Synthesis of 1,4-Dihydropyridine-5-phosphonates and Their Calcium-Antagonistic and Antihypertensive Activities: Novel Calcium-Antagonist 2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate Hydrochloride Ethanol (NZ-105) and Its Crystal Structure[1)]

Ryozo SAKODA,* Yoshimasa KAMIKAWAJI, and Kiyotomo SETO

Central Research Institute, Nissan Chemical Ind. Co., Ltd., 722–1, Tsuboi-cho, Funabashi-shi, Chiba 274, Japan. *Received December 9, 1991*

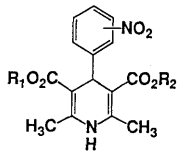
The effect of the 3-carboxylic-ester variation in 2,2-dimethyltrimethylene 3-alkoxycarbonyl-4-aryl-1,4-dihydro-2,6-dimethyl-5-pyridinephosphonates (1) was investigated with relation to the calcium-antagonistic and antihypertensive activities: the analogs containing the alkyl groups of not more than 12 carbons and an amino functionality in the carboxylic-ester moiety were synthesized to be examined for biological activities. Among them, 2-[benzyl(phenyl)amino]-ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridine-carboxylate hydrochloride ethanol (NZ-105) showed particularly beneficial activities and was selected for further pharmacological studies and clinical development. Some aspects of the structure–activity relationships and solid-state structure of NZ-105 by X-ray crystallographic analysis were described.

Keywords 1,4-dihydropyrine-5-phosphonate; NZ-105; calcium antagonist; antihypertensive activity; structure–activity relationship; X-ray analysis

Introduction

During the studies on the search for the biologically active 1,4-dihydropyridine-3,5-dicarboxylates, which have been motivated by the discovery of the pharmacological importance on nifedipine[2)] of a representative prototype (Chart 1), replacement of one of the carboxylic ester functionalities by a phosphonate has recently been tried as a new approach to molecular design, and some types of 1,4-dihydropyridine(DHP)-5-phosphonates have been revealed to maintain the calcium-antagonistic and antihypertensive activities.[3,4)] Also, in our initial works[4)] on the structure–activity relationships in the phosphonic acid derivatives (amide and ester types), the cyclic phosphonates were found to possess considerably high activity and to be worthy of further investigation (Chart 2).

As part of a general program aimed at the discovery of second generation calcium antagonists, we have focused on the 2,2-dimethyltrimethylene DHP-5-phosphonates (**1**) and successfully found a promising calcium antagonist in the



nifedipine : 2-NO_2, R_1 = R_2 = CH_3
nisoludipine : 2-NO_2, R_1 = CH_3, R_2 = $CH(CH_3)_2$
nicardipine : 3-NO_2, R_1 = CH_3, R_2 = $CH_2CH_2N(CH_3)CH_2Ph$
nimodipine : 3-NO_2, R_1 = $CH(CH_3)_2$, R_2 = $CH_2CH_2OCH_3$

Chart 1

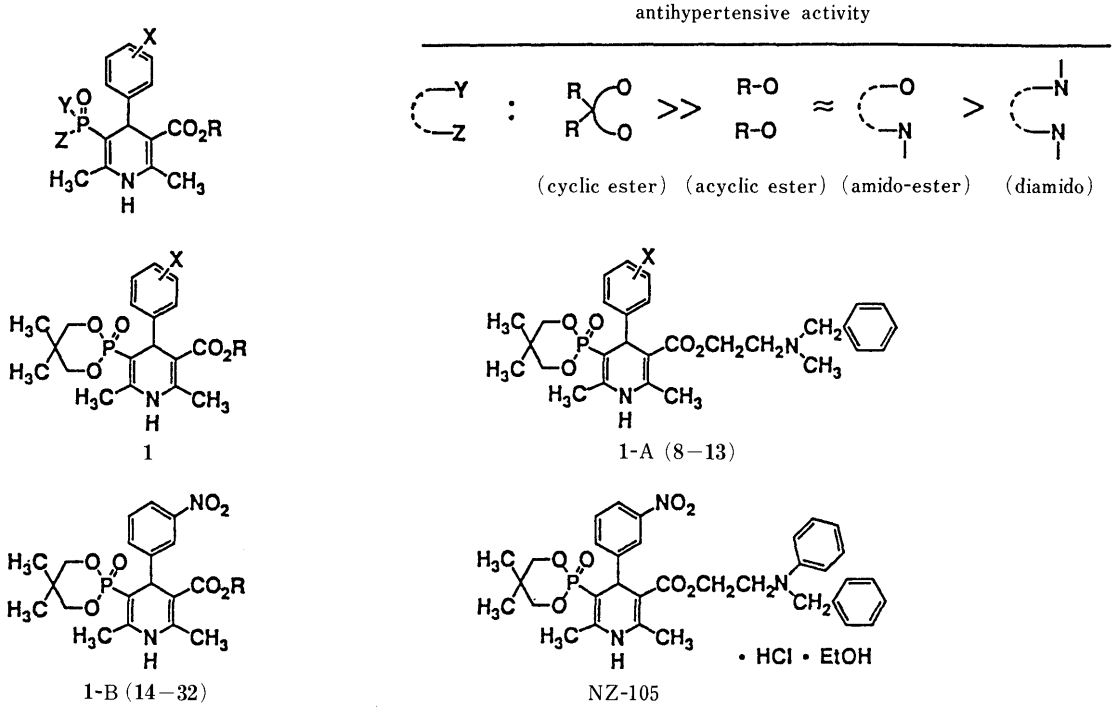


Chart 2

variation of the 3-carboxylic ester substituents.

Herein, we report the synthesis and biological activities (calcium antagonism and antihypertension) of **1**. The pharmacological profiles and crystal structure of the selected compound 2-[benzyl(phenyl)amino]ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate hydrochloride ethanol (NZ-105) are also shown.

Chemistry

The α-acetylstyrylphosphonates (**6**) were allowed to react with the 3-aminocrotonates (**7**) according to the reported method[3,5] to afford **1** in 30—79% yields. Among the compounds synthesized, those containing a basic side chain in the molecule were converted into HCl salts by treatment with HCl in the appropriate solvent to be subjected to pharmacological examinations.

The intermediary phosphonates **6** were synthesized by a Knoevenagel type reaction[6] (method A) and the authors' method[7] through the aminal (**5**) (method B). The reaction of the acetonylphosphonate (**3**) with the benzaldehydes (**4**) by the catalytic action of piperidine–acetic or trifluoroacetic acid gave the corresponding **6** in 12—58% yields (method A). Method B is advantageous particularly to the preparation of **6** containing an electron attracting group in the phenyl ring. For instance, the reaction of **3** with **5a** in the presence of trifluoroacetic acid gave **6a** in 93% yield without the occurrence of Wittig-type olefination which was a major side reaction in method A. The Arbuzov reaction with iodoacetone and 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinane (**2**), which was prepared by transesterification[8] of trimethylphosphite with 2,2-dimethyl-1,3-propanediol, afforded **3** in 33% yield.

