Synthesis and Evaluation of (Piperidinomethylene)bis(phosphonic acid) Derivatives as Anti-osteoporosis Agents

Mitsuo MIMURA, Mitsuo HAYASHIDA, Kiyoshi NOMIYAMA, Satoru IKEGAMI, Yasuhito IIDA, Makoto TAMURA, Yoshiyuki HIYAMA, and Yoshitaka OHISHI*

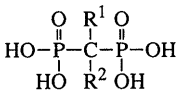
Central Research Institute, Kaken Pharmaceutical Co., Ltd., 14, Minamikawara-machi Shinomiya, Yamashina-ku, Kyoto 607, Japan. Reseived February 10, 1993

Some (piperidinomethylene)bis(phosphonic acid) derivatives were prepared and their activity to inhibit a rise in serum calcium induced by parathyroid hormone in thyroparathyroidectomised rats was evaluated. Several (4-alkylidene-, 4,4-dialkyl-, or 4-alkyl-4-halopiperidinomethylene)bis(phosphonic acid) derivatives showed considerable inhibitory activity. But compounds having aromatic and polar substituents such as azido, hydroxy, amino and amido on the piperidine ring were generally inactive. In this study, two 4-alkylidene compounds (8a and 8b) and a 4,4-cyclic dialkyl compound (61) showed potent activity when administered either intravenously or perorally.

Keywords bone resorption; osteoporosis; hypercalcemia; serum calcium; bisphosphonate; (4-substituted piperidinomethylene)bis(phosphonic acid)

It was reported that inorganic pyrophosphate (containing P–O–P bond) is present in bone[1] and inhibits resorption[2] and precipitation[3] of hydroxyapatite crystals *in vitro*. On the other hand, phosphonate compounds (containing P–C–P bond) have a variety of biological activities, such as antiviral activity,[4] chelating ability to metal ions[5] and activity against calcium metabolism.[6] *gem*-Bisphosphonates inhibit both dissolution[6a] and formation[6b,c] of bone mineral, and they powerfully inhibit bone resorption both *in vivo* and *in vitro*,[7] though their mechanism of action is not fully understood.

Much work has been done to develop bisphosphonates as drugs for treatment of osteoporosis and hypercalcemia.[8] Many kinds of bisphosphonate derivatives have been prepared and examined for bone resorption inhibitory activity.[9] Recently ethane-1-hydroxy-1,1-diphosphonic acid has entered clinical use for treatment of Paget's disease and heterotopic ossification.[10] But no clinically promising bisphosphonate for osteoporosis has yet been found. We describe here the preparation of several kinds of bis(phosphonic acids) and evaluation of their inhibitory activity upon the increase of calcium in blood of thyroparathyroidectomised rats.



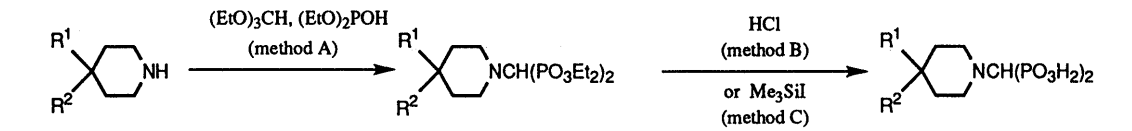
gem-bisphosphonic acids

Fig. 1

It is clinically important that medicines for osteoporosis should also possess analgesic activity. Pethidine, 4-carboethoxy-4-phenyl-1-methylpiperidine, is a well known analgesic agent. We initially designed several derivatives of pethidine with a 4-phenylpiperidino moiety and with a *gem*-bisphosphonic functional group in an attempt to find new bone resorption inhibitory agents.

Chemistry

4-Phenylpiperidine (**1a**) and 4-cyano-4-phenylpiperidine (**1b**) were treated with triethyl orthoformate in the presence of diethyl phosphite to afford tetraethyl (4-phenylpiperidinomethylene)bis(phosphonate) (**2a**) and tetraethyl (4-cyano-4-phenylpiperidinomethylene)bis(phosphonate) (**2b**), respectively (Chart 1, method A).[11] These phosphonates (**2a**, **2b**) were hydrolyzed with hydrochloric acid to give (4-phenylpiperidinomethylene)bis(phosphonic acid) (**3a**) and (4-aminocarboxy-4-phenylpiperidinomethylene)bis(phosphonic acid) (**3b**), respectively (method B). Similarly, by using methods A and B, several compounds with polar functional groups at the 4-position, such as the 4-(1-piperidino)piperidino compound (**3c**) and the 4-hydroxy-



1

a : R^1=C_6H_5, R^2=H
b : R^1=C_6H_5, R^2=CN
c : R^1=$C_5H_{10}N$, R^2=H
d : R^1=HO, R^2=H
g : R^1=$C_6H_5CH_2$, R^2=H

2

a : R^1=C_6H_5, R^2=H
b : R^1=C_6H_5, R^2=CN
c : R^1=$C_5H_{10}N$, R^2=H
d : R^1=HO, R^2=H
e : R^1=CH_3SO_3, R^2=H
f : R^1=N_3, R^2=H
g : R^1=$C_6H_5CH_2$, R^2=H

3

a : R^1=C_6H_5, R^2=H
b : R^1=C_6H_5, R^2=$CONH_2$
c : R^1=$C_5H_{10}N$, R^2=H
d : R^1=HO, R^2=H
f : R^1=N_3, R^2=H
g : R^1=$C_6H_5CH_2$, R^2=H

Chart 1

piperidino compound (**3d**), were prepared. The intermediate phosphonate (**2d**) in this preparation was converted to the 4-azidopiperidino phosphonate (**2f**) *via* the mesyloxy derivative (**2e**). Treatment of **2f** with trimethylsilyl iodide (Me_3SiI) in tetrachloromethane gave **3f** (method C). The 4-benzylpiperidino compound (**3g**) was obtained from the 4-benzylpiperidine (**1g**) *via* the phosphonate (**2g**). All of these compounds (**3a**, **3b**, **3c**, **3d**, **3g**) based on pethidine were inactive.

Then, we tried introduction of an *exo*-double bond function on the piperidine ring.[12] (Alkylidenepiperidinomethylene)bis(phosphonic acids) were synthesized as follows (Chart 2). Reactions of 1-benzyl-4-piperidone (**4**) with several Wittig reagents gave corresponding 4-alkylidene-1-benzylpiperidines (**5a**, **5b**, **5c**, **5d**, **5e**). Treatment of **5a**—**5e** with α-chloroethyl chloroformate afforded the 4-alkylidenepiperidine hydrochlorides (**6a**, **6b**, **6c**, **6d**, **6e**), respectively.[13,14] (4-Alkylidenepiperidinomethylene)bis(phosphonic acids) (**8a**, **8b**, **8c**, **8d**, **8e**) were obtained from **6a**—**6e**, respectively, by applying methods A and C. As the 4-methylenepiperidino compound (**8a**) showed considerable activity, its regioisomeric 3-methylenepiperidino compound (**13**) was prepared from 1-benzyl-3-piperidone (**9**) as shown in Chart 2. Unfortunately, **13** did not show any activity. It was found that the position of the methylidene group on the piperidine ring remarkably affected the activity. 3-Methylenepyrrolidine hydrochloride (**17**) was prepared from 1-benzyl-3-hydroxypyrrolidine (**14**) by way of the ketone (**15**) and the methylene derivative (**16**). But, attempts to convert **17** to the phosphonate (**18**) only yielded several unknown products. A bulkier and more lipophilic compound, [4-(5-dibenzo[*a*,*d*]cycloheptenylidene)piperidinomethylene]bis(phosphonic acid) (**21**) was synthesized from 4-(5-dibenzo[*a*,*d*]cyproheptenylidene)piperidine (**19**), which was obtained by removal of the methyl group from cyproheptadine with α-chloroethyl chloroformate.

As most of the 4-alkylidene compounds (**8**) showed high activity in the screening test, other similar compounds were prepared starting from tetraethyl (4-oxopiperidinomethylene)bis(phosphonate) (**24**) as a key intermediate (Chart 3). 1,4-Dioxa-8-azaspiro[4.5]decane (**22**) afforded the phosphonate (**23**) by the use of method A, in good yield. Treatment of **23** with 80% acetic acid gave the ketone (**24**) in 88% yield. The ketone (**24**) gave the 4-oxopiperidino compound (**25**) in 37% yield by use of method C. In spite of the presence of the phosphonate group, Wittig reactions of **24** with methyl- and hexyltriphenylphosphonium bromide afforded **7b** and **7e**, which were converted to **8b** and **8e**, respectively.[15] Subsequently, reactions of the ketone (**24**) with ethyl cyanoacetate and malononitrile gave the corresponding nitriles (**26a**, **26b**, respectively). The phosphonate (**26b**) was transformed to the dinitrile compound (**27**) by the use of method C. The dinitrilemethylidene compound (**27**) was inactive, in contrast to the activity of the methylidene compound (**8a**). Attempts to prepare the 4-difluoro phosphonate (**28**) by reaction of **24** with $CF_2ClCOONa$ in the presence of triphenylphosphine were unsuccessful.[16] Reaction of **24** with CCl_4 and triphenylphosphine afforded the 4-chloro-3,4-dehydropiperidino phosphonate (**30c**) in 34% yield. Formation of **30c** can be explained in terms of an unstable intermediate (A), which collapses to the stable monochloro derivative (**30c**) by dehydrochlorination.[17] Dehydropiperidino compounds (**31a**, **31b**) were prepared from **29a** and **29b**, respectively, by the use of methods A and C.

