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Synthesis and Antihypertensive Activities of 1,4-Dihydropyridine-5-phosphonate Derivatives. II¹⁾

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A series of 1,4-dihydropyridine-5-cyclic phosphonate derivatives, designed as analogues of 1,4-dihydropyridine-3,5-dicarboxylate calcium antagonists, was synthesized and examined for antihypertensive activity. Several compounds were proved to have activities superior or comparable to that of nifedipine in lowering blood pressure in normotensive and spontaneously hypertensive rats (SHR). Among these compounds, methyl 2,6-dimethyl-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**31**, DHP-218) was approximately 7 times more active than nifedipine in SHR and was selected for further development and clinical evaluation. The structure-activity relationships are discussed.

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

In a previous paper,²⁾ the authors reported the synthesis and antihypertensive activities of 1,4-dihydropyridine-5-phosphonates (I), of these compounds which were expected to have long-lasting activity and good bioavailability. The results showed that the phosphonate function is a good replacement for the carboxylate group in the 1,4-dihydropyridine calcium antagonists, such as nifedipine.³⁾ This led us to search for novel and more potent analogues, and we selected 4-aryl-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylates and their derivatives (II) as candidates. The cyclic phosphonate moiety instead of dialkyl phosphonate could be expected to increase the hydrophilicity of the molecule. Consequently, these compounds with the cyclic phosphonate group were expected to show good bioavailability and long-lasting antihypertensive activity. In this paper, we describe the synthesis and pharmacological evaluations of the title compounds and the structure-activity relationships of various 1,4-dihydropyridine-5-cyclic phosphonates.

Chemistry

The 1,4-dihydropyridines (II) listed in Tables I to III were synthesized *via* the routes shown in Chart 1. In the same manner as described in the previous paper,²⁾ the 1-

Chart 1

arylideneacetonylphosphonates (7) were allowed to react with the appropriate 3-aminocrotonates (8) in 2-propanol under reflux to afford the 1,4-dihydropyridines (II) in 10–86% yields. The 1-arylideneacetonylphosphonates (7) were prepared by the Knoevenagel reaction of the cyclic acetonylphosphonates 4 with the appropriate arylaldehydes (6) in the presence of piperidine-AcOH salt as a catalyst in benzene, with 14–46% yields (Table IV). In this reaction, a side reaction (Horner-Emmons reaction) took place resulting in the formation of benzalacetones.

The intermediates 4⁴⁾ were prepared as follows. The Arbuzov reaction of cyclic phosphites 3 with bromoacetone afforded cyclic phosphonates 4 in 10–55% yields (Table V). The only cyclic phosphonate 4j which was not obtained under the Arbuzov reaction conditions was prepared by reaction of the acetonylphosphonodichloridate (5), obtained from propenyl acetate in two steps,⁵⁾ with diethyl 2,2-bis(hydroxymethyl)malonate. The cyclic phosphites 3 were synthesized by two known methods⁶⁾ (Chart 1). Method A was mainly used as a one-step reaction, but the phosphites which were obtained by method B were of better purity than those obtained by method A.

The 3-aminocrotonates (8) were prepared by the reaction of the appropriate acetoacetates with ammonia in methanol in good yields.⁷⁾

Pharmacology

The compounds listed in Tables I to III were examined for antihypertensive activity. Blood pressure was measured in unanesthetized rats with normal blood pressure (normotensive rats) and spontaneously hypertensive rats (SHR). Male normotensive Wistar rats weighing 310–450 g (18 weeks or older) were placed in a supine position under ether

TABLE I. Physical and Biological Properties of 1,4-Dihydropyridines (II); (Ar = R²-C₆H₄)

Compd. No.		R ¹	R ²	Yield ^{b)} (%)	mp (°C)	Crystn. solvent ^{c)}	Formula ^{d)}	Antihypertensive potency ^{e)}
9	a	Me	3-NO ₂	26	221—223	a	C ₁₈ H ₂₁ N ₂ O ₇ P	3
10	a	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	60	139—140	b	C ₂₇ H ₃₂ N ₃ O ₇ P	4—5
11	b	Me	3-NO ₂	64	208—209	a	C ₂₀ H ₂₅ N ₂ O ₇ P	3
12	b	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	28	125—126	c	C ₂₉ H ₃₆ N ₃ O ₇ P ^{f)}	4
13	c	Me	3-NO ₂	41	198—200	c	C ₂₀ H ₂₅ N ₂ O ₇ P	3—4
14	c	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	39	(Oil)		C ₂₉ H ₃₆ N ₃ O ₇ P	5
15	d	Me	3-NO ₂	73	223—224	c	C ₂₂ H ₂₉ N ₂ O ₇ P	1
16	d	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	42	171—172	a	C ₃₁ H ₄₀ N ₃ O ₇ P	2
17	e	Me	3-NO ₂	54	217—219	a	C ₂₁ H ₂₅ N ₂ O ₇ P	1
18	e	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	44	188—189	a	C ₃₀ H ₃₆ N ₃ O ₇ P	3
19	f	Me	3-NO ₂	76	199—200	d	C ₂₃ H ₂₉ N ₂ O ₇ P	1
20	f	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	76	198—200	d	C ₃₂ H ₄₀ N ₃ O ₇ P	2—3
21	g	Me	3-NO ₂	44	177—179	c	C ₁₉ H ₂₃ N ₂ O ₇ P	5
22	g	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	52	156—158	a	C ₂₈ H ₃₄ N ₃ O ₇ P	4
23	h	Me	3-NO ₂	31	122—123	a	C ₂₀ H ₂₅ N ₂ O ₇ P	4
24	h	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	29	145—146	a	C ₂₉ H ₃₆ N ₃ O ₇ P	3
25	i	Me	3-NO ₂	63	101—102	e	C ₂₁ H ₂₇ N ₂ O ₇ P ^{g)}	3
26	i	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	60	161—162	a	C ₃₀ H ₃₈ N ₃ O ₇ P	2
27	j	Me	3-NO ₂	72	216—217	f	C ₂₄ H ₂₉ N ₂ O ₇ P	1
28	j	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	57	142—143	c	C ₃₀ H ₃₈ N ₃ O ₇ P	1
29	k	Me	3-NO ₂	31	236—237	a	C ₂₁ H ₂₇ N ₂ O ₇ P	1
30	k	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	3-NO ₂	17	186—188	c	C ₃₀ H ₃₈ N ₃ O ₇ P	3
31	a	Me	2-NO ₂	54	245—247 (dec.)	g	C ₁₈ H ₂₁ N ₂ O ₇ P	6
32	b	Me	2-NO ₂	45	249—251	h	C ₂₀ H ₂₅ N ₂ O ₇ P	4
33	c	Me	2-NO ₂	39	125—135	e	C ₂₀ H ₂₅ N ₂ O ₇ P	4
34	d	Me	2-NO ₂	36	235 (dec.)	i	C ₂₂ H ₂₉ N ₂ O ₇ P	1
35	e	Me	2-NO ₂	10	174—177	a	C ₂₁ H ₂₅ N ₂ O ₇ P ^{g)}	4
36	f	Me	2-NO ₂	29	137 (dec.)	d	C ₂₃ H ₂₉ N ₂ O ₇ P	2
37	h	Me	2-NO ₂	31	122—123	a	C ₂₀ H ₂₅ N ₂ O ₇ P	4
38	i	Me	2-NO ₂	43	182—184	a	C ₂₁ H ₂₇ N ₂ O ₇ P ^{f)}	4
39	j	Me	2-NO ₂	39	198—199	j	C ₂₄ H ₂₉ N ₂ O ₇ P	1
40	m	Me	2-NO ₂	46	221—222.5	g	C ₁₉ H ₂₁ N ₂ O ₇ P	4