Pharmacology

The calcium-antagonistic and antihypertensive activities of **1** were measured. The calcium-antagonistic activities were expressed by the pID_{50} values, *i.e.*, the negative logarithm of the molar concentrations required to block the calcium-induced contractions of potassium-depolarized

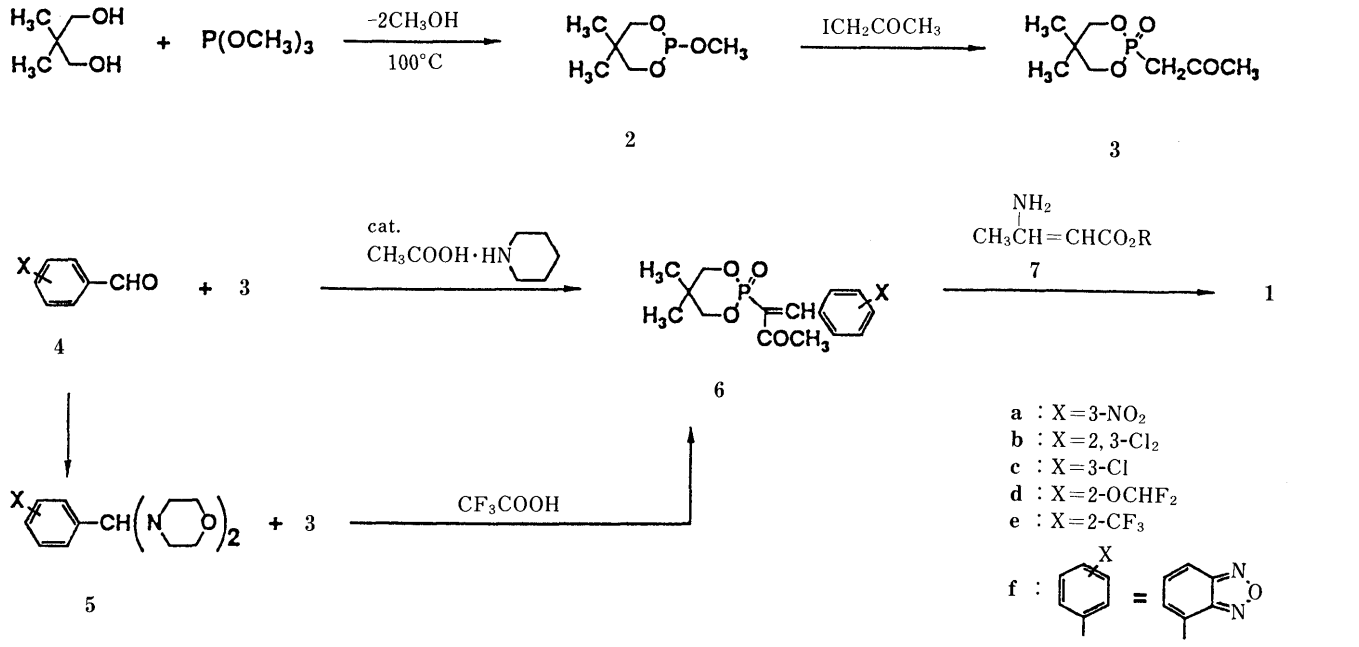
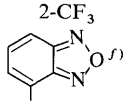
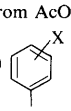


Chart 3

TABLE I. Physical and Biological Properties of Compounds **1**-A

Compd. No.	X (Ar)	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)			Biological activity	
					C	H	N	Ca antagonism[b] pID_{50}	Antihypertensive
8[c]	3-NO_2	60	122.0—123.0	$C_{29}H_{36}N_3O_7P$	61.15 (61.01)	6.37 (6.54)	7.38 (7.10)	8.45 (8.53)	++++
9[c]	2,3-Cl_2	69	195.0	$C_{29}H_{35}Cl_2N_2O_5P$	58.69 (58.57)	5.94 (6.08)	4.72 (4.53)	8.37	++++
10	3-Cl	79	103.0—104.0[d]	$C_{29}H_{36}ClN_2O_5P$	62.31 (62.22)	6.49 (6.64)	5.01 (4.80)	8.35	+++
11	2-$OCHF_2$	70	130.0—131.0[e]	$C_{30}H_{37}F_2N_2O_6P$	61.01 (61.21)	6.31 (6.13)	4.74 (4.53)	8.20	+++
12[c]	2-CF_3	59	78.0—79.0[e]	$C_{30}H_{36}F_3N_2O_5P$	60.81 (61.10)	6.12 (6.39)	4.73 (4.75)	8.37	++++
13	 [f]	33	Oil	$C_{29}H_{35}N_4O_6P$				8.02	++

a) Recrystallized from AcOEt. *b*) pID_{50} for the preparation of rat aorta was presented in ( ). *c*) Reference 3*a*. *d*) Recrystallized from Et_2O. *e*) Recrystallized from AcOEt–Et_2O. *f*)  .

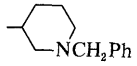
taenia caecum of guinea pigs (KCl 100 mM; $CaCl_2$ 10 mM) by 50%. Some compounds were examined for activity in rat aorta in addition to guinea pig taenia caecum in order to observe organ selectivity. The systolic blood pressure and heart rate were measured in conscious male spontaneously hypertensive rats (SHR) (10—12 weeks) by a tail-cuff method (Natsume KN-210-1) before administration of the test compound and then at 2-h intervals over a period of 12 h after that (*p.o.* 20 mg/kg). The maximum antihypertensive activity was indicated with the number of + mark: one mark (+) represents about a 10% lowering of the blood pressure. The selected compound NZ-105 was subjected to another examination in order to investigate its precise antihypertensive activity: the arterial blood pressure and heart rate were examined successively in conscious catheterized SHR (*p.o.*).

Results of the effect of the substitution on the 4-aryl group in the DHP ring, with fixation of the 3-carboxylic-ester substituent with the [benzyl(methyl)amino]ethyl group (activities of the (**1**-A) group) are summarized in Table I.