On the basis of the activity of simple alkylidene

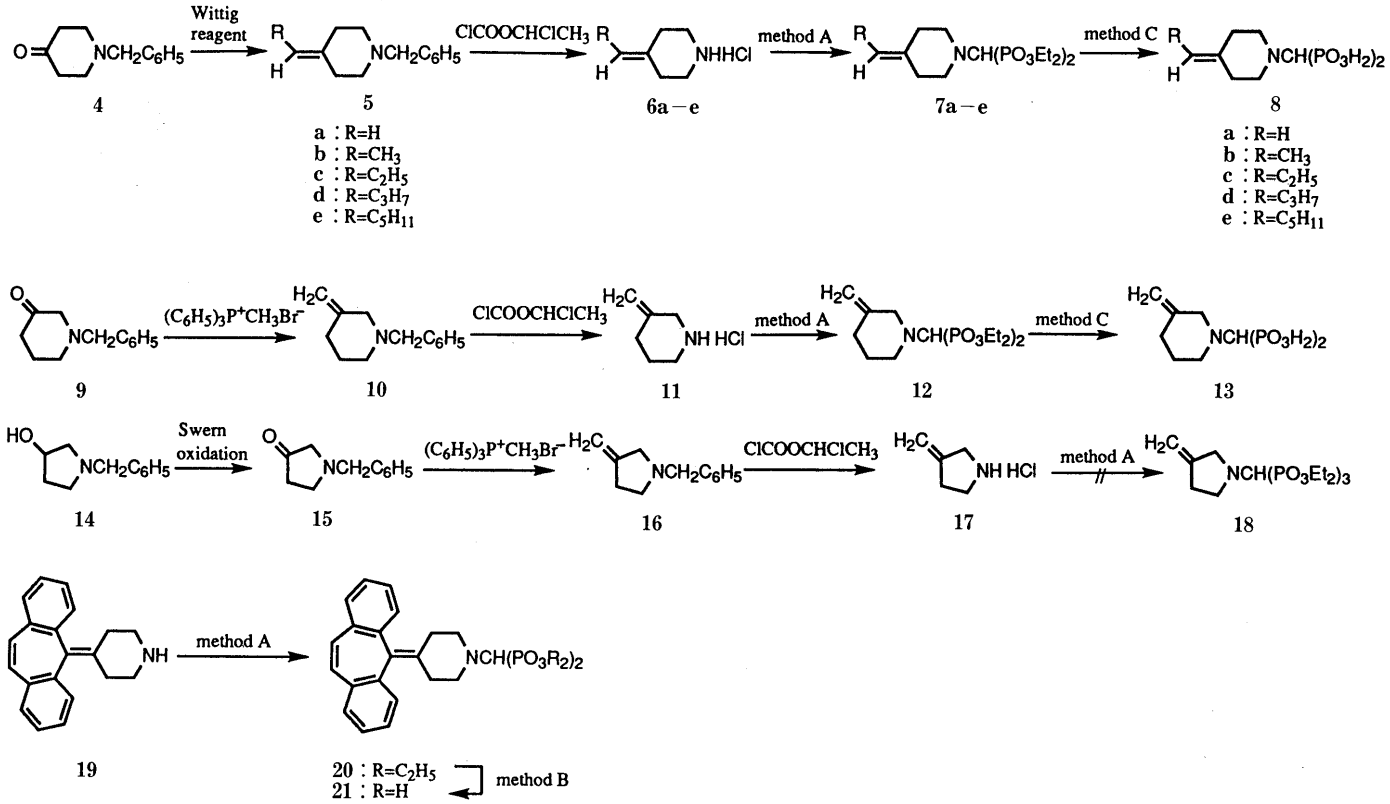


Chart 2

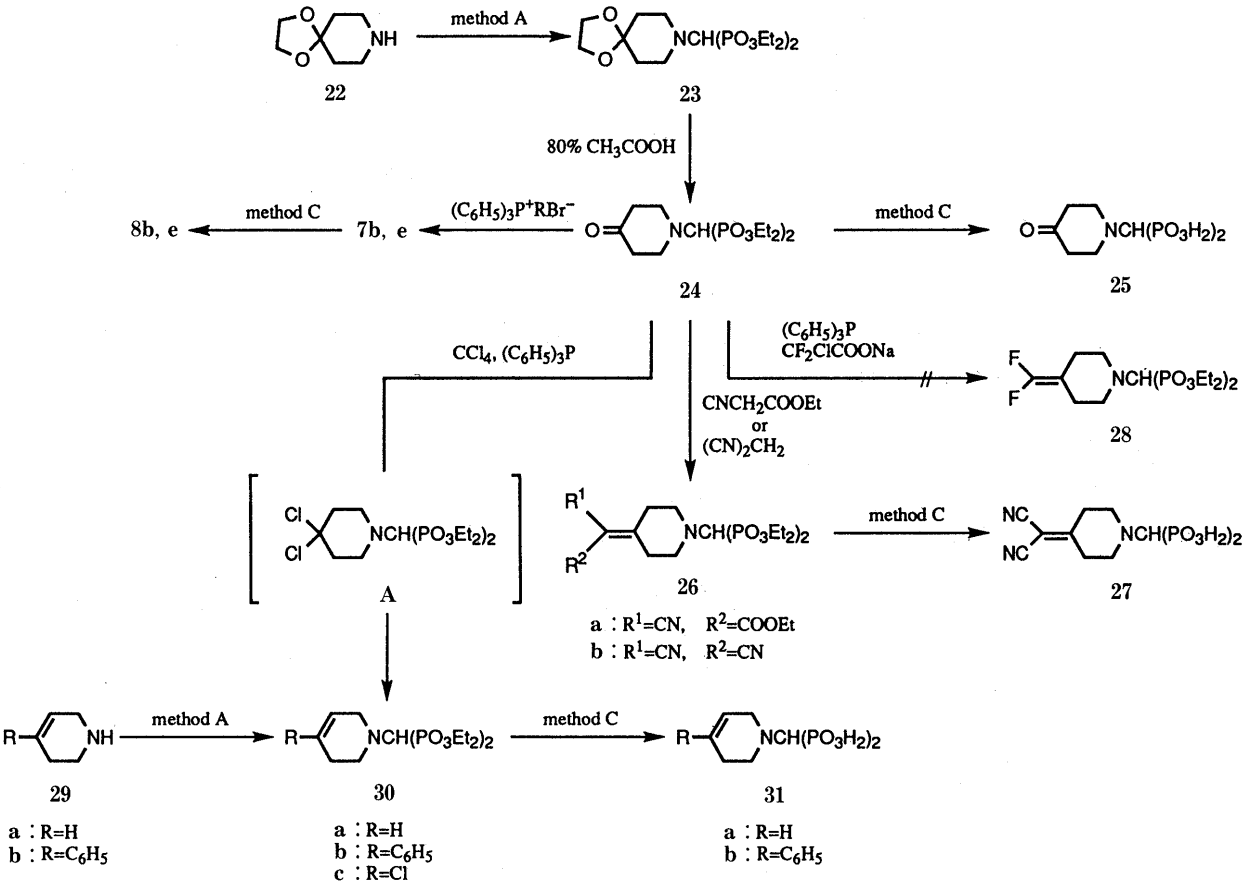


Chart 3

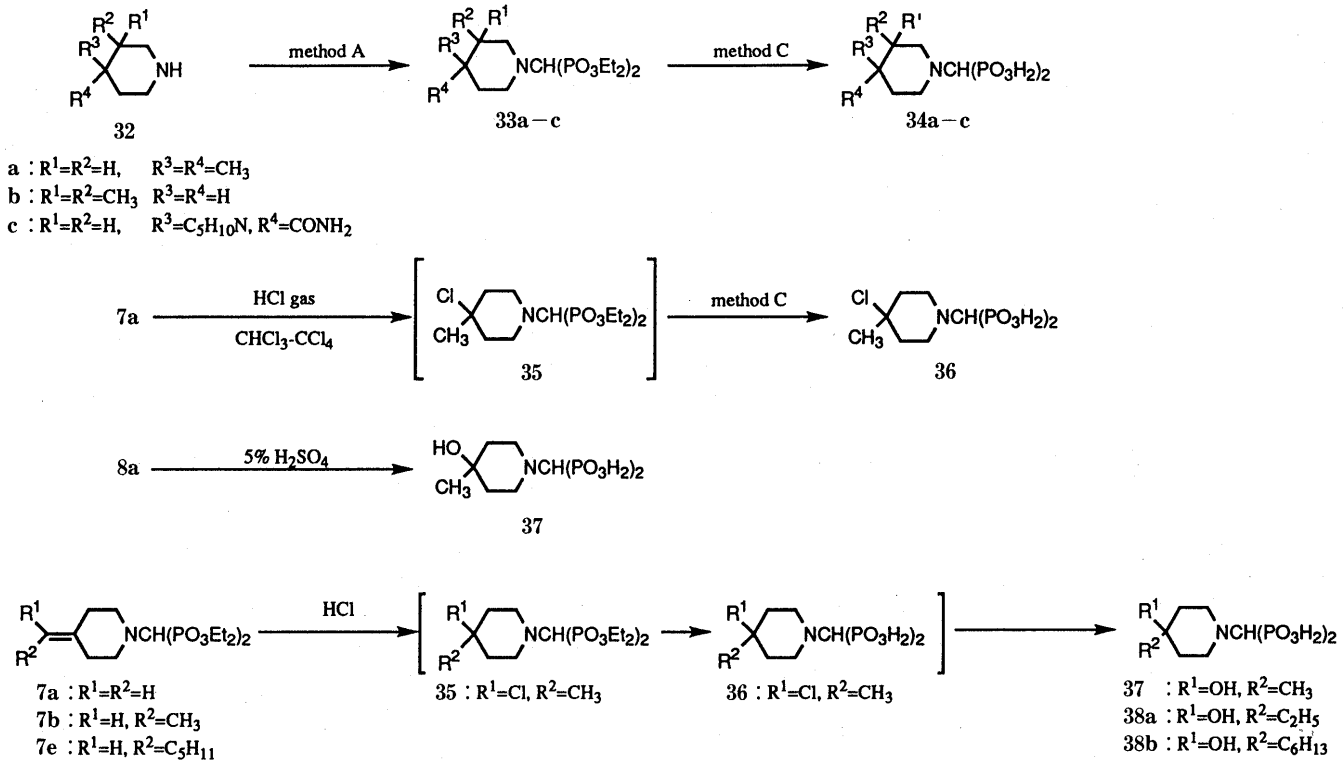


Chart 4

compounds (**8**), several *gem*-dialkyl piperidino compounds were designed and synthesized as follows (Chart 4). Compounds **34a**, **34b** and **34c** were prepared from **32a**, **32b** and **32c**, respectively, by the use of methods A and C. Furthermore, *gem*-disubstituted compounds with a chloride or hydroxy group were also prepared from the 4-alkylidene