a) See Chart 1. b) Yield is after recrystallization or isolated (an oil). c) Solvents for recrystallization: a, AcOEt; b, ether; c, AcOEt-ether; d, AcOEt-iso-Pr₂O; e, MeOH-ether; f, 2-propanol-CHCl₃; g, AcOEt-CHCl₃; h, MeOH; i, EtOH; j, 2-propanol-ether; k, AcOEt-MeOH. d) All compounds were analyzed for C, H and N; the analytical results were within $\pm 0.4\%$ of the calculated values. e) Potency was evaluated as follows: 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; 5, effective at 1 mg/kg; 6, effective at 0.3 mg/kg (nifedipine: 6). The effective dose causes 25% lowering of blood pressure. f) 1/2 H₂O. g) 1/4 H₂O.

anesthesia and a polyethylene catheter filled with heparinized saline was inserted into the femoral artery and connected with a pressure transducer (Nihon Kohden MPU-0.5). Blood pressure measurements were started under restraint after the rats had recovered from anesthesia, and blood pressure levels were recorded continuously on a potentiometric recorder (Toa EPR-10A or EPR) via a preamplifier (Nihon Kohden AP-621G). After the blood pressure had become stable, the test compounds prepared as suspensions in 0.5% methylcellulose (MC) solution, were administered orally at various doses (0.3, 1, 3, 10, or 30 mg/kg).

Some of the compounds with potent antihypertensive activity in normotensive rats were tested for antihypertensive activity in SHR. Male SHR weighing 280—300 g were purchased at the age of 15 weeks and housed in our laboratory. Systolic blood pressure was measured by

TABLE II. Physical and Biological Properties of 1,4-Dihydropyridines (II); (Ar = R²-C₆H₄ or Heterocycles)

Compd. No.		R ¹	R ² (Ar)	Yield ^{b)} (%)	mp (°C)	Crystn. solvent ^{c)}	Formula ^{d)}	Antihypertensive potency ^{e)}
41	a	Me	2-CF ₃	35	209—211	c	C ₁₉ H ₂₁ F ₃ NO ₅ P	6
42	a	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	2-CF ₃	40	(Oil)		C ₂₈ H ₃₂ F ₃ N ₂ O ₅ P	4—5
43	b	Me	2-CF ₃	26	210—212	a	C ₂₁ H ₂₅ F ₃ NO ₅ P	2
44	b	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	2-CF ₃	31	(Oil)		C ₃₀ H ₃₆ F ₃ N ₂ O ₅ P	4—5
45	a	Me	2-OCHF ₂	48	192—193	a	C ₁₉ H ₂₂ F ₂ N ₂ O ₆ P	5
46	a	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	2-OCHF ₂	66	(Oil)		C ₂₈ H ₃₃ F ₂ N ₂ O ₆ P ^{f)}	4
47	b	Me	2-OCHF ₂	39	217—218	a	C ₂₁ H ₂₆ F ₂ N ₂ O ₆ P	1
48	b	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	2-OCHF ₂	41	(Oil)		C ₃₀ H ₃₇ F ₂ N ₂ O ₆ P	3—4
49	a	Me	2,3-Cl ₂	53	275—277	k	C ₁₈ H ₂₀ Cl ₂ NO ₅ P	3
50	b	Me	2,3-Cl ₂	40	167—168	a	C ₂₀ H ₂₄ Cl ₂ NO ₅ P	3
51	b	CH ₂ CH ₂ N(Me)CH ₂ C ₆ H ₅	2,3-Cl ₂	39	197—198	a	C ₂₉ H ₃₅ Cl ₂ N ₂ O ₅ P	4
52	a	Me		57	238—250	i	C ₁₈ H ₂₀ N ₃ O ₆ P	4
53	a	Me		36	106 (dec.)	a	C ₁₈ H ₂₈ N ₂ O ₅ SP	4

a) to f): See footnotes a) to f) in Table I.