Since the electron-donating groups have been found to cause a loss of potency in previous investigations,[9] electron-attracting groups were chosen. Among six compounds listed, HCl salts of **8** (3-NO_2), **9** (2,3-Cl_2) and **12** (2-CF_3) showed high antihypertensive effects. On the basis of the results of some additional works, we have focused on the 3-nitro analogs (**1**-B), the substitution pattern of which is the same as in the known calcium antagonists such as nicardipine[10] and nimodipine.[11]

Seven examples of the C_1- to C_{12}-alkyl groups were shown in section I in Table II. Upon calcium antagonism *n*-hexyl ester (**16**) was best among the compounds listed, and a marked lowering of activity was observed with the lengthening of the carbon chain in the C_9- to C_{12}-homologs. On the contrary, the C_8–C_{12}-homologs were advantageous

TABLE II. Physical and Biological Properties of Compounds **1**-B

Compd. No.	R	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Biological activity Ca antag.[b] pID_{50}	Antihypertensive
Section I									
14[c]	CH_3	40	209.0—209.5	$C_{20}H_{25}N_2O_7P$	55.05 (54.98	5.77 5.81	6.42 6.21)	7.55	+++
15	iso-C_3H_7	38	184.0—184.5[e]	$C_{22}H_{29}N_2O_7P$	56.89 (56.80	6.29 6.51	6.03 5.81)	8.08	++
16	C_6H_{13}	57	101.0—104.0[e]	$C_{25}H_{35}N_2O_7P \cdot 1/2H_2O$	58.24 (57.98	7.04 7.15	5.43 5.20)	8.29	++
17	C_8H_{17}	36	104.0—106.0[d]	$C_{27}H_{39}N_2O_7P$	60.66 (60.53	7.35 7.54	5.24 5.33)	8.13 (8.44)	++++
18	C_9H_{19}	49	84.0[d]	$C_{28}H_{41}N_2O_7P$	61.30 (61.41	7.53 7.58	5.11 4.96)	6.70	++++
19	$C_{10}H_{21}$	50	104.0—106.0[d]	$C_{29}H_{43}N_2O_7P$	61.91 (62.04	7.70 7.84	4.98 4.88)	5.66 (8.48)	+++++
20	$C_{12}H_{25}$	30	99.0—100.0[f]	$C_{31}H_{47}N_2O_7P$	63.03 (62.84	8.02 7.94	4.74 4.82)	4.68	++++
Section II									
21	$(CH_2)_2N(CH_3)CH_2$- 	35	194.0—195.0[e]	$C_{30}H_{36}N_3O_9P$	58.72 (58.50	5.91 5.94	6.85 6.75)	8.39	++++
22	$(CH_2)_6N(CH_3)CH_2Ph$	61	Oil	$C_{33}H_{44}N_3O_7P$				8.28	+++
23	$CH(CH_3)CH_2N(CH_3)CH_2Ph$	49	Oil	$C_{30}H_{38}N_3O_7P$				8.34	+++
24	$(CH_2)_2N(Ph)CH_2Ph$	45	169.0—170.0	$C_{34}H_{38}N_3O_7P$	64.65 (64.51	6.06 6.25	6.65 6.48)	8.17 (8.37)	+++++
25	$(CH_2)_2N(CH_2Ph)_2$	40	110.0—110.5	$C_{35}H_{40}N_3O_7P \cdot 1/2H_2O$	64.21 (64.49	6.31 6.26	6.42 6.29)	7.80	+++++
26		74	99.0—101.5[e]	$C_{31}H_{38}N_3O_7P \cdot 1/2H_2O$	61.58 (61.84	6.50 6.45	6.95 6.87)	8.37	++
Section III									
27	$(CH_2)_2N$-  -$NCH(Ph)_2$	56	173.0—174.0	$C_{38}H_{45}N_4O_7P \cdot 1/2H_2O$	64.30 (64.16	6.53 6.49	7.89 7.60)	7.63 (8.06)	+++
28	$(CH_2)_3N$-  -$NCH(Ph)_2$	49	137.0—138.0	$C_{39}H_{47}N_4O_7P \cdot 1/2H_2O$	64.72 (65.00	6.68 6.91	7.74 7.68)	7.53 (8.26)	++
29	$(CH_2)_2N$-  -$NCH($  $-F)_2$	62	143.0—145.0	$C_{38}H_{43}F_2N_4O_7P \cdot 1/4H_2O$	61.58 (61.55	5.92 5.90	7.56 7.52)	7.39	+++
30	$(CH_2)_2N$-  -$N(CH_2)_3Ph$	44	80.0—82.0[e]	$C_{34}H_{45}N_4O_7P \cdot 1/2H_2O$	61.72 (61.52	7.01 7.00	8.47 8.39)	7.50	+
31	$(CH_2)_2N$-  -$NCH(Ph)_2$	45	95.0—96.0[e]	$C_{39}H_{47}N_4O_7P \cdot 1/2H_2O$	64.72 (64.89	6.68 6.65	7.74 7.69)	7.60	++
32	$(CH_2)_3N$-  -$NCH($  $-F)_2$	46	133.0—135.0	$C_{39}H_{45}F_2N_4O_7P \cdot H_2O$	60.93 (61.08	6.16 6.07	7.29 7.41)	7.20	++

a—*e*) See footnotes *a*—*e*) in Table I. *f*) Recrystallized from EtO_2–hexane.

upon the antihypertensive effect. Of interest are the biological results of *n*-decyl ester (**19**), which showed markedly low calcium-antagonistic activity but had the highest antihypertensive effect. This conflict was resolved by the fact that **19** showed considerably high calcium-antagonistic activity toward rat aorta preparation. These suggest that **19** possesses highly organ-selective calcium-antagonistic activity.

The variation of the substituents containing the basic groups in the carboxylic-ester moiety was summarized in section II (monoamino functionality) and section III (piperazino, homopiperazino functionality) in Table II. The compounds **21**—**26** (HCl salts) showed comparatively high calcium-antagonistic effects. The increase of the carbon number between the O and N atoms, including both the lengthening of the methylene chain and derivation to the branched type in the carboxylic-ester moiety, caused the lowering of the antihypertensive activity. In the variation of the amine moiety, the combination of the benzyl and phenyl groups contributed most to the antihypertensive effect. The generation of the pharmacologically excellent activities by introduction of the benzyl(phenyl)amino group in the ester moiety has not been reported in the previous DHP-series investigations. The compounds **27**—**32** (HCl salts) showed moderate calcium-antagonistic effects. The longer the ester side chain was, the more the antihypertensive activity generally lowered.

The HCl salt of **24** was noteworthy due to the intensity of its biological activities, and it was subjected to precise structural analyses; incorporation of the solvents examined for crystallization into the lattice was observed. On the basis of several other biological results in addition to the above findings, we selected 2-[benzyl(phenyl)amino]ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate hydrochloride ethanol, NZ-105, for further development.

The time course of the antihypertensive effect of NZ-105 and nicardipine is shown in Fig. 1.[12] In conscious SHR, NZ-105 effectively lowered the blood pressure with less tachycardiac effect, and a longer lasting and slower onset of antihypertensive action than nicardipine. Similar profiles were observed in the effect on hypertensive dogs.[13] NZ-105 also exhibited a mild diuretic effect in SHR[12] as well as a highly selective calcium-antagonistic effect on cerebral vessels.[14] Acute oral toxicities of NZ-105 in mice, rats and dogs were considerably lower than those of nicardipine.[15] Therefore, the safety margin is wide. NZ-105 is now successively subjected to further pharmacological studies and clinical development.

