listed in Table I, and their antihypertensive activity was examined in unanesthetized SHR. The results are shown in Table II. In this series, the diallyl phosphonate compound (**11**) had the highest potency. However, it was about 2.5 times less active than nicardipine.

Structural requirements for good antihypertensive activity in this series proved to be essentially the same as those in other known 1,4-dihydropyridines except for the phosphonate moiety at the 5-position. These results indicate that the phosphonate group is comparable to the carboxylate group in terms of its effect in these compounds. Further investigations of phosphonate derivatives are in progress, and the results will be published elsewhere.

Experimental

Melting points were determined with a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi IR-215 spectrophotometer. NMR spectra were recorded on a Varian YX-200 spectrometer. Chemical shifts are given in δ (ppm) with tetramethylsilane as the internal standard.

Preparation of Trialkyl Phosphites (1)——The phosphites **1** were prepared in the same manner as described in the literature.[10] [R^1, bp °C (mmHg), yield %]: cyclopropylmethyl, 116—128 (3), 73; 2-methoxyethyl, 118—124 (0.5), 81.

General Procedure for Acetonylphosphonates (2)[11]——Bromoacetone (0.2 mol) was added to a preheated (70—80 °C) trialkyl phosphite **1** with stirring, and the reaction temperature was then raised to 130—150 °C. The mixture was stirred for 1—2 h at 120 °C. After cooling, the mixture was extracted twice with cold aqueous NaOH. The NaOH layer was neutralized with AcOH, and extracted twice with $CHCl_3$. The extracts were combined and washed with saturated aqueous NaCl, and dried ($MgSO_4$), then the solvent was removed *in vacuo*. The oil obtained was distilled *in vacuo* to give **2** as a colorless oil. All the acetonylphosphonates **2** thus obtained were characterized by measuring their IR and NMR spectra: IR (film): 1720 (C=O), 1260—1280 (P=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.12—2.37 (3H, s, $COCH_3$), 2.97—3.34 (2H, d, J=22—23 Hz, P-CH_2). [R^1, bp °C (mmHg), yield %]: iso-Pr, 93—95 (0.5), 69; 2-methoxyethyl, 140—141 (0.8), 61; allyl, 114—116 (0.5), 51; crotyl, 128—129 (1), 41; cyclopropylmethyl, 139—141 (0.8), 42. The diphenyl ester was prepared from diphenyl methyl phosphite with bromoacetone.[11c]

Dipropargyl Acetonylphosphonate——Phosphorus trichloride (27.5 g) was added dropwise to a stirred solution of propargyl alcohol (33.6 g) and triethylamine (60.7 g) in ether (500 ml) at −10 to −5 °C. The mixture was then kept at room tempeature for 4 h. The precipitated solid was filtered off and washed with ether. The combined filtrate was refluxed for 2 h with stirring. The solvent was removed at a temperature below 10 °C, and the residue was distilled *in vacuo* to afford **3** as an oil (20.8 g, 53%), bp 138—148 °C (2 mmHg).

Warning: The unstable allene compound **3** should be distilled carefully to avoid violent reaction. IR (film): 2140, 1970, 1940 cm^{-1}. NMR ($CDCl_3$) δ: 2.50—2.80 (2H, m), 4.52—5.50 (7H, m). Next, 28% NH_4OH (62 ml) was added dropwise to a solution of the allene **3** (20.5 g) in tetrahydrofuran (THF) (100 ml) at 0—5 °C. The mixture was stirred at room temperature for 2 h. The residue obtained after evaporation of the solvent and any volatile materials *in vacuo* were purified by chromatography on silica gel with hexane–AcOEt (9 : 1, v/v) to give the dipropargyl ester of **2** (16.0 g, 71%) as a pale yellow oil, bp 131—141 °C (0.5 mmHg). IR (film): 2140, 1720 cm^{-1}. NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.55—2.80 (2H, m), 3.19 (2H, d, J=23 Hz), 4.55—4.90 (4H, m).

General Procedure for 1-Arylideneacetonylphosphonates (5)——A solution of **2** (0.1 mol) and **4** (0.1 mol) in benzene (200 ml) containing a catalytic amount of piperidine–AcOH salt was refluxed for 2—24 h with continuous removal of water by the use of a Dean–Stark apparatus. The benzene solution was washed with water, aqueous NaOH, aqueous $NaHSO_3$ and water, then dried ($MgSO_4$) and concentrated to give crude **5** (containing as impurities *ca.* 20—40% benzalacetones). The residue was purified by chromatography on silica gel with hexane–AcOEt (4 : 1—1 : 4, v/v) to give **5** in 15—70% yields as a mixture of (*E*) and (*Z*)-isomers. All these **5** were characterized by measuring their IR and NMR spectra.