TABLE III. Physical and Biological Properties of 1,4-Dihydropyridines (II); (Ar = R²-C₆H₄)

Compd. No.		R ¹	R ²	Yield ^{b)} (%)	mp (°C)	Crystn. solvent ^{c)}	Formula ^{d)}	Antihypertensive potency ^{e)}
54	a	Et	2-NO ₂	48	173—175	a	C ₁₉ H ₂₃ N ₂ O ₇ P	6
55	a	iso-Pr	2-NO ₂	47	159—161	c	C ₂₀ H ₂₅ N ₂ O ₇ P	4
56	a	iso-Bu	2-NO ₂	79	187 (dec.)	a	C ₂₁ H ₂₇ N ₂ O ₇ P	4
57	a	tert-Bu	2-NO ₂	55	120—124	c	C ₂₁ H ₂₇ N ₂ O ₇ P	3
58	a	CH ₂ CH=CH ₂	2-NO ₂	86	(Oil)		C ₂₀ H ₂₃ N ₂ O ₇ P	4
59	a	CH ₂	2-NO ₂	49	206—208	c	C ₂₁ H ₂₅ N ₂ O ₇ P	4
60	a	CH ₂ CH ₂ O-Pr	2-NO ₂	76	(Oil)		C ₂₂ H ₂₉ N ₂ O ₈ P ^{f)}	3
61	a	CH ₂ CH ₂ OCH ₂ C ₆ H ₅	2-NO ₂	72	(Oil)		C ₂₆ H ₂₉ N ₂ O ₈ P ^{f)}	5
62	a	Et	2-CF ₃	64	175—177	c	C ₂₀ H ₂₃ F ₃ NO ₅ P	5
63	a	CH ₂ CH=CH ₂	2-CF ₃	58	192—193	c	C ₂₁ H ₂₃ F ₃ NO ₅ P	4
64	a	CH ₂	2-CF ₃	52	225—225.5	a	C ₂₂ H ₂₅ F ₃ NO ₅ P	2
65	a		2-CF ₃	56	236—238	g	C ₂₃ H ₂₇ F ₃ NO ₅ P	2

a) to e): See footnotes a) to e) in Table I. f) H₂O.

the tail cuff plethysmographic method under mild restraint with a programmable sphygmomanometer (PS-802; Riken Kaihatsu). Before blood pressure measurements, rats were placed in a warm box at 35—37°C for 10 min. The test compounds were administered orally as described above. The dose in mg/kg which produced a 30% drop in blood pressure was calculated from the regression line as the ED₃₀ value (Table VI).

Results and Discussion

The antihypertensive activities of the new 1,4-dihydropyridine derivatives (II) having a

TABLE IV. Cyclic 1-Arylideneacetylphosphonates (7); (Ar = R²-C₆H₄ or Heterocycles)

Compd. No.		R ² (Ar)	Yield ^{b)} (%)	mp (°C)	IR ^{c)} (cm ⁻¹) COCH ₃	NMR (CDCl ₃) (COCH ₃) (E/Z)	Analysis (%)		
							Calcd (Found)	C	H
7an	a	3-NO ₂	19	144—145	1700	2.31, —	50.17 (50.26)	4.53 (4.66)	4.50 (4.54)
7ap	a	2-NO ₂	34	134—143	1700	2.32, 2.60 (10/1)	50.17 (50.21)	4.53 (4.58)	4.50 (4.50)
7aq	a	2-CF ₃	44	(Oil)	1700	2.12, 2.58 (4/1)	50.31 (50.36)	4.22 (4.03)	
7ar	a	2-OCHF ₂	44	85—87	1700	2.24, —	50.61 (50.60)	4.55 (4.63)	
7as	a	2,3-Cl ₂	18	93—95	1705	2.19, —	46.59 (46.71)	3.91 (4.03)	
7at	a		8	(Oil)	1695				^{d)}
7au	a		7	(Oil)	1700	2.22, 2.59 (3/1)			^{d)}
7bn	b	3-NO ₂	24	150—151	1705	2.33, —	53.10 (52.95)	5.34 (5.38)	4.12 (4.01)
7bp	b	2-NO ₂	29	144—146	1695	2.34, 2.61 (5/4)	53.10 (53.06)	5.34 (5.33)	4.12 (4.19)
7bq	b	2-CF ₃	35	80—87	1700	2.15, 2.58 (5/1)	53.05 (53.06)	5.01 (5.09)	
7br	b	2-OCHF ₂	27	(Oil)	1700	2.25, 2.56 (8/1)			^{d)}
7bs	b	2,3-Cl ₂	25	117—119	1710	2.21, —	49.61 (49.63)	4.72 (4.76)	
7cn	c	3-NO ₂	27	120—122	1705	2.27, —	53.10 (53.22)	5.34 (5.40)	4.12 (4.04)
7cp	c	2-NO ₂	25	115—117	1705	2.17, —	53.10 (53.08)	5.34 (5.43)	4.12 (4.17)
7dn	d	3-NO ₂	46	96—97	1710	2.31, —	55.59 (55.53)	6.04 (6.26)	3.81 (3.77)
7dp	d	2-NO ₂	46	(Oil)	1700	2.32, 2.60 (7/3)			^{d)}
7en	e	3-NO ₂	24	152—154	1700	2.33, —	54.71 (54.62)	5.17 (5.22)	3.99 (4.02)
7ep	e	2-NO ₂	26	121—123	1675	2.32, —	54.71 (54.77)	5.17 (5.25)	3.99 (4.05)
7fn	f	3-NO ₂	26	125—129	1700	2.31, —	56.99 (56.89)	6.00 (5.92)	3.69 (3.68)
7fp	f	2-NO ₂	46	(Oil)	1700	2.32, 2.60 (7/3)			^{d)}
7gn	g	3-NO ₂	18	123—125	1700	2.39, —	51.70 (51.62)	4.96 (5.06)	4.31 (4.38)
7gp	g	2-NO ₂	19	83—85	1690	2.23, —	51.70 (51.72)	4.96 (4.93)	4.31 (4.28)
7hn	h	3-NO ₂	21	99—101	1690	2.31, —	53.10 (53.10)	5.35 (5.47)	4.13 (4.18)
7hp	h	2-NO ₂	40	(Oil)	1700	2.30, 2.60 (3/1)			^{d)}
7in	i	3-NO ₂	15	91—94	1695	2.29, 2.41 (3/1)	54.39 (54.46)	5.71 (5.79)	3.96 (4.01)

TABLE IV. (continued)

Compd. No.		R ² (Ar)	Yield ^{b)} (%)	mp (°C)	IR ^{c)} (cm ⁻¹) COCH ₃	NMR (CDCl ₃) (COCH ₃) (E/Z)	Analysis (%) Calcd (Found)		
							C	H	N
7ip	i	2-NO ₂	20	107—108	1700	2.25, —	54.39 (54.35)	5.71 5.85	3.96 (3.94)
7jn	j	3-NO ₂	37	100—101	1695	2.25, —	50.12 (50.07)	4.87 4.99	3.08 (2.91)
7jp	j	2-NO ₂	33	(Oil)	1700	2.19, —		^{d)}	
7kn	k	3-NO ₂	14	180—183	1680	2.36, 2.61 (3/1)	54.39 (54.63)	5.71 5.75	3.96 (4.07)
7mp	m	2-NO ₂	23	(Oil)	1710	2.26, —		^{d)}	

a) See footnote a) in Table I. b) Isolated yield. Yield of an oil which was first isolated by chromatography. c) KBr (crystals) or film (an oil). d) A sample sufficiently pure for analysis was not obtained.