X-Ray Diffraction Analysis Stereoscopic drawings of the molecule and the molecular packing diagram of NZ-105

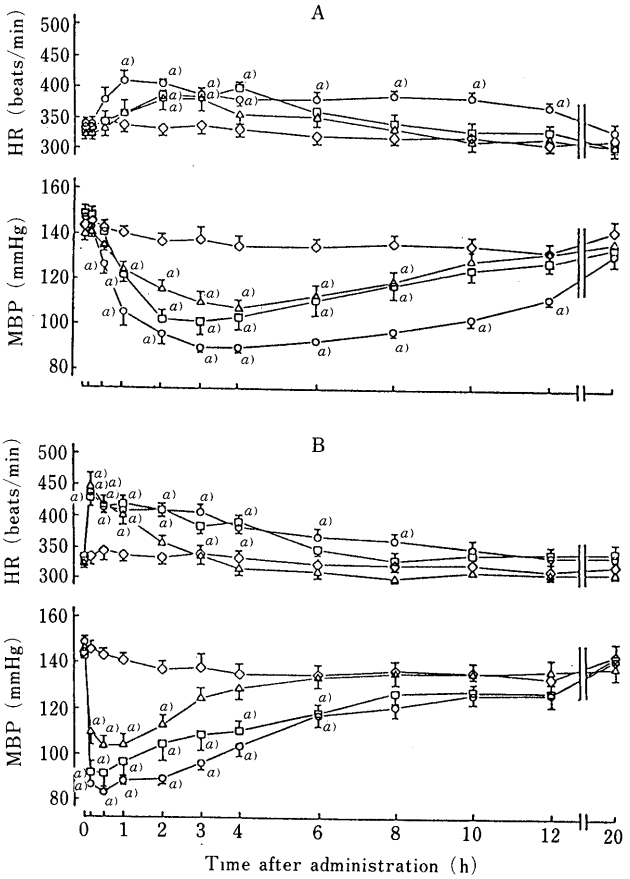


Fig. 1. Time Course of the Effects of NZ-105 (A) and Nicardipine (B) on Mean Blood Pressure (MBP) and Heart Rate (HR) in SHR (*p.o.* Administration, the Mean±S.E.M. of 9 Animals)

◇—◇, control; △—△, 5 mg/kg; □—□, 10 mg/kg; ○—○, 20 mg/kg. *a*) $p<0.05$: significantly different from the corresponding control values.

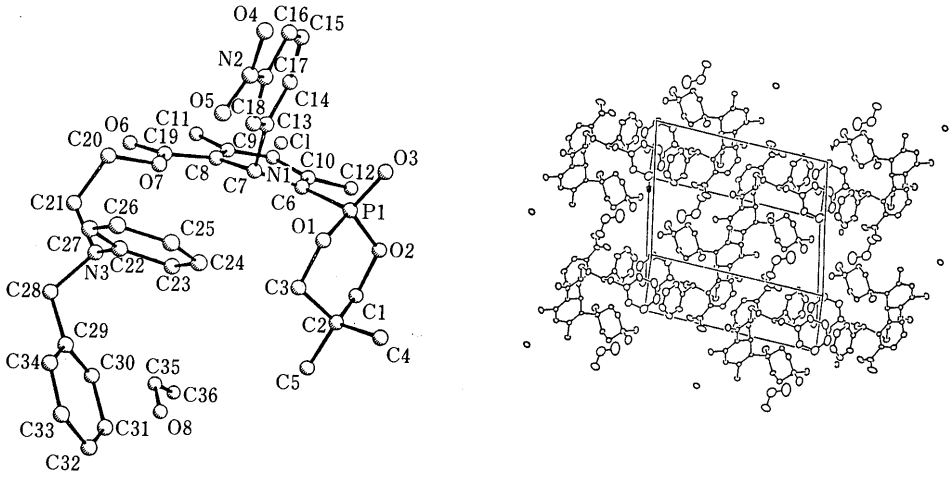


Fig. 2. Stereoscopic Drawings of the Molecule and the Molecular Packing Diagram of NZ-105

were shown in Fig. 2.

The torsion angles of ϕ_1 [C9–C8–C19–O6], ϕ_1 [C8–C7–C13–C18], ϕ_1 [C8–C7–C13–C14], and ϕ_1[C10–C6–P1–O3] were −1 (1), 112.9 (6), −66.7 (7) and 82.7 (6)°, respectively. The carboxyl group had a synperiplanar (*sp*) orientation to the DHP ring double bond and was less torsionally distorted from the synplanar value (0°). The plane of the phenyl ring approximately bisected the DHP ring. This interring orientation may minimize steric strain imposed by the 3-carboxylic and 5-phosphonic-ester groups. The same conformational feature is also observed in studies of the DHP-3,5-dicarboxylates such as the nifedipine and nisoludipine series,[16a–c] Felodipine[16d] and others.[16e] The nitro group, a substituent in the phenyl ring, was pointed away from the DHP ring. The carbonyl and nitro groups of NZ-105 were in the reverse of those of the biologically active *S* enantiomer (free base) in the solid state; the *S* enantiomer has been determined to possess an antiperiplanar (*ap*) carbonyl group and a nitro group pointed toward the DHP ring by the X-ray crystallographic work.[17] Of interest is the orientation of the phosphonyl group in NZ-105. It was approximately perpendicular (82.7°) to the C10–C6 double bond in the DHP ring, being consistent with that of the *S* enantiomer.

The torsion angles (τ_1) of the intra DHP ring around the N1–C9, C9–C8, C8–C7, C7–C6, C6–C10, and C10–N1 bonds were 7 (1), 7 (1), −17.3 (8), 16.4 (8), −5 (1), and −7 (1)°, respectively. The boat-type DHP ring was preferred in NZ-105; the degree of ring distortion was greatest at the C7 position, and the phenyl ring at C7 occupied a pseudo-axial position. This conformational feature is also commonly observed in the solid-state structures of DHP-3,5-dicarboxylates.[16]

The torsin angles (Φ_2, τ_2) related to the 1,3,2-dioxaphosphorinane ring, Φ_2 [C3–O1–P1–O3], Φ_2 [C3–O1–P1–C6], (τ_2) around the P1–O1, O1–C3, C3–C2, C2–C1, C1–O2, and O2–P1 bonds were −162.3 (4), 72.9 (5), −44.6 (5), 55.7 (7), −58.6 (8), 57.6 (8), −55.5 (7) and 45.3 (5)°, respectively. The 1,3,2-dioxaphosphorinane ring adopted the chair-type conformation with an axial P–C orientation. It is somewhat surprising that the extremely bulky substituent on phosphorus is in an axial orientation in the 1,3,2-dioxaphosphorinane ring. The resulting crystal structure also confirms that an ethanol solvent molecule is incorporated into the lattice.