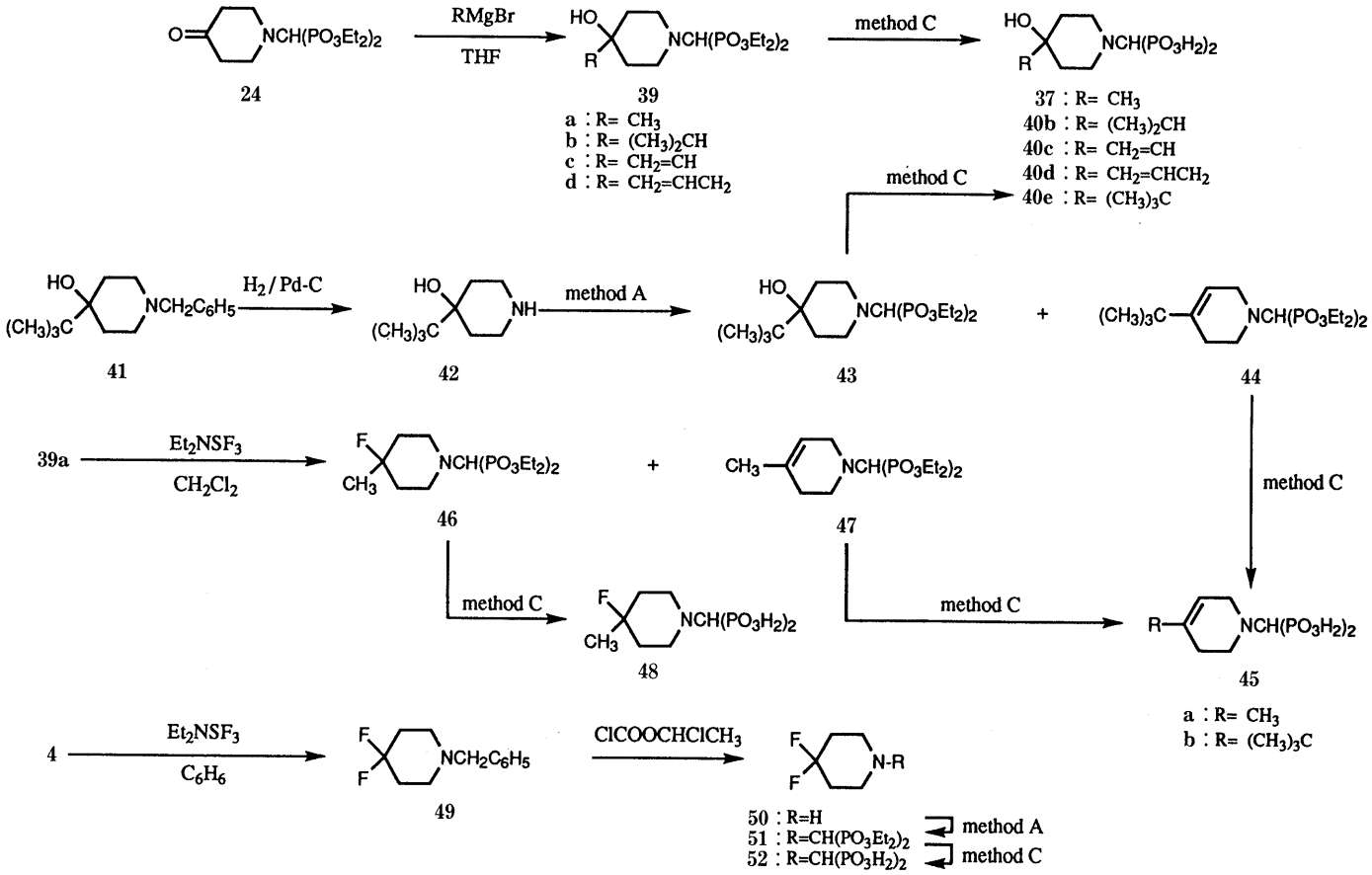


Chart 5

derivatives (**7a**, **7b**, **7e**, **8a**). Hydrogen chloride gas was bubbled into a solution of **7a** in anhydrous $CHCl_3$–CCl_4 at 70 °C to give **35**, from which **36** was obtained by the use of method C. Compound **8a** was heated in 5% H_2SO_4 to produce **37** in 75% yield. When **7a** was treated with 37% hydrochloric acid at 80 °C, the reaction was found to proceed through the intermediates **35** and **36** to furnish **37** alone after 50 h on the basis of ^{1}H-NMR spectral examination of the reaction mixture. This procedure was applied to **7b** and **7e** to provide 4-alkyl-4-hydroxypiperidino compounds (**38a**, **38b**), respectively, in good yields.

Several hydroxypiperidine compounds were prepared from the key intermediate ketone (**24**). Grignard reactions of the ketone (**24**) gave some 4-alkyl and 4-alkenyl-4-hydroxypiperidino phosphonates (**39a**, **39b**, **39c**, **39d**), which were converted to **37**, **40b**, **40c** and **40d**, respectively, by the use of method C (Chart 5). 1-Benzyl-4-*tert*-butyl-4-hydroxypiperidine (**41**) was debenzylated by catalytic reduction to afford **42**. This compound (**42**) gave a mixture of hydroxy phosphonate (**43**) and olefinic phosphonate (**44**) (**43**:**44**=1:1), which were separated by column chromatography. The phosphonates (**43**, **44**) were converted to **40e** and **45b**, respectively. Two fluoro compounds (**48**, **52**) were synthesized using diethylaminosulfur trifluoride (DAST) as follows.[18] Reaction of **39a** with DAST gave a mixture of **46** and **47** (1:1).[19] These results suggested that a halide or hydroxy group as the geminal disubstituent at the 4-position of the piperidine ring would be readily eliminated to afford the coresponding olefin. The phosphonates (**46**, **47**) were converted to **48** and **45a**, respectively. The difluoro compound (**52**) was successfully synthesized starting from **4** by similar fluorination of **4**.

Several spiro compounds were designed to increase the aliphatic character of the active alkylidene and *gem*-dialkyl compounds (Chart 6). Three kinds of spiro compounds (**55**, **61**, **63**) in which a 6-, 5- or 3-membered ring is substituted at the 4-position of the piperidine ring were prepared as follows. 3,3-Tetramethylene glutaric anhydride (**56**) was treated with benzylamine to give the *N*-benzylimide (**57**), which was reduced with $LiAlH_4$ to give *N*-benzyl-4,4-tetramethylenepiperidine (**58**). 8-Azaspiro[4.5]decane (**59**) was obtained by treatment of **58** with α-chloroethyl chloroformate.[20] Compounds **53** and **59** were converted to **55** and **61**, respectively, by the use of methods A and C. The 4-methylidenepiperidino phosphonate (**7a**) was treated with CF_2Br_2 in the presence of Et_2Zn to afford tetraethyl 1,1-difluoro-6-azaspiro[2.5]octane phosphonate (**62**) in 14% yield.[21] The phosphonate (**62**) was converted to **63** by the use of method C. Some other regioisomeric spiro compounds were designed and prepared. 2-Azaspiro[5.5]-undecane (**65**) was synthesized from cyclohexylaldehyde (**64**) according to Liebowitz's method[22] and a regioisomeric compound (**67**) was obtained from **65** by the use of methods A and C. A spiro amine (**75**) was prepared from **69** through **69**—**74** as shown in Chart 6.[23] The amine (**75**) was converted to another regioisomeric compound (**77**) by the use of methods A and C.[24] The pyrrolidino spiro compound (**82**) was also prepared starting from **69** by the route shown in Chart 6.

In order to examine the activity of other *N*-containing

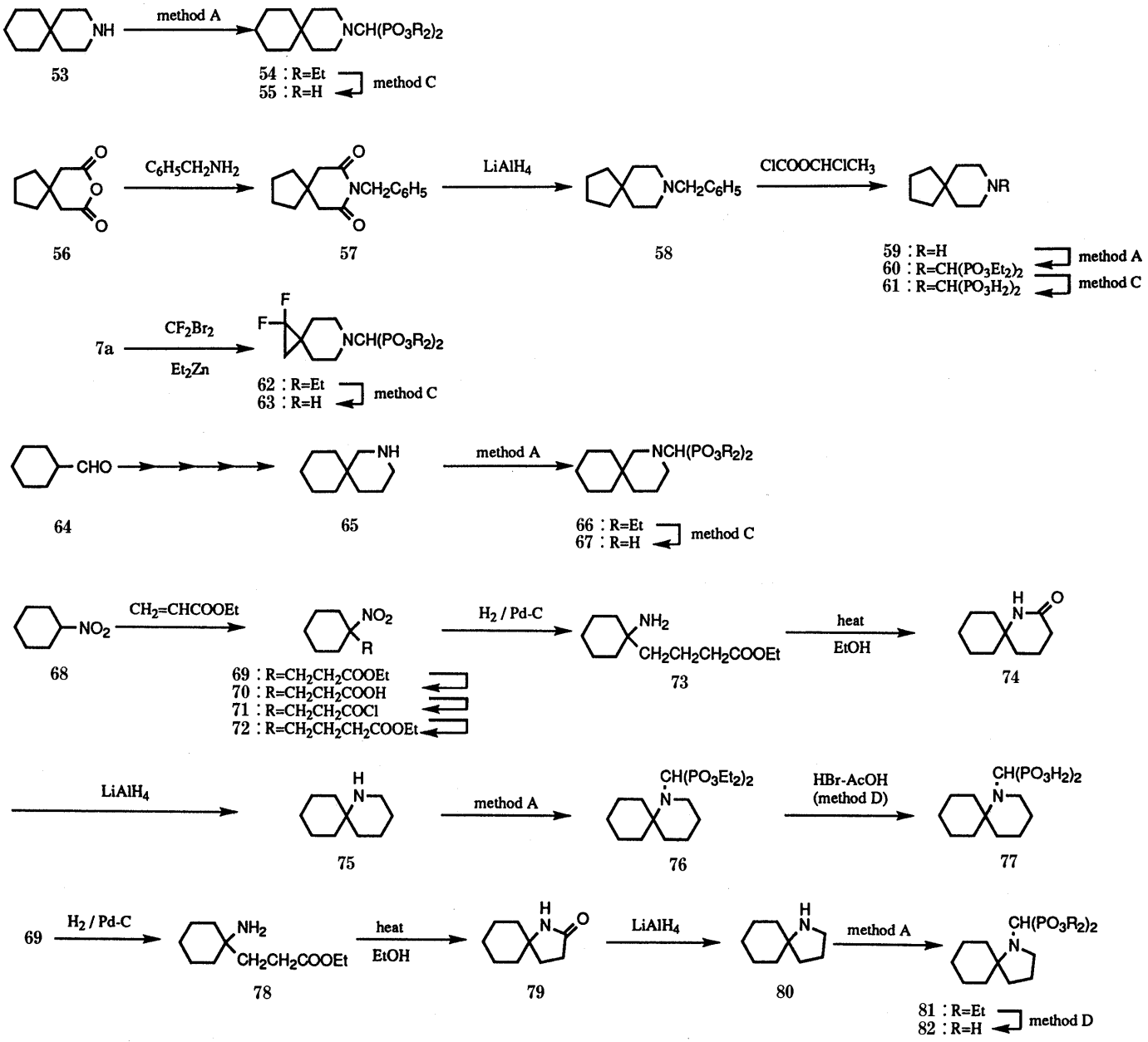


Chart 6

heterocyclic bis(phosphonic acids), several derivatives (**85**, **88**, **91**) were similarly prepared. Some cycloalkylaminomethylenebis(phosphonic acids) were also prepared (Chart 7). The 1-adamantanamino compound (**94**) was obtained from 1-adamantanamine (**92**) by the use of methods A and C. The 1,4-cyclohexanedione mono-ethylene ketal (**95**) was treated with $NaBH_4$ to give the hydroxy derivative (**96**), and this was reacted with methanesulfonyl chloride to give the methanesulfonyloxy derivative (**97**). Compound **97** was treated with NaN_3 in dimethylformamide (DMF) to give the azido compound (**98**), which was reduced to the amino derivative (**99**) with $LiAlH_4$. The amine (**99**) gave the phosphonate (**100**), which was treated with AcOH to give the keto phosphonate (**101**). The ketone (**101**) was derived to the methylidene phosphonate (**102**) by use of the Wittig reaction. The methylidene compound (**103**) was obtained from **102** by the use of method C. An attempt at preparation of the 1-aminohomopiperidino phosphonate (**105**) from 1-aminohomopiperidine (**104**) by the use of method A was unsuccessful and a mixture of homopiperidino phosphonate (**106**) and aminomonophosphonate (**107**) (**106**:**107**=1:1) was obtained. It was presumed that **107** was formed from the desired compound (**105**) by elimination of a phosphonate group.

Physical data for the bis(phosphonic acids) and their tetraethyl phosphonates are shown in Tables I and II, respectively.