TABLE V. Cyclic Acetonylphosphonates 4

Compd. No.	bp (°C) (mmHg) or mp (°C) ^{a)}	Yield ^{b)} (%)	IR ^{c)} max (cm ⁻¹)	NMR (CDCl ₃) -CH ₂ COCH ₃	Formula ^{d)}	MS (m/z) M ⁺ ^{e)}	Analysis (%) Calcd (Found)	
							C	H
4a	163—165 (1)	35	1710 1270	2.38 (3H, s) 3.21 (2H, d)	C ₆ H ₁₁ O ₄ P · 1/2 H ₂ O	178 (25)	38.50 (38.67)	6.46 (6.59)
4b	91—92 (Ether)	51	1705 1270	2.39 (3H, s) 3.20 (2H, d)	C ₈ H ₁₅ O ₄ P	206 (16)	46.60 (46.48)	7.33 (7.01)
4c	146—148 (1)	55	1710 1265	2.35 (3H, s) 3.15 (2H, d)	C ₈ H ₁₅ O ₄ P · 1/2 H ₂ O	206 (35)	44.64 (45.04)	7.49 (7.12)
4d	161—165 (0.5)	46	1710 1275	2.38 (3H, s) 3.19 (2H, d)	C ₁₀ H ₁₉ O ₄ P · 1/2 H ₂ O	234 (6)	49.38 (49.27)	8.29 (8.26)
4e	105—106 (AcOEt-ether)	46	1710 1270	2.37 (3H, s) 3.17 (2H, d)	C ₉ H ₁₅ O ₄ P	218 (5)	49.54 (49.41)	6.93 (6.87)
4f	178—183 (0.5)	53	1710 1280	2.38 (3H, s) 3.19 (2H, d)	C ₁₁ H ₁₉ O ₄ P · 1/4 H ₂ O	246 (3)	52.69 (52.82)	7.84 (7.90)
4g	81—82 (Ether)	30	1710 1260	2.39 (3H, s) 3.21 (2H, d)	C ₇ H ₁₃ O ₄ P	192 (35)	43.76 (43.67)	6.82 (6.92)
4h	152—156 (0.5)	40	1710 1280	2.36 (3H, s) 3.18 (2H, d)	C ₈ H ₁₅ O ₄ P · 3/4 H ₂ O	206 (9)	43.74 (44.03)	7.57 (7.93)
4i	158—162 (0.5)	51	1710 1280	2.36 (3H, s) 3.17 (2H, d)	C ₉ H ₁₇ O ₄ P · 3/4 H ₂ O	220 (10)	46.25 (46.60)	7.98 (7.69)
4j	(Oil) ^{f)}	20	1760—1730 1710	2.31 (3H, s) 3.19 (2H, d)				
4k	151—153 (0.5)	38	1710 1265	2.36 (3H, s) 3.22 (2H, d)	C ₉ H ₁₇ O ₄ P	220 (33)	49.09 (49.05)	7.78 (7.86)
4m	150—153 (0.5)	10	1715 1270	2.40 (3H, s) 3.23 (2H, d)	C ₇ H ₁₁ O ₄ P · 1/2 H ₂ O	190 (16)	42.20 (42.16)	6.07 (5.43)

a) Solvents for recrystallization. b) Isolated yield after chromatography. c) KBr (crystals) or film (an oil). d) The oil show low hygroscopicity. e) M⁺ (relative intensity, %). f) The oil, which was isolated by chromatography, could not be distilled and a sample sufficiently pure for analysis was not obtained.

cyclic phosphonate group at the 5-position in the 1,4-dihydropyridine (1,4-DHP) ring are shown in Tables I to III.

The 1,4-dihydropyridine-5-phosphonates (I), as mentioned in the previous paper,²⁾ had milder antihypertensive activity than the corresponding carboxylate compounds, but several

TABLE VI. Antihypertensive Activity of the Active Compounds, **31** (DHP-218), **41**, **45**, **54**, **61**, and Nifedipine in SHR

Compound	R ¹	R ²	ED ₃₀ ^{a)} (mg/kg)	Relative ^{b)} potency
31 (DHP-218)	Me	2-NO ₂	0.2	7.5
41	Me	2-CF ₃	0.6	2.5
45	Me	2-OCHF ₂	1.5	1.0
54	Et	2-NO ₂	0.4	3.8
61	CH ₂ CH ₂ OCH ₂ C ₆ H ₅	2-NO ₂	0.7	2.1
Nifedipine			1.5	1.0

a) See pharmacology section. b) Potency relative to that of nifedipine.

Fig. 2. Antihypertensive Activity of **31** (DHP-218), **41** and Nifedipine in SHR (1 mg/kg, *p.o.*)
 —, control ---○, DHP-218; ----△, **41**;
 -----●, nifedipine.

compounds in the present group of cyclic phosphonate derivatives (II) surprisingly showed excellent antihypertensive activity, superior to that of nifedipine.

Table I lists the 4-(2- or 3-nitrophenyl)-1,4-dihydropyridines which contain various cyclic phosphonates at the 5-position. Of the compounds with a 3-nitro substituent, 4,6-dimethyl (**c**), 5-methyl (**g**) and nonsubstituted (**a**) 2-oxo-1,3,2-dioxaphosphorinan-2-yl derivatives were strongly active, and of the compounds with a 2-nitro substituent, the phosphonate (**a**) (**31**) showed the most potent antihypertensive activity in this series. In both cases, the 5,5-dimethyl (**b**), 5-ethyl (**h**) and 5-isopropyl (**i**) derivatives were moderately active, and the 5,5-diethyl (**d**), 5,5-trimethylene (**e**), and 5,5-pentamethylene (**f**) derivatives were less active, while the 5,5-bis(ethoxycarbonyl) (**j**) derivative was essentially inactive. The compounds having five-membered (**k**) or seven-membered (**m**) ring phosphonates showed mild activity. In general, the activity decreased with the size of the substituents of cyclic phosphonates, especially in the disubstituted six-membered cyclic phosphonates.