Discussion

Although replacement of the carboxylic ester group by the different functionalities has been generally recognized to afford unfavorable results for calcium-antagonistic activity,[18] the generation of a new type of calcium antagonists has been expected by an optimum in structural variation in the DHP-5-phosphonates.

Since stereoselective antagonism was demonstrated in the DHP-3,5-dicarboxylates,[19] several crystallographic studies have correlated the biological activities (antagonism or agonism) with the three dimensional structure. Based on results from X-ray crystallographic analyses for the DHP-3,5-dicarboxylates[16a–d] or 5-nitro-DHP-3-carboxylates[20] and theoretical calculations of their conformational energies,[21] the following conformational distinction between the antagonist and agonist has been proposed[20a]; one *sp* carbonyl group produces an antagonist response, and the *ap* carbonyl group or *ap* oxygen of nitro group produces an agonist response. However, such studies are confined to the analogs of the representative antagonists and agonists, and the conformational feature of the DHP bearing a phosphonate functionality has not been reported.

The phosphonate group of NZ-105 is considered not to be free to fully rotate around the C–P bond because of its ring structure from the molecular model. In addition to the conformational constraint of the cyclic phosphonate group, a large difference in biological activity between cyclic phosphonates and acyclic also suggests that the oxygen orientation of the phosphonyl group is an important factor for biological activity. Although it remains to be determined to what extent the conformational preference in the crystal is conserved in the receptor binding mode, the pharmacological feature of NZ-105 indicates that the perpendicular phosphonyl orientation (82.7°) scarcely lowers antagonist response. The phosphonate group seems to play a great role in the addition of valuable pharmacological profiles rather than by its effect upon the magnitude of the antagonistic activity. The difference in the orientation of the carbonyl group between racemic NZ-105 and the *S* enantiomer is considered to be associated with the difference of their intra- or inter-molecular hydrogen-bonding patterns since the *ap* and *sp* conformations have been in a variety of crystalline environments and do not differ much in terms of energy.[16d]

Recent studies on the active conformation of the DHPs have correlated biological activity with the orientation of the substituent on the phenyl ring and suggest a preference at the DHP receptor for the 3′-phenyl substituent pointed toward the DHP ring.[22] Racemic NZ-105 and the *S* enantiomer were orientated in two different minimum energy conformations to each other with respect to the position of the nitro group. This inconsistency suggests that a significant energetic bias toward either of two conformations does not also exist.

Fossheim *et al.* have studied the correlation between DHP ring puckering and calcium-antagonistic activity. They noted that the DHP ring puckering parameter ($\Sigma|\tau_1|$) ranges from 51.7° to 112.5° in the examined DHP-3,5-dicarboxylates,[16c,d] and the activity increased with an increase in DHP ring planarity in the studies on the crystal structures of nifedipine and nisoludipine series. The value of NZ-105 was 59.7° and demonstrates that NZ-105 takes up a position near the flattest compound among them. On the other hand, the value of the *S* enantiomer was 111°.[17] A large difference in parameters between these two indicates the difficulty in correlating DHP puckering in the solid state with biological activity.

Experimental

General All solvents were of a special grade purchased from Kosoh Kagaku Co., Ltd. Anhydrous Na_2SO_4 and 35% aqueous HCl were of a special grade purchased from Junsei Kagaku Co., Ltd. Other materials were of a reagent grade purchased from Tokyo Kasei Kogyo Co., Ltd. or Aldrich Chemical Co. As necessary, the solvents were dried over 3A or 4A molecular sieves. Melting points were determined on a Yanagimoto (Yanaco) micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at 20 °C on JEOL instruments, PMX60SI (60 MHz) and JMN-GSX500 (500 MHz). Chemical shifts were recorded in δ (parts per million) down-field from

tetramethylsilane (TMS) ($\delta=0.00$) as an internal standard. All coupling constants were reported in hertz. Mass spectra (MS) were measured on a JEOL instrument, JMS-DX300. Column chromatography was performed by use of silica gel (type 60 Merck) as a stationary phase. Thin layer chromatography (TLC) was performed on Silica gel 60F-254 (Merck). X-Ray diffraction analysis was performed at Toray Research Center, Inc.

2-Methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinane (2) A stirred mixture of 24.0 g (0.23 mol) of 2,2-dimethyl-1,3-propanediol and 26.0 g (0.21 mol) of trimethylphosphite was heated in an oil bath at 100 °C until the evaporation of methanol ceased. The residue was distilled under reduced pressure to give 11.2 g (33%) of **2** as a clear, colorless liquid, bp 60—63 °C (12 mmHg) [lit.[3a] bp 63—70 °C (13 mmHg)]. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.72 (s, 3H, C–C$\underline{H}_3$), 1.23 (s, 3H, C–C$\underline{H}_3$), 3.48 (d, $J=12.0$ Hz, 3H, O–C$\underline{H}_3$), 3.00—4.25 (m, 4H, P–O–C$\underline{H}_2\times2$). MS *m/z* (%): 69 (66%), 133 (100%), 164 (M^+, 7%).

2-Acetonyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (3) To a stirred, refluxing solution of 11.24 g (68.5 mmol) of **2** in 50 ml of ether was added 11.04 g (60.0 mmol) of iodoacetone over a 1-h period. The mixture was stirred for an additional 7 h under reflux and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt–EtOH (20 : 1, v/v, $Rf=0.4$ in TLC) as an eluent to give 8.13 g (65.8%) of **3** as colorless crystals. An analytical sample was obtained by recrystallization from toluene, mp 89—93 °C. [lit.[3a] mp 91—92 °C (Et_2O)]. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.04 (s, 3H, C–C$\underline{H}_3$), 1.13 (s, 3H, C–C$\underline{H}_3$), 2.24 (s, 3H, C(O)–C$\underline{H}_3$), 3.22 (d, 2H, $J=22.0$ Hz, P–C$\underline{H}_2$), 3.84—4.34 (m, 4H, P–O–C$\underline{H}_2\times2$). MS *m/z* (%): 97 (100%), 164 (21%), 206 (M^+, 11%).