Activity and Discussion

These methylenebis(phosphonic acid) compounds were tested for ability to inhibit the rise in serum calcium induced by parathyroid hormone (PTH) in thyroparathyroidectomised rats.[25] First, their inhibitory activities were examined by administration *via* the subcutaneous (10 mg/kg) or intravenous route (0.2 mg/kg). The inhibitory activities (%) *versus* the control are shown in Table III, in which the

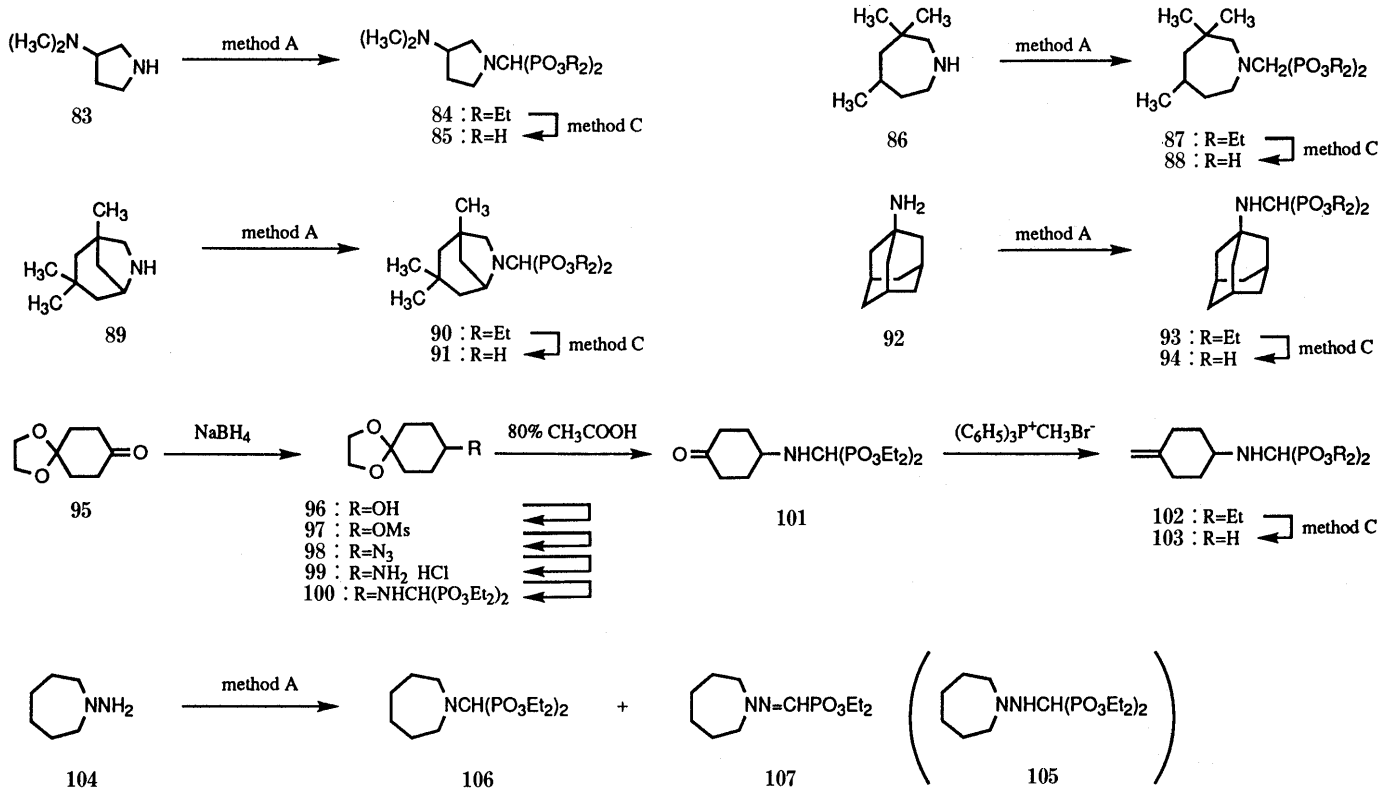


Chart 7

compounds are classified into 10 types (I—X).

The compounds of type I have aromatic substituents (**3a**, **3g**) or polar functional groups such as amino (**3c**), hydroxy (**3d**) and azido (**3f**) at the 4-position of the piperidine ring, and all of these compounds were inactive. The compounds of type II have an *exo*-double bond on the piperidine ring. Although 4-alkylidene derivatives (**8a**, **8b**, **8d**, **8e**) showed the inhibitory activity, changing the 4-alkylidene group to an aromatic moiety (**21**) is not effective. Change of the position of the *exo*-double bond considerably influenced the activity; for example, the 3-methylene compound (**13**) was inactive in contrast to the activity of the 4-methylene compound (**8a**). The 4-oxo compound (**25**) and 4-dicyanomethylidene compound (**27**) were both inactive. The simple 4-alkylidene compounds series showed the activity, but the polar compounds (**25**, **27**) with an oxo and a cyano group were inactive. The compounds of type III have a 3,4-dehydropiperidine ring and both the unsubstituted compound (**31a**) and the 4-methyl compound (**45a**) showed the activity. But the 4-phenyl (**31b**) and the 4-*tert*-butyl compounds (**45b**) were inactive. An aromatic substituent was not suitable in compounds of this type. The compounds of type IV have geminal disubstituents (same or different functional groups) at the 3- or 4-position. Two kinds of dimethyl compounds (**34a**, **34b**) were active, but the compounds (**3b**, **34c**) having an aromatic or polar functional group were inactive in this type. The compounds of type V have hydroxy and various alkyl groups at the 4-position, and these compounds were inactive except for **38b**. Though the 4-dimethyl compound (**34a**) showed the activity, the hydroxy compound (**37**) had no activity. The 4-hydroxy compound (**3d**) of type I was also inactive. These data suggested that introduction of a hydroxy group on the piperidine ring is ineffective. On the contrary, halogen substitution of one methyl group of **34a** preserved the activity. In type VI, the chloro compound (**36**) was active, but both fluoro compounds (**48**, **52**) were inactive. In type VII, there are several spiro compounds and two (**61**, **55**) involving a five- or six-membered ring and the piperidine ring at the 4-position showed the activity. But, the three-membered ring analogue (**63**) showed no activity. Among the three regioisomers (**55**, **67**, **77**), the location of the spiro union considerably influenced the activity. The compounds (**77**, **55**) having the spiro union at the 2- or 4-position of the piperidine ring showed the activity, but the compound (**67**) having the spiro union at the 3-position of the piperidine ring was inactive. Changing the piperidine ring of the spiro compound (**77**) to a pyrrolidine ring retained the activity. The spiro pyrrolidine compound (**82**) showed the activity, but the polar 3-dimethylamino-pyrolidine compound (**85**) had no activity. On the other hand, two homopiperidinemethylenebis(phosphonic acid) derivatives (**88**, **91**) substituted with a methyl group were both active. The examinations of *N*-methylenebis(phosphonic acid) derivatives of pyrollidine and homopiperidine, piperidine analogues, might yield novel active compounds. By way of trial, two cyclohexylamino-*N*-methylenebis(phosphonic acid) derivatives (**94**, **103**) were prepared and tested for the inhibitory activity. Compound **94** was active but **103**, which is similar to the active compound (**8a**), was inactive.

It was reported that cyclic *gem*-bisphosphonic acid derivatives were active, especially those containing a nitrogen atom in the ring, such as pyridine derivatives.[26] The *N*-methylenebis(phosphonic acid) derivatives of piperidine showed considerable activity and the degree of the