Of the substituents (Ar) at the 4-position in 1,4-DHP, seven substituents containing phenyl and heterocyclic rings were selected on the basis of the result with dialkyl phosphonates (I)²⁾ (Tables I and II). Among the substituents (R²) on the phenyl ring, ortho

substituents were most active in the compounds having phosphonate (**a**) and a methyl ester at R^1 , the order of potency being 2-NO₂, 2-CF₃, 2-OCHF₂, 2,3-Cl₂, and 3-NO₂. Heterocyclic substituents showed moderate activity. On the other hand, the order of potency of compounds possessing cyclic phosphonate (**b**) was 2-NO₂, 3-NO₂, 2,3-Cl₂, 2-CF₃, and 2-OCHF₂. However, with a 2-(*N*-benzyl-*N*-methylamino)ethyl ester moiety at R^1 , variation of the substituent (R^2) did not appreciably change the activity of the compounds.

Varying the ester substituents (R^1) at the 3-position of 1,4-DHP, with a cyclic phosphonate (**a**) and 2-nitrophenyl substituent, weakened the activity with increasing substituent size, except for 2-benzyloxyethyl ester (Table III). The order of activity was methyl, ethyl, allyl, 2-benzyloxyethyl, iso-Pr, iso-Bu, cyclopropylmethyl, *tert*-Bu, and 2-propoxyethyl. With 2-trifluoromethylphenyl as a substituent, similar results were obtained. The 2-(*N*-benzyl-*N*-methylamino)ethyl ester, which showed potent activity in the dialkyl phosphonates (I), had weaker activity than the methyl and ethyl esters.

Some of the effective 1,4-dihydropyridines (II) were selected from those listed in Tables I to III, and their antihypertensive activities were examined in unanesthetized SHR. Among them, the five compounds listed in Table VI showed activity superior or comparable to that of nifedipine. The most active compound **31** (DHP-218) was approximately seven times more potent than nifedipine and had longer lasting action. DHP-218 also exhibited potent antihypertensive activities in other hypertensive rats, as well as cats, and dogs with normal blood pressure.⁷⁾ The time courses of antihypertensive effects of DHP-218, **41**, and nifedipine are shown in Fig. 2, after an oral dose of 1 mg/kg. DHP-218 was also shown to have a selective vasodilatory effect due to calcium antagonism with the pA_2 value of 9.11⁸⁾ (nifedipine: pA_2 9.58). Despite its weaker vasodilatory action than that of nifedipine *in vitro*, the oral administration of DHP-218 produced a much more potent and long-lasting antihypertensive effect. This might be due partly to its good bioavailability (dogs) and its lower serum protein binding (rats and dogs).⁹⁾ The structure of DHP-218 differs from that of nifedipine only in that the methoxycarbonyl moiety at the 5-position is replaced by the cyclic phosphonate (**a**). This presumably makes DHP-218 more hydrophilic than nifedipine. Actually, the water solubility of DHP-218 was approximately 10 times greater than that of nifedipine, and the log *P* values¹⁰⁾ of DHP-218 and nifedipine were 1.3 and 2.4, respectively. The *Rm* values,^{11,12)} which are parameters of lipophilicity, are -0.32 (DHP-218) and 0.00 (nifedipine); drugs with lower values are less lipophilic. These values substantiate the above discussion. Similar characteristics have been demonstrated in the β -blockers,¹³⁾ atenolol and nadolol.

The results of acute oral toxicity tests⁹⁾ of DHP-218 in mice and rats were very similar to those of nifedipine; consequently the safety margin is wide. DHP-218 was therefore selected for further development and clinical evaluation.

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. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian YX-200 spectrometer. Chemical shifts are given in δ (ppm) with tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra (MS) were measured on a Hitachi RMU-6M instrument. Column chromatography was performed on Wakogel C-200.

General Procedure for Cyclic Phosphites (3)⁶⁾—Method A: Equimolar quantities of trimethylphosphite and the appropriate diol (**1**) were heated at about 100 °C until reflux began. The methanol was removed by distillation at atmospheric pressure in an oil bath at temperatures up to 130 °C, and the desired product was obtained by reduced pressure distillation. [3, bp °C (mmHg), yield (%): **3a**, 63–68 (20), 26; **3b**, 65–70 (13), 49; **3c**, 85–88 (25), 34; **3d**, 135–136 (15), 32; **3e**, 105–115 (26), 34; **3f**, 107–118 (10), 31; **3g**, 75–85 (45), 38; **3h**, 83–88 (18), 42; **3i**, 85–97 (15), 46; **3k**, 58–60 (8), 31; **3m**, 60–65 (20), 14.

Method B: A diol (**1**) (1 mol) and triethylamine (202 g, 2 mol) were added dropwise to a well-stirred, ice-cooled

ether-CH₂Cl₂ solution (1000 ml–300 ml) of phosphorus trichloride (87 ml, 1 mol). The mixture was stirred for an additional 2 h at room temperature. The triethylamine hydrochloride was removed by filtration and washed with ether, and the filtrate and washing were combined and concentrated to dryness. The residue was distilled to give the corresponding **2** in ca. 40% yield. A solution of absolute methanol (14.1 g, 0.44 mol) and triethylamine (40.5 g, 0.4 mol) in 400 ml of dry ether was added dropwise to a well-stirred, ice-cooled dry ether solution of **2** (0.4 mol). The mixture was stirred for an additional 2 h at room temperature and then filtered. The residue was washed with ether, and the filtrate and washing were combined and were concentrated to dryness. The residue was distilled to give the corresponding cyclic phosphite (**3**) in high yield.

The cyclic phosphites **3** were prepared by one of the two methods described above.