2-[1-Acetyl-2-(3-nitrophenyl)ethenyl]-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (6a) (Method A) To a mixture of 1.03 g (5.0 mmol) of **3** and 0.85 g (5.6 mmol) of 3-nitrobenzaldehyde (**4a**) in 20 ml of benzene were added 60 mg of piperidine and 55 mg of acetic acid. The stirred mixture was heated at reflux with the azeotropical removal of water for 6.5 h, cooled to room temperature and then diluted with 10 ml of toluene and 10 ml of water. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt–hexane (1 : 1, v/v, $Rf=0.4$ in TLC) as an eluent to give 0.53 g (31%) of **6a** ($E/Z=85/15$) as yellow crystals. A ratio of *E* to *Z* isomer was determined on the basis of singlet peaks for the acetyl group in the ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from toluene, mp 148—151 °C [a mixture of *E* and *Z* isomers (95/5)] [lit.[3a] mp 150—151 °C (*E* isomer)]. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.83, 1.06 (s, 3H, (5 : 95, *Z*/*E*), C(CH_3)–$_{eq}$C$\underline{H}_3$), 1.16, 1.21 (s, 3H, (95 : 5, *E*/*Z*), C(CH_3)–$_{ax}$C$\underline{H}_3$), 2.32, 2.58 (s, 3H, (95 : 5, *E*/*Z*), C(O)–C$\underline{H}_3$), 3.50—4.47 (m, 4H, P–O–C$\underline{H}_2\times2$), 7.05—8.40 (m, 5H, Ar$\underline{H}$ + P–C=C$\underline{H}$). MS *m/z* (%): 69 (25%), 228 (34%), 296 (100%), 339 (M^+, 47%). *Anal.* Calcd for $C_{15}H_{18}NO_6P$: C, 53.10; H, 5.35; N, 4.13. Found: C, 53.12; H, 5.35; N, 4.06.

2-[1-Acetyl-2-(2-trifluoromethylphenyl)ethenyl]-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (6e) (Method A) To a mixture of 1.03 g (5.0 mmol) of **3** and 0.95 g (5.5 mmol) of 2-trifluoromethylbenzaldehyde (**4e**) in 20 ml of toluene were added 60 mg of piperidine and 110 mg of trifluoroacetic acid. The stirred mixture was heated at reflux with the azeotropical removal of water for 8 h, cooled to room temperature and then diluted with 10 ml of toluene and 10 ml of water. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt–hexane (1 : 1, v/v, $Rf=0.5$ in TLC) as an eluent to give 0.76 g (42%) of **6e** ($E/Z=75/25$) as a pale yellow solid. An analytical sample was obtained by recrystallization from toluene–hexane, mp 76—84 °C [a mixture of *E* and *Z* isomers (80 : 20)] (lit.[3a] mp 80—87 °C). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.77, 1.04 (s, 3H, (20 : 80, *Z*/*E*), $_{eq}$C$\underline{H}_3$), 1.18, 1.21 (s, 3H, (20 : 80, *Z*/*E*), $_{ax}$C$\underline{H}_3$), 2.13, 2.57 (s, 3H, (80 : 20, *E*/*Z*), C(O)–C$\underline{H}_3$), 3.95—4.35 (m, 4H, P–O–C$\underline{H}_2\times2$), 7.20—8.25 (m, 5H, Ar$\underline{H}$ + P–C=C$\underline{H}$). MS *m/z* (%): 225 (13%), 293 (100%), 319 (19%), 362 (M^+, 2%). *Anal.* Calcd for $C_{16}H_{18}F_3O_4P$: C, 53.05; H, 5.01. Found: C, 52.94; H, 5.10.

2,3-Dichlorophenyl (**6b**), 3-chlorophenyl (**6c**), 2-difluoromethoxyphenyl (**6d**) and 2,1,3-benzoxadiazol (**6f**) analogs were obtained, in the same manner, in 28%, 58%, 18% and 12%, respectively.

Preparation of 6a (Aminal Method: Method B) To a stirred mixture of 6.19 g (30.0 mmol) of **3** and 6.63 g (58.2 mmol) of trifluoroacetic acid in 35 ml of toluene was added 8.49 g (29.1 mmol) of bismorpholino-3-nitrophenylmethane (**5a**). The mixture was stirred at room temperature for 2.5 h and then diluted with 20 ml of water. The stirred mixture was cooled to 5 °C in an ice bath and filtered. The cake was washed with 10 ml of water and then with two 9-ml portions of cold toluene and dried *in vacuo* to give 8.89 g (90.0%) of **6a** ($E/Z=95/5$) as yellow crystals. The organic layer of the filtrate and the toluene washings were combined, dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt as an eluent to give additional **6a** (0.32 g, 3.2%) as yellow crystals.

2-[Benzyl(methyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-chlorophenyl)-3-pyridinecarboxylate (10) A stirred mixture of 1.04 g (3.17 mmol) of **6c** and 0.79 g (3.19 mmol) of 2-[benzyl(methyl)amino]ethyl 3-aminocrotonate in 20 ml of toluene was heated at reflux with the azeotropical removal of water for 11 h and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt–EtOH (10 : 1, v/v, $Rf=0.5$ in TLC) as an eluent to give 1.39 g (79%) of **10** as yellow crystals. An analytical sample was obtained by recrystallization from Et_2O, mp 103.0—104.0 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.86 (s, 3H, C(CH_3)–$_{eq}$C$\underline{H}_3$), 0.96 (s, 3H, C(CH_3)–$_{ax}$C$\underline{H}_3$), 2.19 (s, 3H, N–C$\underline{H}_3$), 2.22 (s, 3H, NH–C_2–C$\underline{H}_3$), 2.30 (d, 3H, $J_{P-H}=2.5$ Hz, NH–C_6–C$\underline{H}_3$), 2.63 (t, 2H, $J=6.0$ Hz, O–CH_2C$\underline{H}_2$–N), 3.48 (s, 2H, N–C$\underline{H}_2$–Ph), 3.20—4.40 (m, 4H, P–O–C$\underline{H}_2\times2$), 4.15 (t, 2H, $J=6.0$ Hz, O–C$\underline{H}_2$$CH_2$–N), 4.74 (d, 1H, $J_{P-H}=11.0$ Hz, Ar-C$\underline{H}$), 6.10—6.55 (br, 1H, N$\underline{H}$), 7.15 (s, 5H, CH_2–$C_6\underline{H}_5$), 6.85—7.30 (m, 4H, (3-Cl)$C_6\underline{H}_4$). MS *m/z* (%): 147 (100%), 300 (13%), 410 (6%), 558 (M^+, 7%). *Anal.* Calcd for $C_{29}H_{36}ClN_2O_5P$: C, 62.31; H, 6.49; N, 5.01. Found: C, 62.22; H, 6.64; N, 4.80.