General Procedure for 1,4-Dihydropyridines (I)——Method A: A solution of **5** (0.01 mol) and **6** (0.01 mol) in 2-propanol (20 ml) was refluxed for 3—24 h with stirring. The solvent was removed, and the residue was purified by crystallization from solvents (AcOEt or ether) or by chromatography on silica gel with hexane–AcOEt to give the 1,4-dihydropyridines (I) in 12—47% yields. When R^2 of carboxylates was the basic ester, the residue obtained was extracted with aqueous HCl, the acid extract was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with aqueous K_2CO_3 and water, then dried ($MgSO_4$) and concentrated to give crude (I). The residue obtained was crystallized from solvents or purified by chromatography on silica gel with hexane–AcOEt.

Method B: Purification of the crude **5** was omitted, and condensation with **6** was carried out in the same manner as in method A (2—35%).

Method C: A solution of 0.01 mol each of **2**, **4** and **6** in 2-propanol (20 ml) containing a catalytic amount of piperidine–AcOH salt was refluxed for 24 h with stirring. The solvent was removed, and the residue was treated as in method A to afford the 1,4-dihydropyridines (I) (for example, **16**) in 16% yield.

The 1,4-dihydropyridines (**7**—**37**) were prepared by method A or B. Typical examples are given below.

2-(*N*-Benzyl-*N*-methylamino)ethyl 5-Diisopropoxyphosphinyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine 3-Carboxylate (8)——A solution of diisopropyl 1-(3-nitrobenzylidene)acetonylphosphonate (5.33 g) and 2-(*N*-benzyl-*N*-methylamino)ethyl 3-aminocrotonate (3.73 g) in 2-propanol (75 ml) was refluxed for 3 h with stirring. The solvent was removed, then the residue was diluted with AcOEt–ether (50 ml, 1 : 1, v/v) and extracted with 50 ml of 1 N HCl then twice with 20 ml each of water. The aqueous phase was extracted twice with $CHCl_3$, and the $CHCl_3$ layer was washed with aqueous K_2CO_3 and water, then dried ($MgSO_4$) and concentrated to dryness. The residue was crystallized from AcOEt–ether to give **8** (2.64 g). Recrystallization from hexane–AcOEt gave pale yellow crystals (2.21 g, 25%), mp 113—115 °C. *Anal.* Calcd for $C_{30}H_{40}N_3O_7P$: C, 61.53; H, 6.88; N, 7.18; P, 5.29. Found: C, 61.32; H, 7.06; N, 7.14; P, 5.09. IR (KBr): 3275, 3210, 1700, 1530, 1355, 1235 cm^{-1}. NMR ($CDCl_3$) δ: 0.96 (3H, d, J=6 Hz), 1.11 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 1.25 (3H, d, J=6 Hz), 2.19 (3H, s), 2.30 (3H, d, J=2.5 Hz), 2.34 (3H, s), 2.60—2.67 (2H, m), 3.49 (2H, s), 4.08—4.59 (4H, m), 4.91 (1H, d, J=10 Hz), 5.79 (1H, d, J=5 Hz), 7.16—7.35 (6H, m), 7.64—7.72 (1H, m), 7.92—7.99 (1H, m), 8.11 (1H, t, J=2 Hz).