TABLE I. Physical Data for (Piperidinomethylene)bis(phosphonic acid) Derivatives

Compd.	mp (°C)	^{1}H-NMR (ppm, in D_2O)	Formula	*Anal.* Calcd (Found) C	H	N	FAB-MS (*m/z*)	Method	Yield (%)
3a	247—249	2.12 (4H, m, 3-, 5-CH_2), 2.96 (1H, m, 4-CH), 3.26 (1H, t, J=18.2 Hz, NCH), 3.82 (4H, m, 2-, 6-CH_2), 7.41 (5H, m, aromatic H), (as Na salt)	$C_{12}H_{19}NO_6P_2$	42.99 (42.95	5.71 5.51	4.18 4.29)	N.D	B	78
3b	>280	2.02—2.92 (4H, m, 3-, 5-CH_2), 3.30 (1H, t, J=17.0 Hz, $NCHP_2$), 3.65—3.94 (4H, m, 2-, 6-CH_2), 7.31—7.55 (5H, m, aromatic H)	$C_{13}H_{20}N_2O_7P_2$	41.28 (41.46	5.33 5.56	7.41 7.72)	377 $[M-H]^-$	B	85
3c	257—260	1.35—2.52 (10H, m, 3-, 5-, 3′-, 4′-, 5′-CH_2), 3.06 (1H, t, J=15.0 Hz, $NCHP_2$), 3.51—3.94 (9H, m, 2-, 6-, 2′-, 6′-CH_2, 4-CH)	$C_{11}H_{24}N_2O_6P_2$	38.60 (38.84	7.07 7.26	8.18 8.36)	341 $[M-H]^-$	B	73
3d	250—252	1.71—2.26 (4H, m, 3-, 5-CH_2), 3.32 (1H, t, J=17.0 Hz, $NCHP_2$), 3.50—4.09 (5H, m, 2-, 6-CH_2, 4-CH)	$C_6H_{15}NO_7P_2$	26.19 (26.34	5.50 5.89	5.09 5.37)	274 $[M-H]^-$	B	89
3f	274—276	1.82—2.31 (4H, m, 2-. 6-CH_2), 3.29 (1H, t, J=17.0 Hz, $NCHP_2$), 3.50—3.97 (5H, m, 3-, 5-CH_2, 4-CH)	$C_6H_{14}N_4O_6P_2$	24.01 (24.31	4.70 4.65	18.67 18.83)	299 $[M-H]^-$	B	81
3g	266—269	1.56 (2H, m, 3- or 5-CH_2), 1.90 (1H, m, 4- CH), 1.96 (2H, m, 3- or 5-CH_2), 2.64 (2H, d, J=15.0 Hz, $CH_2C_6H_5$), 3.21 (1H, t, J=18.0 Hz, $NCHP_2$), 3.66 (4H, m, 2-, 6-CH_2), 7.36 (5H, m, C_6H_5), (as Na salt)	$C_{13}H_{21}NO_6P_2$	44.71 (44.92	6.06 6.18	4.01 4.32)	N.D.	B	71
8a	231.5—233	2.54—2.59 (4H, m, 3-, 5-CH_2), 3.21 (1H, t, J=17.0 Hz, $NCHP_2$), 3.67—3.71 (4H, m, 2-, 6-CH_2), 4.94 (2H, s, CH_2=), (as Na salt)	$C_6H_{15}NO_6P_2$	37.45 (37.26	5.06 5.16	4.68 4.87)	270 $[M-H]^-$	C	86
8b	228—229.5	1.62 (3H, d, $C\underline{H}_3CH$=), 2.43—2.71 (4H, m, 3-, 5-CH_2) 3.30 (1H, t, NCH) 3.58—3.71 (4H, m, 2-, 6-CH_2), 5.49 (1H, q, $CH_3C\underline{H}$=)	$C_8H_{17}NO_6P_2$	33.69 (33.91	6.01 5.86	4.91 4.72)	N.D.	C	88
8c	235—237	0.88—0.99 (3H, m, CH_3), 1.96—2.12 (2H, m, $CH_3C\underline{H}_2$), 2.42—2.66 (4H, m, 3-, 5-CH_2), 3.15 (1H, t, J=15.0 Hz, NCH), 3.56—3.71 (4H, m, 2-, 6-CH_2), 5.44 (1H, m, =CH)	$C_9H_{19}NO_6P_2$	36.13 (36.02	6.40 6.29	4.68 4.78)	298 $[M-H]^-$	C	25
8d	226—228	0.81—0.62 (3H, m, CH_3), 1.32—1.44 (2H, m, $CH_3C\underline{H}_2$), 1.97—2.07 (2H, m, $C\underline{H}_2CH$=), 2.44—2.67 (4H, m, 3-, 5-CH_2), 3.33 (1H, t, J=17.0 Hz, NCH), 3.60—3.69 (4H, m, 2-, 6-CH_2), 5.46 (1H, t, J=7.0 Hz, CH=)	$C_{10}H_{21}NO_6P_2$	38.35 (38.21	6.76 6.53	4.47 4.88)	312 $[M-H]^-$	C	53
8e	223.5—225.0	0.87 (3H, t, $-CH_2CH_2C\underline{H}_3$), 1.29—1.39 (6H, m, $-CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.03—2.06 (2H, m, $=CHC\underline{H}_2$), 2.50—2.75 (4H, m, 3-, 5-CH_2), 3.30 (1H, t, NCH), 3.60—3.72 (4H, m, 2-, 6-CH_2), 5.45 (1H, t, =CH–), (as Na salt)	$C_{12}H_{25}NO_6P_2$	42.23 (42.59	7.38 7.63	4.10 4.27)	N.D.	C	97
13	237—239	1.71—2.53 (4H, m, 4-, 5-CH_2), 3.67 (1H, t, J=25.0 Hz, NCH), 3.74—3.85 (2H, m, 6-CH_2), 4.03 (1H, d, J=13.0 Hz, one of 2-CH_2), 4.37 (1H, d, J=13.0 Hz, one of 2-CH_2), 5.15 (2H, br s, CH_2=)	$C_7H_{15}NO_6P_2$	31.01 (31.25	5.58 5.41	5.17 5.37)		C	43
21	212—215	2.36—2.77 (4H, m, $NCH_2C\underline{H}_2 \times 2$), 3.26 (1H, t, J=18.0 Hz, NCH), 3.45—3.82 (4H, m, $NCH_2 \times 2$), 0.76 (2H, s, CH=CH), 7.35—7.50 (8H, m, phenyl H)	$C_{21}H_{23}NO_6P_2$	56.38 (56.63	5.18 5.38	3.13 3.24)	446 $[M-H]^-$	C	59
25	260—264	2.06—2.17 (4H, m, 3-, 5-CH_2), 3.67 (1H, t, J=25.0 Hz, NCH), 3.74—3.85 (2H, m, 6-CH_2), 4.03 (1H, d, J=13.0 Hz, one of 2-CH_2), 5.15 (2H, br s, CH_2=)	$C_6H_{13}NO_7P_2$	26.39 (26.58	4.80 4.63	5.13 5.33)	272 $[M-H]^-$	C	37
27	250—254	3.13—3.24 (4H, m, 3-, 5-CH_2), 3.80 (1H, t, J=19.0 Hz, NCH), 3.88—3.98 (4H, m, 2-, 6-CH_2)	$C_9H_{13}NO_6P_2$	33.66 (33.59	4.08 4.26	3.08 3.38)	320 $[M-H]^-$	C	62
31a	248—252	2.44—2.53 (2H, m, 5-CH_2), 3.40 (1H, t, J= 18.0 Hz, NCH), 3.72—3.81 (2H, m, 6-CH_2), 4.06—4.26 (2H, m, 2-CH_2), 5.70—5.79 (1H, m, 3- or 4-H), 5.92—6.02 (1H, m, 3- or 4-H)	$C_6H_{13}NO_6P_2$	28.03 (28.51	5.10 5.27	5.45 5.63)	256 $[M-H]^-$	B	66
31b	246—249	2.89—2.96 (2H, m, 5-CH_2), 3.46 (1H, t, J= 17.0 Hz, NCH), 3.90—3.96 (2H, m, 6-CH_2), 4.35—4.42 (2H, m, 2-CH_2), 6.13—6.19 (1H, m, =CH), 7.36—7.60 (5H, m, phenyl H)	$C_{12}H_{17}NO_6P_2$	43.25 (43.41	5.14 5.32	4.20 4.03)	332 $[M-H]^-$	C	47

TABLE I. (continued)

Compd.	mp (°C)	^{1}H-NMR (ppm, in D_2O)	Formula	*Anal.* Calcd (Found) C	H	N	FAB-MS (*m/z*)	Method	Yield (%)
34a	168—170	1.04 (6H, s, $CH_3 \times 2$), 1.65—1.78 (4H, m, 3-, 5-CH_2), 3.31 (1H, t, J=18.0 Hz, NCH), 3.35—4.03 (4H, m, 2-, 6-CH_2)	$C_8H_{19}NO_6P_2$	33.46 (33.82	6.67 6.45	4.88 4.69)	286 $[M-H]^-$	B	57
34b	226—229	1.04 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.32—1.63 (2H, m, 4-CH_2), 1.81—2.05 (2H, m, 5-CH_2), 3.24 (1H, t, J=18.0 Hz, NCH), 3.21—3.46 (2H, m, 2-CH_2), 3.48—3.65 (2H, m, 6-CH_2)	$C_8H_{19}NO_6P_2$	33.46 (33.62	6.67 6.37	4.88 4.65)	286 $[M-H]^-$	B	27
34c	>280	1.55 (6H, m, $NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2$), 1.82 (4H, m, $NCH_2C\underline{H}_2CC\underline{H}_2CH_2$), 2.57 (4H, m, $NC\underline{H}_2CH_2CH_2CH_2C\underline{H}_2$), 3.40 (1H, t, J=18.0 Hz, NCH), 3.82 (4H, m, $NC\underline{H}_2CH_2C$-$CH_2C\underline{H}_2$)	$C_{12}H_{25}N_3O_7P_2$	37.41 (37.26	6.54 6.38	10.91 10.51)	N.D.	B	70
36	217—220	1.71 (3H, s, CH_3), 2.12—2.30 (4H, m, 3-, 5-CH_2), 3.48—3.68 (2H, m, ax H of 2-, 6-CH_2), 4.13—4.28 (2H, m, eq H of 2-, 6-CH_2), 3.64 (1H, t, J=18.0 Hz, NCH)	$C_7H_{16}ClNO_6P_2$	27.33 (27.69	5.24 5.47	4.85 4.61)	308 $[M+H]^+$	C	47
37	224—227	1.33 (3H, s, CH_3), 1.86—1.98 (4H, m, 3-, 5-CH_2), 3.17 (1H, t, J=18.0 Hz, NCH), 3.38—3.73 (2H, m, ax H of 2-, 6-CH_2), 3.73—4.06 (2H, m, eq H of 2-, 6-CH_2)	$C_7H_{17}NO_7P_2$	29.08 (28.86	5.93 6.13	4.84 5.08)	290 $[M+H]^+$		75
38a	245—247	0.92 (3H, t, J=8.1 Hz, CH_3), 1.57 (2H, q, J=8.1 Hz, $C\underline{H}_2CH_3$), 1.83—1.95 (4H, m, 3-, 5-CH_2), 3.34 (1H, t, J=18.0 Hz, NCH), 3.51—3.65 (2H, m, two of CH_2NCH_2), 3.80—4.10 (2H, m, two of 2- or 6-CH_2)	$C_8H_{19}NO_7P_2$	31.69 (31.89	6.32 6.57	4.62 4.86)	304 $[M+H]^+$	B	81
38b	258—260	0.85 (3H, m, CH_3), 1.19—1.43 (8H, m, $C\underline{H}_2$-$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.82—1.95 (2H, m, $CC\underline{H}_2CH_2CH_2$), 3.18 (1H, t, J=18.2 Hz, NCH), 3.43—3.57 (4H, m, 3-, 5-CH_2), 3.85—4.12 (4H, m, 2-, 6-CH_2), (as Na salt)	$C_{12}H_{27}NO_7O_2$	40.11 (40.36	7.57 7.69	3.90 4.13)	404 $[M+H]^+$	B	72
40b		0.90 [6H, d, J=7.0 Hz, $(CH_3)_2CH$], 1.64—1.76 [1H, m, $(CH_3)_2CH$], 1.84—1.96 (4H, m, 3-, 5-CH_2), 3.14 (1H, t, J=18 Hz, NCH), 3.78—4.06 (4H, m, 2-, 6-CH_2)	$C_9H_{21}NO_7P_2$	34.08 (34.29	6.67 6.92	4.42 4.71)			
40c	239—241	1.82—2.22 (4H, m, 3-, 5-CH_2), 3.46—4.22 (4H, m, 2-, 6-CH_2), 3.62 (1H, t, J=18.0 Hz, NCH), 5.17 [1H, d, J=10.0 Hz, CH_2=(*cis* H)], 5.30 [1H, d, J=16.0 Hz, CH_2=*trans*-H)], 5.97 (1H, q, J=10.2 Hz, CH=)	$C_8H_{17}NO_7P_2$	31.90 (32.24	5.69 5.82	4.65 4.60)	300 $[M-H]^-$	C	89
40d	236—238	1.85—2.10 (4H, m, 3-, 5-CH_2), 2.29 (2H, d, J=8.0 Hz, $CHCH_2$=), 3.45—4.14 (4H, m, 2-, 6-CH_2), 3.65 (1H, t, J=18.0 Hz, NCH), 5.16 [1H, d, J=11.0 Hz, CH_2=(*trans*-H)], 5.21 [1H, d, J=9.0 Hz, CH_2=(*cis*-H)], 5.81—5.96 (1H, m, CH=)	$C_8H_{19}NO_7P_2$	34.30 (34.62	6.08 6.24	4.44 4.69)	314 $[M-H]^-$	C	64
40e	251—254	0.81 [9H, s, $(CH_3)_3C$], 1.72—2.00 (4H, m, 3-, 5-CH_2), 3.07 (1H, t, J=17.0 Hz, NCH), 3.29—3.39 (2H, m, ax H of 2-, 6-CH_2), 3.82—3.95 (2H, m, eq H of 2-, 6-CH_2)	$C_{10}H_{23}NO_7P_2$	36.26 (36.51	7.00 7.25	4.23 4.16)	330 $[M-H]^-$	C	69
45a	237—240	1.77 (3H, s, CH_3), 2.36—2.47 (2H, m, 5-CH_2), 3.43 (1H, t, J=17.0 Hz, NCH), 3.69—3.79 (2H, m, 6-CH_2), 3.98—4.23 (2H, m, 2-CH_2), 5.43—5.48 (1H, m, =CH)	$C_7H_{15}NO_6P_2$	31.01 (31.26	5.58 5.24	5.17 4.93)	270 $[M-H]^-$	C	62
45b	228—230	1.07 (9H, s, $CH_3 \times 3$), 2.48—2.56 (2H, m, 5-CH_2), 3.21 (1H, t, J=18.0 Hz, NCH), 3.72—3.78 (2H, m, 6-CH_2), 4.12—4.22 (2H, m, 2-CH_2), 5.49—5.54 (1H, m, CH=)	$C_{10}H_{21}NO_6P_2$	38.35 (38.71	6.76 6.92	4.47 4.85)	312 $[M-H]^-$	C	60
48	236—239	1.46 (3H, d, J=22.0 Hz, CH_3), 2.10—2.26 (4H, m, 3-, 5-CH_2), 3.36 (1H, t, J=17.0 Hz, NCH), 3.55—3.65 (2H, m, ax H of 2-, 6-CH_2), 3.87—4.01 (2H, m, eq H of 2-, 6-CH_2)	$C_7H_{16}NFO_6P_2$	28.88 (29.05	5.54 5.76	4.81 4.96)	286 $[M-H]^-$	C	97
52	218—220	2.42 (4H, m, 3-, 5-CH_2), 3.50 (1H, t, J=17.0 Hz, NCH), 3.89 (4H, m, 2-, 6-CH_2), (as Na salt)	$C_6H_{13}NO_6P_2$	26.10 (26.28	4.75 4.61	5.07 5.24)	294 $[M-H]^-$	B	55