2-[Benzyl(methyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)-3-pyridinecarboxylate (12) A stirred mixture of 1.39 g (3.84 mmol) of **6e** and 0.95 g (3.82 mmol) of 2-[benzyl(methyl)amino]ethyl 3-aminocrotonate in 20 ml of toluene was heated at reflux with the azeotropical removal of water for 9 h and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt–EtOH (10 : 1, v/v, $Rf=0.5$ in TLC) as eluent to give 1.35 g (59%) of **12** as pale yellow crystals. An analytical sample was obtained by recrystallization from AcOEt–Et_2O, mp 78.0—79.0 °C (lit.[3a] oil). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.80 (s, 3H, C(CH_3)–$_{eq}$C$\underline{H}_3$), 1.00 (s, 3H, C(CH_3)–$_{ax}$C$\underline{H}_3$), 2.15 (s, 3H, N–C$\underline{H}_3$), 2.20 (s, 3H, NH–C_2–C$\underline{H}_3$), 2.26 (d, 3H, $J_{P-H}=2.5$ Hz, NH–C_6–C$\underline{H}_3$), 2.60 (t, 2H, $J=6.0$ Hz, O–CH_2C$\underline{H}_2$–N), 3.20—4.50 (m, 8H, P–O–C$\underline{H}_2\times2$ + O–C$\underline{H}_2$$CH_2$–N + C$\underline{H}_2$–Ph), 5.28 (d, 1H, $J_{P-H}=10.0$ Hz, Ar-C$\underline{H}$), 7.20 (s, 5H, CH_2–$C_6\underline{H}_5$), 7.00—7.70 (m, 4H, (3-NO_2)$C_6\underline{H}_4$). MS *m/z* (%): 147 (100%), 300 (15%), 447 (10%), 592 (M^+, 5%). *Anal.* Calcd for $C_{30}H_{36}F_3N_2O_5P$: C, 60.81; H, 6.12; N, 4.73. Found: C, 61.10; H, 6.39; N, 4.75.

Methyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate (14) A stirred mxiture of 0.68 g (2.0 mmol) of **6a** and 0.23 g (2.0 mmol) of methyl 3-aminocrotonate in 15 ml of toluene was heated at reflux with the azeotropical removal of water for 15 h and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt ($Rf=0.35$ in TLC) as an eluent to give 0.35 g (40%) of **14** as yellow crystals. An analytical sample was obtained by recrystallization from AcOEt, mp 209.0—209.5 °C [lit.[3a] mp 208—209 °C (AcOEt)]. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.83—1.23 (m, 6H, C–C$\underline{H}_3\times2$), 2.29 (s, 3H, NH–C_2–C$\underline{H}_3$), 2.34 (d, 3H, $J_{P-H}=2.5$ Hz, NH–C_6–C$\underline{H}_3$), 3.66 (s, 3H, CO_2C$\underline{H}_3$), 3.73—4.40 (m, 4H, P–O–C$\underline{H}_2\times2$), 4.48 (d, 1H, $J_{P-H}=11.0$ Hz, Ar-C$\underline{H}$), 7.25—8.20 (m, 4H, (3-NO_2)$C_6\underline{H}_4$). MS *m/z* (%): 314 (100%), 419 (39%), 436 (M^+, 6%). *Anal.* Calcd for $C_{20}H_{25}N_2O_7P$: C, 55.05; H, 5.77; N, 6.42. Found: C, 54.98; H, 5.81; N, 6.21.

Decyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate (19) A stirred mixture of 0.85 g (2.5 mmol) of **6a** and 0.60 g (2.5 mmol) of *n*-decyl 3-aminocrotonate in 20 ml of toluene was heated at reflux with the azeotropical removal of water for 8.5 h and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt ($Rf=0.40$ in TLC) as an eluent to give 0.70 g (50%) of **19** as a yellow solid. An analytical sample was obtained by recrystallization from Et_2O, mp 104.0—106.0 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.99 (s, 3H, C(CH_3)–$_{eq}$C$\underline{H}_3$), 1.08 (s, 3H, C(CH_3)–$_{ax}$C$\underline{H}_3$), 0.60—1.90 (m, 19H, OCH_2–$C_9\underline{H}_{19}$), 2.28 (s, 3H, NH–C_2–C$\underline{H}_3$), 2.30 (d, 3H, $J_{P-H}=2.5$ Hz, NH–C_6–C$\underline{H}_3$), 4.01 (t, 2H, $J=6.0$ Hz, O–C$\underline{H}_2$), 3.30—4.35 (m, 4H, P–O–C$\underline{H}_2\times2$), 4.84 (d, 1H, $J_{P-H}=11.0$ Hz, Ar-C$\underline{H}$), 6.70—7.00 (br, 1H, N$\underline{H}$), 7.10—8.10 (m, 4H, (3-NO_2)$C_6\underline{H}_4$). MS *m/z* (%): 440 (100%), 545 (51%), 560 (54%), 562 (M^+, 10%). *Anal.* Calcd for $C_{29}H_{43}N_2O_7P$: C, 61.91; H, 7.70; N, 4.98. Found: C, 62.04; H, 7.84; N, 4.88.

2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate (24) A stirred mixture of 1.0 g (3.0 mmol) of **6a** and 0.93 g

(3.0 mmol) of 2-[benzyl(phenyl)amino]ethyl 3-aminocrotonate in 20 ml of toluene was heated at reflux with the azeotropical removal of water for 5 h and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt (Rf=0.4 in TLC) as an eluent to give 0.85 g (45%) of **24** as yellow crystals. An analytical sample was obtained by recrystallization from AcOEt, mp 169.0—170.0 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (s, 3H, $C(CH_3)$-$_{eq}C\underline{H}_3$), 1.00 (s, 3H, $C(CH_3)$-$_{ax}C\underline{H}_3$), 2.26 (s, 3H, NH-C_2-$C\underline{H}_3$), 2.32 (d, 3H, J_{P-H}=2.5 Hz, NH-C_6-$C\underline{H}_3$), 3.58 (ddd, 1H, J_{P-H}=16.8 Hz, J_{gem}=11.1 Hz, J_{e-e}=2.2 Hz, P-O-$CH_{eq}\underline{H}$), 3.66 (ddd, 1H, J_{P-H}=16.8 Hz, J_{gem}=11.1 Hz, J_{e-e}=2.2 Hz, P-O-$CH_{eq}\underline{H}$), 3.67 (t, 2H, J=6.6 Hz, O-$CH_2C\underline{H}_2$-N), 4.16 (dd, 1H, J_{P-H}=6.5 Hz, J_{gem}=11.1 Hz, P-O-$CH_{ax}\underline{H}$), 4.20 (dd, 1H, J_{P-H}=6.5 Hz, J_{gem}=11.1 Hz, P-O-$CH_{ax}\underline{H}$), 4.30 (td, 2H, J=6.7 Hz, J_{P-H}=3.1 Hz, O-$C\underline{H}_2CH_2$-N), 4.53 (s, 2H, N-$C\underline{H}_2$-Ph), 4.90 (d, 1H, J_{P-H}=10.9 Hz, Ar-C$\underline{H}$), 6.68 (t, 1H, J=7.3 Hz, 4-$\underline{H}$ for N-C_6H_5), 6.70 (d, 2H, J=8.1 Hz, 2-, 6-$\underline{H}$ for N-C_6H_5), 6.86 (d, 1H, J=4.2 Hz, N$\underline{H}$), 7.14—7.27 (m, 7H, 3-, 5-$\underline{H}$ for N-C_6H_5 + $CH_2C_6\underline{H}_5$), 7.31 (dd, 1H, J=7.9, 7.9 Hz, 5-$\underline{H}$ for (3-NO_2)C_6H_4), 7.60 (d, 1H, J=7.9 Hz, 6-$\underline{H}$ for (3-NO_2)C_6H_4), 7.98 (ddd, 1H, J=7.9, 2.1, 1.0 Hz, 4-$\underline{H}$ for (3-NO_2)C_6H_4), 8.09 (dd, 1H, J=2.1, 2.1 Hz, 2-$\underline{H}$ for (3-NO_2)C_6H_4). MS m/z (%): 196 (61%), 209 (100%), 631 (M^+, 7%). *Anal.* Calcd for $C_{34}H_{38}N_3O_7P$: C, 64.65; H, 6.06; N, 6.65. Found: C, 64.51; H, 6.25; N, 6.48.