2-(*N*-Benzyl-*N*-methylamino)ethyl 5-Diallyloxyphosphinyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (11)——A solution of diallyl acetonylphosphonate (3.0 g) and 3-nitrobenzaldehyde (2.08 g) in benzene (30 ml) containing a catalytic amount of piperidine–AcOH salt was refluxed for 2 h with continuous removal of water by the use of a Dean–Stark apparatus. The benzene solution was washed with aqueous NaOH, aqueous $NaHSO_3$, water, dried ($MgSO_4$) and concentrated to give crude **5** as an oil. A solution of the oil and 2-(*N*-benzyl-*N*-methylamino)ethyl 3-aminocrotonate (3.41 g) in 2-propanol (30 ml) was refluxed for 8 h with stirring. Concentration followed by treatment as in method B gave **11** (1.38 g, 17%), as pale yellow crystals (from AcOEt–ether), mp 80—82 °C. *Anal.* Calcd for $C_{30}H_{36}N_3O_7P$: C, 61.95; H, 6.24; N, 7.22. Found: C, 61.85; H, 6.42; N, 7.27. IR (KBr): 3290, 3230, 1700 cm^{-1}. NMR ($CDCl_3$) δ: 2.20 (3H, s), 2.31 (3H, d, J=2.5 Hz), 2.34 (3H, s), 2.64 (2H, t, J=6 Hz), 3.49 (2H, s), 3.96—4.39 [4H, m, 4.18 (2H, t-like)], 4.88 (1H, d, J=10 Hz), 4.98—5.29 (4H, m), 5.53—5.94 (2H, m), 6.17 (1H, d, J=6 Hz), 7.20—7.35 (6H, m), 7.63—7.72 (1H, m), 7.92—8.00 (4H, m), 8.10 (1H, t, J=1.5 Hz).

2-(*N*-Benzyl-*N*-methylamino)ethyl 5-Diallylphosphinyl-2,6-dimethyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate (24)——A solution of diallyl 1-(2-trifluoromethylbenzylidene)acetonylphosphonate (11.3 g, 21.2 mmol, *ca.* 70% purity) and 2-(*N*-benzyl-*N*-methylamino)ethyl 3-aminocrotonate (5.30 g, 21.2 mmol) in 2-propanol (120 ml) was refluxed for 48 h with stirring. The solvent was removed, and the residue was diluted with AcOEt (80 ml) and extracted with 100 ml of 1 N HCl then twice with 40 ml each of water. The aqueous phase was extracted twice with $CHCl_3$, and the $CHCl_3$ layer was washed with aqueous K_2CO_3 and water, then dried ($MgSO_4$) and concentrated to dryness. The residue was purified by chromatography on silica gel with hexane–AcOEt to give **24** (1.70 g, 13%) as a plae yellow oil. *Anal.* Calcd for $C_{31}H_{36}F_3N_2O_5P$: C, 61.58; H, 6.00; N, 4.63. Found: C, 61.50; H, 6.17; N, 4.62. IR (film): 3300, 3230, 3110, 1700 cm^{-1}. NMR ($CDCl_3$) δ: 2.19 (3H, s), 2.17 (3H, s), 2.39 (3H, d, J=2.5 Hz), 2.60—2.67 (2H, m), 3.49 (2H, s), 3.50—3.67 (1H, m), 3.99—4.47 (5H, m), 4.82—4.96 (2H, m), 5.14

(1H, d, $J=10$ Hz), 5.22—5.52 (3H, m), 5.72 (1H, d, $J=5$ Hz), 5.80—6.01 (1H, m), 7.18—7.60 [4H, m, 7.26 (5H, s)].

Methyl 5-Diallyloxyphosphinyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (28)——A solution of diallyl 1-(2-nitrobenzylidene)acetonylphosphonate (2.0 g) and methyl 3-aminocrotonate (0.46 g) in 2-propanol (15 ml) was refluxed for 15 h with stirring. The solvent was removed, and the residue was purified by chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to yield **28** (0.90 g, 31%) as yellow crystals (from hexane–AcOEt), mp 132—133 °C. *Anal.* Calcd for $C_{21}H_{25}N_2O_7P$: C, 56.25; H, 5.62; N, 6.25. Found: C, 56.25; H, 5.69; N, 6.22. IR (KBr): 3290, 3225, 3100, 1700 cm^{-1}. NMR ($CDCl_3$) δ: 2.29 (3H, s), 2.41 (3H, d, $J=2$ Hz), 3.52 (3H, s), 3.77—3.93 (1H, m), 4.13—4.31 (1H, m), 4.77—4.93 (2H, m), 5.20 (1H, d, $J=10$ Hz), 5.31—5.47 (2H, m), 5.53 (1H, d, $J=5$ Hz), 5.89—6.10 (2H, m), 7.18—7.29 (1H, m), 7.39—7.50 (1H, m), 7.55 (1H, dd, $J=1.5$, 8 Hz), 7.65 (1H, dd, $J=1.5$, 8 Hz).

References and Notes

1) This work was presented at the 106th Annual Meeting of the Pharmaceutical Society of Japan, Chiba, April 1986.
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