TABLE I. (continued)

Compd.	mp (°C)	^{1}H-NMR (ppm, in D_2O)	Formula	*Anal.* Calcd (Found) C	H	N	FAB-MS (*m/z*)	Method	Yield (%)
55	232—234	1.25—1.65 (12H, m, ring CH_2 × 6), 1.83—2.02 (2H, m, ring CH_2), 3.17 (1H, dd, CH), 3.32—3.48 (2H, m, NCH_2), 3.76—3.98 (2H, m, NCH_2)	$C_{11}H_{23}NO_6P_2$	40.37 (40.53	7.08 7.32	4.28 4.46)	326 $[M-H]^-$	B	54
61	177—181	1.39—1.69 (8H, m, 1-, 2-, 3-, 4-CH_2), 1.68—1.86 (4H, m, 6-, 10-CH_2), 3.15 (1H, t, J=18.0 Hz, NCH), 3.35—3.65 (2H, m, 7- or 9-CH_2), 3.65—3.98 (2H, m, 7- or 9-CH_2)	$C_{10}H_{21}NO_6P_2$	38.35 (38.14	6.76 6.53	4.47 4.26)	312 $[M-H]^-$	B	63
63	231—233	2.08—2.16 (4H, m, 4-, 8-CH_2), 2.94 (2H, t, J=16.0 Hz, 2-CH_2), 3.65 (1H, t, J=18.0 Hz, NCH), 4.03—4.17 (2H, m, 5- or 7-CH_2)	$C_8H_{15}NO_6P_2$	29.92 (30.15	4.71 4.92	4.36 4.48)	320 $[M-H]^-$	B	54
67	240—245	1.11—1.98 (14H, m, 4-, 5-, 7-, 8-, 9-, 10-, 11-CH_2), 3.17 (1H, t, J=18.0 Hz, NCH), 3.38 (2H, s, 1-CH_2), 3.46—3.65 (2H, m, 3-CH_2)	$C_{11}H_{23}NO_6P_2$	40.37 (40.62	7.08 7.27	4.28 4.56)	326 $[M-H]^-$	B	53
77	240—245	1.13—2.19 (16H, m, 3-, 4-, 5-, 7-, 8-, 9-, 10-, 11-CH_2), 3.62—3.85 (2H, m, 2-CH_2), 3.70 (1H, t, J=19.0 Hz, NCH), (as Na salt)	$C_{11}H_{21}NO_6P_2$	40.37 (40.48	7.08 7.31	4.28 4.15)	326 $[M-H]^-$	D	36
82	>290 (as 2Na salt)	1.13—2.16 (14H, m, 3-, 4-, 6-, 7-, 8-, 9-, 10-CH_2), 3.53 (1H, t, J=17.0 Hz, NCH), 3.70—3.87 (2H, m, 2-CH_2), (as 2Na salt)	$C_{10}H_{21}NO_6P_2$	38.35 (38.71	6.76 6.92	4.47 4.68)	312 $[M-H]^-$	D	67
85	223—227	2.20—3.10 (2H, m, 4-CH_2), 3.00 (6H, s, CH_3 × 2), 3.40—4.61 (5H, m, 2-, 5-CH_2, 3-CH), 3.63 (1H, t, J=17.0 Hz, NCH)	$C_7H_{18}NO_6P_2$	29.18 (29.45	6.30 6.57	9.72 10.02)	287 $[M-H]^-$	B	76
88	237—239	0.96—1.02 (9H, m, CH_3 × 3), 1.06—2.20 (5H, m, ring CH_2 × 2, ring CH), 3.32 (1H, dd, NCH), 3.40—3.75 (4H, m, ring CH_2 × 2)	$C_{10}H_{22}NO_6P_2$	38.22 (37.95	7.06 7.26	4.46 4.59)	313 $[M-H]^-$	B	69
91	239—241	1.03 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.53—1.76 (4H, m, ring CH_2 × 2), 2.12—2.28 (2H, m, ring CH_2), 3.41 (1H, J=25.0 Hz, $NCHP_2$), 3.62 (1H, d, J=12.0 Hz, one H of NCH_2), 3.94 (1H, d, J=12.0 Hz, one H of NCH_2), 4.63—4.70 (1H, m, $CH_2\underline{C}HN$)	$C_{11}H_{23}NO_6P_2$	40.37 (40.62 (40.38	7.08 7.34 7.16	4.28 4.65) 4.47)	326 $[M-H]^-$	B	72
94	250—253	1.62—2.27 (15H, m, adamantane ring H), 3.36 (1H, t, J=25.0 Hz, $NCHP_2$)	$C_{11}H_{21}NO_6P_2$	40.62 (40.49	6.51 6.37	4.31 4.21)	324 $[M-H]^-$	B	72
103	224—225	1.44—1.62 (2H, m, cyclohexane ring CH_2), 2.10—2.52 (6H, m, cyclohexane ring CH_2 × 3), 3.37 (1H, t, J=25.0 Hz, NCH), 4.77 (2H, s, $=CH_2$)	$C_8H_{17}NO_6P_2$	33.69 (33.85	6.01 6.34	4.91 5.23)	284 $[M-H]^-$	C	44

activity of individual bisphosphonic acids varied greatly from compound to compound.[27] In this study, the activity was considerably influenced by the kinds of substituent groups and their position on the piperidine ring. Several structure–activity profiles were obtained. Most of the compounds substituted with alkyl groups (alkyl, alkylidene, dialkyl, cyclic dialkyl) at the 4-position of the piperidine ring showed considerable inhibitory activity. But aromatic substitution resulted in loss of activity. When polar groups such as hydroxy, amino, amide and azido group were present on the piperidine ring, the compounds also showed no activity.

The ED_{50} values[28] of ten active compounds (**8a**, **8b**, **8d**, **34a**, **36**, **55**, **61**, **77**, **82**, **88**) and the fluoro compound (**48**)[29] were determined by administration *via* the intravenous or peroral route (Table IV).

Three compounds (**8a**, **8b**, **61**) showed potent activity after administration *via* the intravenous route. The other compounds (**8d**, **34a**, **36**, **48**) displayed about 1/2—1/3 the inhibitory activity of **8a**, **8b** and **61**. The activity of the three compounds (**8a**, **8b**, **61**) was also observed on administration by the peroral route but other compounds (**8d**, **48**, **55**, **77**, **82**, **88**) showed no activity. The results suggested that lipophilic substituent groups might cause the absorption *via* the peroral route to be less. Detailed pharmacological examinations of **8a**, **8b** and **61** are in progress.[30]

Experimental

All melting points were measured with a Thomas Hoover capillary melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded with a JMN-EX270 spectrometer. Chemical shifts are given in δ values with tetramethylsilane (TMS) as an internal standard and the following abbreviations are used: s, singlet; d, doublet; t, triplet; br s, broad singlet; m, multiplet. Low-resolution mass spectra (MS) were obtained with a Shimadzu QP-1000 EX instrument and FAB-MS were recorded on a JEOL JMS DX-300 spectrometer equipped with a JMA 3500 data system.

Tetraethyl (4-Phenylpiperidinomethylene)bis(phosphonate) (2a) Method A: General procedure for all tetraethyl phosphonates: A mixture of 4-phenylpiperidine (5.0 g, 30.0 mmol), triethyl orthoformate (5.3 g, 36.0 mmol) and diethylphosphite (12.8 g, 93.0 mmol) was stirred for 8 h at 140 °C. $CHCl_3$ (270 ml) was added to the reaction mixture. The $CHCl_3$ layer was washed with 2 N NaOH and brine, and dried over Na_2SO_4. Removal of $CHCl_3$ left an oily residue which was purified by column chromatography (SiO_2, $CHCl_3$: MeOH = 9 : 1). The title compound was obtained as a colorless oil 10.2 g (77%). Physical data, see Table II. When phenylpiperidine HCl was used, 3 eq of triethylamine was added to the reaction mixture.