General Procedure for Cyclic Acetonylphosphonates (4)—Bromoacetone (0.5 mol) and a cyclic phosphite **3** (0.5 mol) were mixed and stirred at room temperature. An exothermic reaction occurred, and the reaction temperature rose to 80–120 °C. After the evolution of methyl bromide gas had almost ceased, the mixture was heated to 80 °C for an additional 1 h, then evaporated *in vacuo*. The residual oil was diluted with AcOEt (500 ml) and extracted with cold 1 N NaOH (3 × 250 ml). The aqueous phase was neutralized with AcOH, extracted with CHCl₃ (3 × 250 ml) by salting-out, dried (MgSO₄), and evaporated *in vacuo*. The residue was chromatographed on silica gel with hexane–AcOEt to afford the corresponding **4** in 10–55% yield as an oil or crystals. The oil obtained was distilled *in vacuo*, and the crystals were recrystallized from the solvents listed in Table V. All these cyclic acetonylphosphonates **4** were characterized by IR and NMR analyses.

A typical example is described below.

2-Acetyl-2-oxo-1,3,2-dioxaphosphorinane (4a)—Bromoacetone (61.7 g, 0.45 mol) and phosphite **3a** (61.2 g, 0.45 mol) were mixed and stirred at 0 °C. An exothermic reaction occurred, and then reaction temperature rose to 80 °C. When the evolution of methyl bromide gas had almost ceased, the mixture was heated to 60 °C for 1 h, then evaporated *in vacuo*. The residual oil was diluted with AcOEt (400 ml) and extracted with water (3 × 250 ml). The aqueous phase was extracted with CHCl₃ (3 × 250 ml) by salting-out, dried (MgSO₄), and evaporated *in vacuo*. The residue obtained was chromatographed on silica gel with hexane–AcOEt (1 : 1—AcOEt only) to afford **4a** (35%) as an oil. The product (**4a**) obtained was purified by distillation, bp 163–165 °C (1 mmHg). MS *m/z* (%): 178 (M⁺, 25.7), 136 (100). NMR (CDCl₃) δ: 1.96–2.22 (2H, m, CH₂), 2.38 (3H, s, COCH₃), 3.21 (2H, d, *J* = 22 Hz, PCH₂), 4.26–4.65 (4H, m, 2 × OCH₂).

Preparation of 2-Acetyl-5,5-bis(ethoxycarbonyl)-2-oxo-1,3,2-dioxaphosphorinane (4j)—The known intermediate **5** was prepared according to the procedure described by Lutsenko and Kirilov.⁵ A solution of 2,2-bis(hydroxymethyl)malonate (30.5 g) and triethylamine (28 g, 2 eq) in dry ether (100 ml) was added dropwise to a stirred solution of **5** in dry ether (250 ml) at –5 °C over a period of 1 h. After the addition was complete, the mixture was removed from the ice-bath and stirred for 15 h at room temperature. The precipitate was collected by filtration and, washed with ether. The filtrate and washing were combined and concentrated to dryness. The residue obtained was chromatographed on silica gel with hexane–AcOEt to afford **4j** (8.9 g, 20%) as a pale yellow oil. IR (film): 1760–1730 (C=O, CO₂Et) cm^{–1}. NMR (CDCl₃) δ: 1.29 (3H, t, *J* = 7.5 Hz, CH₂CH₃), 1.31 (3H, t, *J* = 7.5 Hz, CH₂CH₃), 2.31 (3H, s, COCH₃), 3.19 (2H, d, *J* = 23 Hz, PCH₂), 4.25 (2H, q, *J* = 7.5 Hz, CH₂CH₃), 4.28 (2H, q, *J* = 7.5 Hz, CH₂CH₃), 4.78 (2H, d, *J* = 11 Hz, OCH₂), 4.79 (2H, d, *J* = 12 Hz, OCH₂).

General Procedure for Cyclic 1-Arylideneacetonylphosphonates (7)—A solution of a cyclic acetonylphosphonate (**4**, 0.1 mol) and an arylaldehyde (**6**, 0.1 mol) in benzene (200 ml) containing a catalytic amount of piperidine·AcOH salt was refluxed for 12–24 h with continuous removal of water by means of a Dean–Stark apparatus. The benzene solution was washed with water, aqueous NaOH, aqueous NaHSO₃, and water, then dried (MgSO₄) and concentrated to dryness. The residue obtained was purified by chromatography on silica gel with hexane–AcOEt to give the corresponding **7** in 14–46% yield as a mixture of *E* (major) and *Z* isomers (listed in Table IV). The crystals obtained were recrystallized from the indicated solvents. All these compounds **7** were characterized by IR and NMR analyses.

A typical example is given below.

2-[1-(2-Nitrobenzylidene)acetyl]-2-oxo-1,3,2-dioxaphosphorinane (7ap)—A solution of **4a** (8.5 g), 2-nitrobenzaldehyde (7.2 g) and piperidine·AcOH (1.72 g, 0.25 eq) in benzene (100 ml) was azeotropically refluxed for 16 h with stirring. The benzene solution was treated as mentioned above. The residue obtained was chromatographed on silica gel (150 g) with hexane–AcOEt (4 : 1–1 : 4, v/v) to give **7ap** (3.66 g, 34%) as crystals. An analytical sample was recrystallized from AcOEt, mp 134–143 °C (a mixture of *E* and *Z* isomers, 10/1). IR (KBr): 1700 (C=O), 1575, 1350, 1270, 1070 cm^{–1}. NMR (CDCl₃) δ: 1.90–2.04 (1H, m, >CH), 2.20–2.45 [1H, m, >CH, and total 3H, 2.32 (s, COCH₃, *E* isomer) and 2.61 (s, COCH₃, *Z* isomer), ratio of 10/1], 4.10–4.25 and 4.48–4.65 (total 4H, m, 2 × OCH₂), 7.23–7.28 (1H, m, ArH), 7.57–7.73 (2H, ArH), 7.90 [ca. 1H, d, *J* = 24 Hz, PC=CH(*E*)], 8.22–8.27 (1H, m, ArH).

In the above chromatography, the first component was the *E*-isomer, mp 155–156 °C (from AcOEt), and the final component was the *Z*-isomer, mp 174–175 °C (from AcOEt). **7ap** (*E*): Anal. Found: C, 50.06; H, 4.59; N, 4.49. IR (KBr): 1695, 1600 cm^{–1}. NMR (CDCl₃) δ: 2.32 (3H, s, COCH₃), 7.90 [1H, d, *J* = 23.5 Hz, =CH–(*E*)^{14b}]. **7ap** (*Z*): Anal. Found: C, 50.07; H, 4.44; N, 4.52. IR (KBr): 1680, 1595 cm^{–1}. NMR (CDCl₃) δ: 2.61 (3H, s, COCH₃), 8.32

[1H, d, $J=48$ Hz, =CH- (Z)].