2-(4-Diphenylmethyl-1-piperazinyl)ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate (27) A stirred mixture of 1.29 g (3.81 mmol) of **6a** and 1.43 g (3.80 mmol) of 2-(4-diphenylmethyl-1-piperazinyl)ethyl 3-aminocrotonate in 20 ml of toluene was heated at reflux with the azeotropical removal of water for 9 h and then concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using AcOEt (Rf=0.5 in TLC) as an eluent to give 1.48 g (56%) of **27** as yellow crystals. An analytical sample was obtained by recrystallization from AcOEt, mp 173.0—174.0 °C. ^{1}H-NMR (60 Mz, $CDCl_3$) δ: 0.85 (s, 3H, $C(CH_3)$-$_{eq}C\underline{H}_3$), 1.02 (s, 3H, $C(CH_3)$-$_{ax}C\underline{H}_3$), 2.25 (s, 3H, NH-C_2-$C\underline{H}_3$), 2.31 (d, 3H, J_{P-H}=2.5 Hz, NH-C_6-$C\underline{H}_3$), 2.00—2.70 (m, 10H, N-$C\underline{H}_2C\underline{H}_2$-N×2+O-$CH_2C\underline{H}_2$-N), 3.20—4.35 (m, 7H, O-$C\underline{H}_2CH_2$-N+P-O-$C\underline{H}_2$×2+$C\underline{H}Ph_2$), 4.81 (d, 1H, J_{P-H}=11.0 Hz, Ar-C$\underline{H}$), 6.30—6.50 (br, 1H, N$\underline{H}$), 6.90—7.00 (m, 14H, Ar$\underline{H}$). MS m/z (%): 167 (100%), 246 (28%), 361 (15%), 683 (M^+-17, 10%). *Anal.* Calcd for $C_{38}H_{45}N_4O_7P\cdot 1/2H_2O$: C, 64.30; H, 6.53; N, 7.89. Found: C, 64.16; H, 6.49; N, 7.60.

Preparation of NZ-105 (24·HCl·EtOH) To a stirred solution of 2.77 g (4.38 mmol) of **24** in 40 ml of EtOH was added 1.68 g (4.60 mmol as HCl) of 10% aqueous HCl at 50—60 °C. The mixture was cooled in an ice bath and then filtered. The cake was washed with 5 ml of cold EtOH and then dried *in vacuo* at 40 °C for an 8-h period (a weight decrease of the product had ceased) to give 3.00 g (96%) of NZ-105 as yellow crystals composed of **24**, HCl and EtOH (1:1:1 molar ratio), mp 151 °C (dec.) *Anal.* Calcd for $C_{34}H_{39}ClN_3O_7P\cdot C_2H_6O$: C, 60.54; H, 6.35; N, 5.88. Found: C, 60.68; H, 6.42; N, 5.73.

Crystallographic Work Crystal data and experimental conditions are summerized in Table III.

Single crystals of NZ-105 were grown by slow evaporation from an ethanol solution. Cell constants were obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range of $57.67° < 2\theta < 60.13°$. The intensities of three representative reflections, which were measured after every 150 reflections, remained constant throughout data collection, indicating crystal and electronic stability. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods using the program package MITHRIL[23] and refined by full-matrix least-squares techniques. The non-hydrogen atoms were refined anisotropically. The R-value was 0.081 (R_w=0.114) for 3,517 reflections. The magnitude of R factors is a function of the fact that hydrogen atoms were not requested for the structure analysis and consequently were not included in the model. Fractional atomic parameters, thermal parameters and tables of observed and calculated structure factors are available from the author on request.

TABLE III. Experimental Details in X-Ray Crystallography

	Crystal data
Empirical formula	$C_{36}H_{45}O_8N_3PCl$
Formula weight	714.19
Crystal color, habit	Pale, prism
Crystal dimensions (mm)	0.200×0.150×0.200
Crystal system	Triclinic
Lattice parameters:	a=11.993 (4) Å
	b=15.085 (4) Å
	c=11.566 (3) Å
	α=102.13 (2)°
	β=114.14 (2)°
	γ= 87.06 (2)°
	V=1865.4 (9) Å^3
Space group	$P\bar{1}$ (#2)
z value	2
D_{calc}	1.271 g/cm^3
F_{000}	756
μ (CuK_α)	17.53 cm^{-1}
	Intensity measurements
Diffractometer	Rigaku AFC5R
Radiation	CuK_α (λ=1.54178 Å)
Temperature	23 °C
Attenuators	Zr foil (factors: 3.6, 12.2, 44.0)
Take-off angle	6.0°
Detector aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to detector distance	40 cm
Scan type	ω-2θ
Scan rate	16.0°/min (in omega) (2 rescans)
Scan width	(1.26+0.30 tan θ)°
$2\theta_{max}$	118.1°
No. of reflections measured	Total: 5684 unique: 5383 (R_{int}=.011)
Corrections	Lorentz-polarization absorption (trans. factors: 0.91—1.22)
	Structure solution and refinement
Structure solution	Direct methods
Refinement	Full-matrix least-squares
Function minimized	$\Sigma w(\|F_o\|-\|F_c\|)^2$
Least-squares weights	$4F_o^2/\sigma^2(F_o^2)$
p-Factor	0.05
Anomalous dispersion	All non-hydrogen atoms
No. observations ($I>3.00\ \sigma(I)$)	3517
No. variables	442
Reflection/parameter ratio	7.96
Residuals: R; R_w	0.081; 0.114

References and Notes

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