(4-Phenylpiperidinomethylene)bis(phosphonic acid) (3a) Method B: One of the procedures for preparation of bis(phosphonic acids) from their phosphonates: A mixture of the phopsphonate (**2a**) (2.5 g, 5.6 mmol) and

TABLE II. Physical Data for (Piperidinomethylene)bis(phosphonate) Derivatives

Compd.	TLC *Rf*	^{1}H-NMR (ppm, in $CDCl_3$)	Formula	*Anal.* Calcd (Found) C	H	N	MS (EI) *m/z*	Yield (%)
2a	0.79	1.38 (12H, m, CH_3 ×4), 1.82 (4H, m, 3-, 5-CH_2), 2.53 (1H, m, CH_2CHCH_2), 3.14 (4H, m, 2-. 6-CH_2), 3.43 (1H, m, *J*=25.0 Hz, NCH), 4.25 (8H, m, CH_2CH_3 ×4), 7.26 (5H, m, aromatic H)	$C_{20}H_{35}NO_6P_2$	53.69 (53.78	7.88 7.64	3.13 3.01)	447	77
2b	191—193[a]	1.35—1.44 (12H, m, CH_3 ×4), 1.98—2.20 (4H, m, 3-, 5-CH_2), 3.20—3.48 (4H, m, 2-, 6-CH_2), 3.45 (1H, t, *J*=25.0 Hz, NCH), 4.17—4.33 (8H, m, CH_3CH_2 ×4), 7.27—7.53 (5H, m, aromatic H)	$C_{21}H_{34}N_2O_7P_2$	53.39 (52.98	7.25 7.38	5.93 5.42)	422	64
2c	0.32	1.31—1.39 (12H, m, CH_3 ×4), 1.41—1.98 (10H, m, 3-, 5-, 3′-, 4′-, 5′-CH_2), 2.30—3.22 (9H, m, 2-, 6-, 2′-, 6′-CH_2, 4-CH), 3.37 (1H, t, *J*=24.0 Hz, NCH), 4.13—4.27 (8H, m, CH_3CH_2 ×4)	$C_{19}H_{40}N_2O_6P_2$	50.21 (50.43	8.87 8.63	6.16 6.33)	455	30
2d	0.66	1.31—1.39 (12H, m, CH_3 ×4), 1.46—1.94 (4H, m, 3-, 5-CH_2), 2.19 (1H, br s, OH), 2.87—3.17 (4H, m, 2-, 6-CH_2), 3.37 (1H, t, *J*=25.0 Hz, NCH), 3.61—3.72 (1H, m, 4-CH), 4.13—4.27 (8H, m, CH_3CH_2, ×4)	$C_{14}H_{31}NO_7P_2$	43.41 (43.05	8.07 8.34	3.62 3.52)	387	25
2e	0.43	1.32—1.41 (12H, m, CH_3CH_2 ×4), 1.77—2.11 (4H, m, 3-, 5-CH_2), 2.93—3.27 (4H, m, 2-, 6-CH_2), 3.02 (3H, s, SO_2CH_3), 3.37 (1H, t, *J*=24.0 Hz, NCH), 4.13—4.27 (8H, m, CH_3CH_2 ×4), 4.65—4.75 (1H, m, 4-CH)	$C_{15}H_{33}NO_9P_2$	38.71 (38.41	7.15 7.01	3.01 3.22)	466	86
2f	0.78	1.30—1.39 (12H, m, CH_3 ×4), 1.50—1.96 (4H, m, 3-, 5-CH_2), 2.88—3.22 (4H, m, 2-, 6-CH_2), 3.31—3.45 (1H, m, 4-CH), 3.35 (1H, t, *J*=25.0 Hz, NCH), 4.12—4.27 (8H, m, CH_3CH_2 ×4)	$C_{14}H_{30}N_4O_6P_2$	40.78 (40.96	7.33 7.05	13.59 13.86)	412	36
2g	0.89	1.34 (12H, m, CH_3 ×4), 1.63 (4H, m, 3-, 5-CH_2), 2.50 (2H, d, *J*=16.0 Hz, $C_6H_5CH_2$), 2.73 (1H, m, 4-CH), 2.97 (4H, m, 2-, 6-CH_2), 3.36 (1H, t, *J*=25.0 Hz, NCH), 4.20 (8H, m, CH_2CH_3 ×4), 7.19 (5H, m, aromatic H)	$C_{21}H_{37}NO_6P_2$	54.66 (54.48	8.08 8.29	3.04 3.26)	413	69
7a	180—185[b]	1.35 (12H, t, CH_3 ×4), 2.20—2.24 (4H, m, 3-, 5-CH_2), 2.99—3.03 (4H, m, 2-, 6-CH_2), 3.41 (1H, t, NCH), 4.14—4.29 (8H, m, CH_3CH_2 ×4), 4.65 (2H, s, =CH_2)	$C_{15}H_{21}NO_6P_2$	48.26 (48.03	5.67 5.23	3.75 3.29)	383 (M^+), 246	58
7b	0.87	1.35 (12H, t, $-OCH_2CH_3$ ×4), 1.56 (3H, d, =$CHCH_3$), 2.13—2.25 (4H, m, 3-, 5-CH_2), 2.95—3.00 (4H, m, 2-, 6-CH_2), 3.41 (1H, t, NCH), 4.15—4.30 (8H, m, CH_2CH_3 ×4), 5.18 (1H, q, =CH)	$C_{16}H_{33}NO_6P_2$	48.36 (48.21	8.37 8.18	3.52 3.35)	397 (M^+), 260	59
7c	0.67	0.93 (3H, t, *J*=8.0 Hz, CH_3CH_2CH), 1.32—1.38 (12H, m, CH_3CH_2O ×4), 1.92—2.04 (2H, m, CH_3-CH_2CH=), 2.12—2.20 (4H, m, 2-, 6-CH_2), 2.93—3.02 (4H, m, 3-, 5-CH_2), 3.41 (1H, t, *J*=25.0 Hz, NCH), 4.16—4.27 (8H, m, CH_3CH_2O ×4), 5.13 (1H, t, *J*=6.0 Hz, CH_3CH_2CH=)	$C_{17}H_{35}NO_6P_2$	49.63 (49.76	8.57 8.64	3.40 3.52)	411 (M^+)	93
7d	0.51	0.88 (3H, t, *J*=7.0 Hz, CH_3CH_2), 1.26—1.39 (2H, m, CH_3CH_2), 1.90—2.00 (2H, m, CH_2CH=), 2.12—2.26 (4H, m, 3-, 5-CH_2), 2.94—3.02 (4H, m, 2-, 6-CH_2), 3.40 (1H, t, *J*=25.0 Hz, NCH), 4.14—4.28 (8H, m, CH_3CH_2O ×4), 5.12 (1H, t, *J*=7.0 Hz, =CH)	$C_{18}H_{37}NO_6P_2$	50.82 (50.71	8.77 8.63	3.29 3.12)	425 (M^+)	17
7e	0.71	0.88 (3H, t, $CH_2CH_2CH_3$), 1.35 (12H, t, OCH_2CH_3 ×4), 1.25—1.35 (6H, m, $CH_2CH_2CH_2CH_2CH_3$), 1.92—2.13 (2H, m, =$CHCH_2$–), 2.15—2.24 [4H, m, 3-, 5-CH_2), 2.95–2.98 (4H, m, 2-, 6-CH_2), 3.40 (1H, t, NCH), 4.14—4.29 (8H, m, OCH_2CH_3 ×4), 5.12 (1H, t, =CH)	$C_{20}H_{41}NO_6P_2$	52.97 (53.15	9.11 9.25	3.09 3.28)	453 (M^+), 316	71
12	0.67	1.29—1.38 (12H, m, CH_3 ×4), 1.57—1.66 (2H, m, 5-CH_2), 2.08—2.15 (2H, m, 4-CH_2), 3.04—3.10 (2H, m, 6-CH_2), 3.37 (1H, t, *J*=25.0 Hz, NCH), 3.47—3.49 (2H, m, 2-CH_2), 4.13—4.27 (8H, m, CH_3CH_2 ×4), 4.66 (1H, br s, one of =CH_2), 4.72 (1H, br s, one of =CH_2)	$C_{15}H_{31}NO_6P_2$	47.00 (47.24	8.15 8.32	3.65 3.56)	383 (M^+)	43
20	0.70	1.28—1.37 (12H, m, CH_3 ×4), 2.05—2.36 (4H, m, NCH_2CH_2 ×2), 2.76—3.07 (4H, m, NCH_2 ×2), 3.37 (1H, t, *J*=25.0 Hz, NCH), 4.09—4.27 (8H, m, CH_3-CH_2 ×4), 6.89 (2H, s, CH=CH), 7.15—7.34 (8H, m, aromatic H)	$C_{29}H_{39}NO_6P_2$	62.25 (62.03	7.03 7.12	2.50 2.73)	559 (M^+)	60
23	0.51	1.35 (12H, t, *J*=7.0 Hz, CH_3 ×4), 1.68—1.75 (4H, m, 3-, 5-CH_2), 3.05—3.13 (4H, m, 2-, 6-CH_2), 3.41 (1H, t, *J*=25.0 Hz, NCH), 3.94 (4H, s, OCH_2CH_2O), 4.13—4.30 (8H, m, CH_3CH_2 ×4)	$C_{16}H_{33}NO_8P_2$	44.76 (44.62	7.75 7.58	3.26 3.37)	429 (M^+), 292	86

TABLE II. (continued)