General Procedure for 1,4-Dihydropyridines (II)—A solution of a cyclic 1-arylideneacetonlphosphonate (7, 0.01 mol) and a 3-aminocrotonate (8, 0.01 mol) in 2-propanol (20 ml) was refluxed for 3–30 h with stirring. The solvent was removed, and the residue was purified by crystallization from a suitable solvent (AcOEt or ether) or by chromatography on silica gel with hexane–AcOEt to give the corresponding 1,4-dihydropyridine (II) in 10–86% yields. When R^1 of the carboxylate was a basic ester [2-(*N*-benzyl-*N*-methylamino)ethyl or 2-(*N,N*-dimethylamino)ethyl], 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 , then water, dried ($MgSO_4$) and concentrated to give crude II. The residue obtained was purified as described above.

Typical examples are given below.

2-(*N*-Benzyl-*N*-methylamino)ethyl 2,6-Dimethyl-5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (12)—A solution of **7bn** (1.19 g) and 2-(*N*-benzyl-*N*-methylamino)-ethyl 3-aminocrotonate (0.868 g) in 2-propanol (20 ml) was refluxed for 5 h with stirring. The solvent was removed *in vacuo*, then the residue was diluted with AcOEt (20 ml) and first extracted with 15 ml of 1 *N* HCl then twice with 10 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 chromatographed on silica gel (70 g) with hexane–AcOEt to give **12** (0.875 g, 44%) as an oil. The oil obtained was crystallized from ether, and recrystallization from AcOEt–ether gave yellow crystals (0.56 g, 28%), mp 125–126 °C. *Anal.* Calcd for $C_{29}H_{36}N_3O_7P \cdot 1/2H_2O$: C, 60.20; H, 6.45; N, 7.07. Found: C, 60.21; H, 6.64; N, 7.07. *MS* m/z (%): 569 (M^+ , 5.6), 134 (100). IR (KBr): 3290, 3225, 3105, 1700, 1650, 1535, 1355, 1250, 1065 cm^{-1} . NMR ($CDCl_3$) δ : 0.87 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.22 (3H, s, C_2-CH_3), 2.30 (3H, s, NCH_3), 2.39 (3H, d, $J_{P-H}=2.5$ Hz, C_6-CH_3), 2.68 (2H, t, $J=6$ Hz, NCH_2), 3.41–3.74 [4H, (2H, m, OCH_2), 3.52 (2H, s, NCH_2)], 4.14–4.28 (4H, m, $2 \times POCH_2$), 4.94 (1H, d, $J_{P-H}=11$ Hz, C_4-H), 6.28 (1H, br, NH), 7.26–7.36 (6H, m, ArH), 7.64–7.69 (1H, m, ArH), 7.96–8.01 (1H, m, ArH), 8.11 (1H, t, $J=2$ Hz, ArH).

Methyl 2,6-Dimethyl-5-(5-methyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (21)—A solution of **7gn** (1.15 g) and methyl 3-aminocrotonate (0.41 g) in 2-propanol (20 ml) was refluxed for 5 h with stirring. The solvent was removed *in vacuo*, and the residue was crystallized from ether to give **21**. Recrystallization from 2-propanol–ether gave yellow crystals (0.65 g, 44%), mp 177–179 °C. *Anal.* Calcd for $C_{19}H_{23}N_3O_7P$: C, 54.03; H, 5.49; N, 6.63. Found: C, 53.72; H, 5.63; N, 6.45. IR (KBr): 3300, 3250, 3210, 1685, 1645, 1530, 1350, 1250 cm^{-1} . NMR ($CDCl_3$) δ : 0.83 (3H, d, $J=6$ Hz), 2.15–2.40 [7H, m, 2.32 (3H, s), 2.34 (3H, d, $J=2.5$ Hz)], 3.67 (3H, s), 3.95–4.27 (4H, m), 4.86 (1H, d, $J=12$ Hz), 6.72 (1H, br), 7.37 (1H, t, $J=8$ Hz), 7.62 (1H, d, $J=8$ Hz), 7.95–8.04 (1H, m), 8.09 (1H, t, $J=2$ Hz).

Methyl 2,6-Dimethyl-5-(4,4,5,5-tetramethyl-2-oxo-1,3,2-dioxaphospholan-2-yl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (29)—A solution of **7kn** (0.75 g) and methyl 3-aminocrotonate (0.244 g) in 2-propanol (10 ml) was refluxed for 3 h with stirring. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel to afford **29** as crystals (0.36 g). Recrystallization from AcOEt gave yellow crystals (0.295 g, 31%), mp 236–237 °C. *Anal.* Calcd for $C_{21}H_{27}N_3O_7P$: C, 56.00; H, 6.04; N, 6.22. Found: C, 56.06; H, 6.18; N, 6.25. IR (KBr): 3290, 3220, 3110, 1700, 1655, 1530, 1355, 1235 cm^{-1} . NMR ($CDCl_3$) δ : 1.22 (3H, s), 1.26 (3H, s), 1.46 (3H, s), 1.48 (3H, s), 2.28 (3H, d, $J=2.5$ Hz), 2.32 (3H, s), 3.67 (3H, s), 4.94 (1H, d, $J=11$ Hz), 6.31 (1H, d, $J=5$ Hz), 7.38 (1H, t, $J=8$ Hz), 7.64 (1H, d, $J=8$ Hz), 7.98–8.03 (1H, m), 8.08 (1H, t, $J=2$ Hz).

Methyl 2,6-Dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate (31, DHP-218)—A solution of **7ap** (4.04 g) and methyl 3-aminocrotonate (1.49 g) in 2-propanol (80 ml) was refluxed for 20 h with stirring. After removal of the solvent, the residue was chromatographed on silica gel with hexane–AcOEt to afford **31** (3.16 g) as crystals. Recrystallization from $CHCl_3$ –AcOEt gave yellow prisms (2.86 g, 54%), mp 245–247 °C (dec.). *Anal.* Calcd for $C_{18}H_{21}N_3O_7P$: C, 52.95; H, 5.18; N, 6.86. Found: C, 52.86; H, 5.33; N, 6.73. *MS* m/z (%): 408 (M^+ , 8.7), 391 (100). IR (KBr): 3280, 3200, 3080, 1690, 1645, 1520, 1350, 1250, 1100 cm^{-1} . NMR ($CDCl_3$) δ : 1.65–1.78 (1H, m), 2.27 (3H, s), 2.34–2.64 [4H, m, 2.47 (3H, d, $J=2.4$ Hz)], 3.57 (3H, s), 3.82–4.68 (4H, m), 5.60 (1H, d, $J=10$ Hz), 6.01 (1H, br), 7.18–7.30 (1H, m), 7.45 (1H, t, $J=8$ Hz), 7.52 (1H, d, $J=8$ Hz), 7.70 (1H, d, $J=8$ Hz).

Methyl 2,6-Dimethyl-4-(2-nitrophenyl)-5-(2-oxo-4,7-dihydro-1,3,2-dioxaphosphepin-2-yl)-1,4-dihydropyridine-3-carboxylate (40)—A solution of **7mp** (1.30 g) and methyl 3-aminocrotonate (0.461 g) in 2-propanol (15 ml) was refluxed for 10 h with stirring. After removal of the solvent, the residue was chromatographed on silica gel to afford **40** (0.774 g, 46%) as yellow prisms (from $CHCl_3$ –AcOEt), mp 221–222.5 °C. *Anal.* Calcd for $C_{19}H_{21}N_3O_7P$: C, 54.29; H, 5.04; N, 6.66. Found: C, 54.33; H, 5.04; N, 6.59. IR (KBr): 3280, 3220, 3090, 1695, 1650, 1535, 1365, 1260, 1050 cm^{-1} . NMR ($CDCl_3$) δ : 2.27 (3H, s), 2.31 (3H, d, $J=2.6$ Hz), 3.56 (3H, s), 4.04–4.30 (1H, m), 4.48–4.76 (3H, m), 5.55–5.78 (3H, m), 6.34 (1H, br), 7.18–7.32 (1H, m), 7.40–7.62 (2H, m), 7.69 (1H, dd, $J=1.5, 8$ Hz).

Methyl 2,6-Dimethyl-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate (41)—A solution of **7aq** (1.70 g) and methyl 3-aminocrotonate (0.586 g) in 2-propanol (20 ml) was refluxed for 22 h with stirring. After removal of the solvent, the residue was chromatographed on silica gel to afford **41** (0.76 g, 35%) as colorless prisms (from AcOEt–ether), mp 209–211 °C. *Anal.* Calcd for $C_{19}H_{21}F_3NO_5P$: C, 52.91;

H, 4.91; N, 3.25. Found: C, 52.94; H, 5.15; N, 3.16. IR (KBr): 3280, 3220, 3100, 1695, 1645, 1240, 1105 cm^{-1} . NMR (CDCl_3) δ : 1.62—1.80 (1H, m), 2.10—2.30 [4H, m, 2.23 (3H, s)], 2.32 (3H, d, $J=2.4$ Hz), 3.60 (3H, s), 3.90—4.25 (2H, m), 4.32—4.62 (2H, m), 5.31 (1H, d, $J=10$ Hz), 6.98 (1H, d, $J=5$ Hz), 7.18—7.57 (4H, m).

Methyl 4-(2,1,3-Benzoxadiazol-4-yl)-2,6-dimethyl-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate (52)—A solution of **7at** (0.85 g) and methyl-3-aminocrotonate (0.32 g) in 2-propanol (20 ml) was refluxed for 20 h with stirring. After removal of the solvent, the residue was chromatographed on silica gel with hexane–AcOEt to afford **52** (0.64 g, 57%) as crystals, mp 248—250 $^{\circ}\text{C}$ (from ethanol). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_6\text{P}$: C, 53.34; H, 4.97; N, 10.37. Found: C, 53.47; H, 5.01; N, 10.22. IR (KBr): 3290, 3210, 3095, 1700, 1645, 1240, 1215, 1050 cm^{-1} . NMR (CDCl_3) δ : 1.62—1.78 (1H, m), 2.06—2.27 (1H, m), 2.31 (3H, s), 2.35 (3H, d, $J=2.5$ Hz), 3.59 (3H, s), 3.64—3.86 (1H, m), 4.12—4.63 (3H, m), 5.30 (1H, d, $J=10$ Hz), 6.16 (1H, br), 7.23—7.34 (2H, m), 7.63 (1H, dd, $J=1.5, 8$ Hz).

2-Benzyloxyethyl 2,6-Dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate (61)—A solution of **7ap** (1.56 g) and 2-benzyloxyethyl 3-aminocrotonate (1.41 g) in 2-propanol (20 ml) was refluxed for 20 h with stirring. After removal of the solvent, the residue was purified by chromatography on silica gel with hexane–AcOEt to afford **61** (1.91 g, 72%) as an oil. Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_8\text{P} \cdot \text{H}_2\text{O}$: C, 57.14; H, 5.72; N, 5.13. Found: C, 57.18; H, 5.36; N, 5.15. MS m/z (%): 528 (M^+ , 3.1), 91 (100). IR (film): 3400, 3280, 3200, 3080, 1695, 1640, 1530, 1355, 1230, 1050 cm^{-1} . NMR (CDCl_3) δ : 1.62—1.78 (1H, m), 2.18—2.48 [7H, m, 2.24 (3H, s), 2.37 (3H, d, $J=2.5$ Hz)], 3.56—3.76 (2H, m), 3.88—4.62 [8H, m, 4.50 (2H, s)], 5.69 (1H, d, $J=11$ Hz), 6.91 (1H, d, $J=5$ Hz), 7.16—7.36 (6H, m), 7.43 (1H, t, $J=8$ Hz), 7.53 (1H, d, $J=8$ Hz), 7.70 (1H, d, $J=8$ 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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- 9) Data are not presented.
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- 11) The R_m value was calculated by means of the formula $R_m = \log(1/R_f - 1)$. The R_f value was determined by reversed-phase thin-layer chromatography on silica gel (60 F₂₅₄ silanized by Merck) in acetone–water (60:40), and represents the mean of 5 determinations.
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