Compd.	TLC *Rf*	^{1}H-NMR (ppm, in $CDCl_3$)	Formula	*Anal.* Calcd (Found)			MS (EI) *m/z*	Yield (%)
				C	H	N		
24	0.63	1.39 (12H, t, J=7.0 Hz, CH_3 ×4), 2.42—2.48 (4H, m, 3-, 5-CH_2), 3.28—3.36 (4H, m, 2-, 6-CH_2), 3.52 (1H, t, J=25.0 Hz, NCH), 4.26—4.29 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{14}H_{29}NO_7P_2$	43.64 (43.81	7.59 7.92	3.64 3.91)	386 (M^+), 248	88
26a	0.74	1.22—1.40 (15H, m, CH_3 ×5), 2.70—3.25 (8H, m, 2-, 3-, 5-, 6-CH_2), 3.41 (1H, t, J=25.0 Hz, NCH), 4.06—4.32 (10H, m, $CH_3C\underline{H}_2$ ×5)	$C_{19}H_{34}N_2O_8P_2$	47.50 (47.29	7.13 7.35	5.83 5.99)	480 (M^+)	64
26b	0.73	1.32—1.40 (12H, m, CH_3 ×4), 2.74—2.78 (4H, m, 3-, 5-CH_2), 3.17—3.24 (4H, m, 2-, 6-CH_2), 3.42 (1H, t, J=24.0 Hz, NCH), 4.14—4.26 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{16}H_{29}N_3O_6P_2$	45.61 (45.85	6.94 7.08	9.97 10.24)	434 (M^+)	43
30a	0.83	1.29—1.39 (12H, m, CH_3 ×4), 2.10—2.19 (2H, m, 5-CH_2), 3.10—3.17 (2H, m, 6-CH_2), 3.43 (1H, t, J=25.0 Hz, NCH), 3.45—3.52 (2H, m, 2-CH_2), 4.16—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4), 5.58—5.66 (1H, m, 3- or 4-H), 5.66—5.76 (1H, m, 3- or 4-H)	$C_{14}H_{29}NO_6P_2$	45.53 (45.26	7.91 7.85	3.79 3.49)	369 (M^+)	57
30b	0.67	1.30—1.41 (12H, m, CH_3 ×4), 2.51—2.60 (2H, m, 5-CH_2), 3.26—3.33 (2H, m, 6-CH_2), 3.51 (1H, t, J=25.0 Hz, NCH), 3.67—3.73 (2H, m, 2-CH_2), 4.13—4.30 (8H, m, $CH_3C\underline{H}_2$ ×4), 6.03—6.09 (1H, m, 3-H), 7.18—7.44 (5H, m, phenyl H)	$C_{20}H_{33}NO_6P_2$	53.93 (53.81	7.47 7.25	3.14 3.01)	445 (M^+), 308	67
30c	0.57	1.32—1.42 (12H, m, CH_3 ×4), 2.37—2.45 (2H, m, 5-CH_2), 3.21—3.28 (2H, m, 6-CH_2), 3.44 (1H, t, J=25.0 Hz, NCH), 3.53—3.58 (2H, m, 2-CH_2), 4.15—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4), 5.71—5.77 (1H, m, 3-H)	$C_{14}H_{28}ClNO_6P_2$	41.64 (41.98	6.99 7.24	3.47 3.59)	403 (M^+), 266	34
33a	0.87	0.91 (6H, s, CH_3 ×2), 1.32—1.41 (16H, m, CH_3CH_2 ×4, 3-, 5-CH_2), 2.95—3.01 (4H, m, 2-, 6-CH_2), 3.38 (1H, t, J=25.0 Hz, NCH), 4.15—4.28 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{16}H_{35}NO_6P_2$	48.12 (48.62	8.83 9.06	3.51 3.73)	399 (M^+), 262	91
33b	0.88	0.92 [6H, s, $(CH_3)_2C$], 1.18—1.26 (2H, m, 4-CH_2), 1.37 (12H, m, $CH_2C\underline{H}_3$ ×4), 1.51—1.60 (2H, m, 5-CH_2), 1.62—1.66 (2H, s, 2-CH_2), 1.89—1.97 (2H, m, 6-CH_2), 3.33 (1H, t, J=25.0 Hz, NCH), 4.08—4.27 (8H, m, $C\underline{H}_2CH_3$ ×4)	$C_{16}H_{35}NO_6P_2$	48.12 (48.48	8.83 8.96	3.51 3.74)	400 (M^+), 262	87
33c	192—193.5[a]	1.35 (12H, m, CH_2CH_3 ×4), 1.50 (6H, m, 3′-, 4′-, 5′-CH_2), 1.83 (4H, m, 3-, 5-$C\underline{H}_2$), 2.52 (4H, m, 2′-, 6′-CH_2), 3.30 (4H, m, 2-, 6-CH_2), 3.39 (1H, t, J=20.0 Hz, NCH), 4.21 (8H, m, $C\underline{H}_2CH_3$ ×4), 6.55 (2H, br s, NH_2)	$C_{20}H_{41}N_3O_7P_2$	48.28 (48.39	8.31 8.57	8.45 8.66)	453 (M^+ − $CONH_2$), 316	66
39a	0.53	1.22 (3H, s, CH_3), 1.32—1.41 (12H, m, $C\underline{H}_3CH_2$ ×4), 1.59—1.65 (4H, m, 3-, 5-CH_2), 2.89—3.21 (4H, m, 2-, 6-CH_2), 3.39 (1H, t, J=25.0 Hz, NCH), 4.13—4.28 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{15}H_{33}NO_7P_2$	44.89 (44.68	8.29 8.31	3.49 3.67)	401 (M^+)	67
39b	0.28	0.91 [6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$], 1.34 (12H, t, J=7.0 Hz, $C\underline{H}_3CH_2$ ×4), 1.47—1.67 [5H, m, 3-, 5-CH_2, $(CH_3)_2C\underline{H}$], 2.87—3.27 (4H, m, 2-, 6-CH_2), 3.38 (1H, t, J=25.0 Hz, NCH), 4.13—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{17}H_{37}NO_7P_2$	47.55 (47.39	8.68 8.97	3.26 3.61)	429 (M^+)	39
39c	0.21	1.36 (12H, t, J=7.0 Hz, CH_3 ×4), 1.54—1.80 (4H, m, 3-, 5-CH_2), 2.90—3.28 (4H, m, 2-, 6-CH_2), 3.40 (1H, t, J=25.0 Hz, NCH), 4.12—4.28 (8H, m, $CH_3C\underline{H}_2$ ×4), 5.07 [1H, d, J=10.0 Hz, =CH_2 (*cis* H)], 5.27 [1H, d, J=16.0 Hz, =CH_2 (*trans* H)], 5.95 (1H, q, J=16.0 Hz, =CH)	$C_{16}H_{32}N_2O_7P_2$	45.07 (45.36	7.56 7.62	6.57 6.71)	413 (M^+)	37
39d	0.47	1.35 (12H, t, J=7.0 Hz, CH_3 ×4), 1.52—1.67 (4H, m, 3-, 5-CH_2), 2.23 (2H, d, J=7.0 Hz, =$CHC\underline{H}_2$), 2.90— 3.33 (4H, m, 2-, 6-CH_2), 3.39 (1H, t, J=25.0 Hz, NCH), 4.15—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4), 5.13 [1H, d, J=14.0 Hz, =CH_2 (*trans* H)], 5.17 [1H, d, J=8.0 Hz, =CH_2 (*cis* H)], 5.80—5.96 (1H, m, =CH_2)	$C_{17}H_{35}NO_7P_2$	47.77 (47.59	8.25 8.51	3.28 3.49)	427 (M^+)	44
43	0.49	0.92 [9H, s, $(CH_3)_3C$], 1.35 (12H, t, J=7.0 Hz, $C\underline{H}_3CH_2$ ×4), 1.45—1.80 (4H, m, 3-, 5-CH_2), 2.86—3.24 (4H, m, 2-, 6-CH_2), 3.38 (1H, t, J=25.0 Hz, NCH), 4.09—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{18}H_{39}NO_7P_2$	48.75 (48.96	8.86 9.01	3.16 3.34)	443 (M^+)	16
44	0.65	1.02 [9H, s, $(CH_3)_3C$], 1.28—1.37 (12H, m, $C\underline{H}_3CH_2$ ×4), 2.09—2.17 (2H, m, 5-CH_2), 3.07—3.15 (2H, m, 6-CH_2), 3.45—3.52 (2H, m, 2-CH_2), 3.45 (1H, t, J=25.0 Hz, NCH), 4,13—4.26 (8H, m, $CH_3C\underline{H}_2$ ×4), 5.33—5.37 (1H, m, C$\underline{H}$OH)	$C_{18}H_{37}NO_6P_2$	50.82 (50.68	8.77 8.61	3.29 3.18)	425 (M^+)	19

TABLE II. (continued)

Compd.	TLC *Rf*	^{1}H-NMR (ppm, in $CDCl_3$)	Formula	*Anal.* Calcd (Found) C	H	N	MS (EI) *m/z*	Yield (%)
46[c]	0.52	1.31—1.43 (15H, m, $C\underline{H}_3CH_2$ ×4, $CFC\underline{H}_3$), 1.64—2.17 (4H, m, 3-, 5-CH_2), 3.17—3.72 (4H, m, 2-, 6-CH_2), 3.49 (1H, t, J=25.0 Hz, NCH), 4.14—4.30 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{15}H_{32}FNO_6P_2$	44.67 (44.29	8.00 8.23	3.47 3.58)	403 (M^+)	31
47	0.60	1.30—1.38 (12H, m, $C\underline{H}_3CH_2$ ×4), 1.99—2.08 (2H, m, 3-CH_2), 3.09—3.16 (2H, m, 6-CH_2), 3.44 (1H, t, J=25.0 Hz, NCH), 3.40—3.46 (2H, m, 2-CH_2), 4.13—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4), 5.28—5.33 (1H, m, =CH)	$C_{15}H_{31}NO_6P_2$	47.00 (47.26	8.15 8.37	3.65 3.92)	383 (M^+)	21
51	0.46	1.36 (12H, m, CH_3 ×4), 1.96 (4H, m, 3-, 5-CH_2), 3,11 (4H, m, 2-, 6-CH_2), 3.42 (1H, t, J=25.0 Hz, NCH), 4.22 (8H, m, CH_2 ×4)	$C_{14}H_{29}F_2NO_6P_2$	41.28 (41.39	7.18 7.34	3.44 3.25)	407 (M^+)	70
54	0.57	1.33 (2H, t, CH_3 ×4), 1.34—1.45 (14H, m, ring CH_2 ×7), 2.91—2.99 (4H, m, 2-, 6-CH_2), 1.36 (1H, dd, CH), 4.10—4.28 (8H, m, $C\underline{H}_2CH_3$ ×4)	$C_{19}H_{39}NO_6P_2$	51.93 (51.67	8.95 8.56	3.19 3.21)	439 (M^+), 302	78
60	0.63	1.31—1.43 (12H, m, CH_3 ×4), 1.35—1.48 (8H, m, 1-, 2-, 3-, 4-CH_2), 1.55—1.63 (4H, m, 6-, 10-CH_2), 2.92—3.00 (4H, m, 7-, 9-CH_2), 3.36 (1H, t, J=25.0 Hz, NCH), 4.23—4.30 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{18}H_{37}NO_6P_2$	50.82 (51.13	8.77 8.79	3.29 3.38)	425 (M^+), 288	43
62	0.63	1.32—1.40 (6H, m, CH_3 ×2), 1.71—1.77 (4H, m, 4-, 8-CH_2), 2.75 (2H, t, J=17.0 Hz, 2-CH_2), 2.85—2.96 (2H, m, 5- or 7-CH_2), 3.16—3.30 (2H, m, 5- or 7-CH_2), 3.36 (1H, t, J=25.0 Hz, NCH), 4.13—4.26 (4H, m, $CH_3C\underline{H}_2$ ×2)	$C_{16}H_{31}F_2NO_6P_2$	44.34 (44.65	7.21 7.43	3.23 3.52)	433 (M^+)	77
66	0.63	1.27—1.38 (12H, m, CH_3 ×4), 1.22—1.60 (14H, m, 4-, 5-, 7-, 8-, 9-, 10-, 11-CH_2), 2.75 (2H, s, 1-CH_2), 2.90—2.96 (2H, m, 3-CH_2), 3.32 (1H, t, J=25.0 Hz, NCH), 4.13—4.26 (8H, m, $CH_3C\underline{H}_2$, ×4)	$C_{19}H_{39}NO_6P_2$	51.93 (52.16	8.95 9.24	3.19 3.58)	439 (M^+)	72
76	0.71	1.28—1.36 (12H, m, CH_3 ×4), 1.20—1.82 (16H, m, 3-, 4-, 5-, 7-, 8-, 9-, 10-, 11-CH_2), 3.21—3.27 (2H, m, 2-CH_2), 4.10 (1H, t, J=26.0 Hz, NCH), 4.09—4.27 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{19}H_{39}NO_6P_2$	51.93 (52.24	8.95 9.14	3.19 3.36)	439 (M^+)	45
81	0.72	1.18—1.78 (14H, m, 3-, 4-, 6-, 7-, 8-, 9-, 10-CH_2), 1.28—1.39 (12H, m, CH_3 ×4), 3.29—3.38 (2H, m, 2-CH_2), 3.81 (1H, t, J=25.0 Hz, NCH), 4.10—4.26 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{18}H_{37}NO_6P_2$	50.82 (50.63	8.77 8.67	3.29 3.38)	425 (M^+), 381	75
84	0.15	1.32—1.42 (12H, t, J=12.0 Hz, $C\underline{H}_3CH_2$ ×4), 1.73—2.07 (2H, m, 4-CH_2), 2.29 (6H, s, NCH_3 ×2), 2.83—3.57 (5H, m, 2-, 4-CH_2, 3-CH), 3.63 (1H, t, J=25.0 Hz, NCH), 4.14—4.29 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{15}H_{34}N_2O_6P_2$	45.00 (45.29	8.56 8.73	7.00 7.26)	400 (M^+)	3
87	0.79	0.84 (3H, d, CH_3), 0.90 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.22—1.95 (6H, m, ring CH_2 ×3), 1.33—1.41 (12H, m, $C\underline{H}_3CH_2$ ×2), 2.60—2.75 (1H, m, ring CH), 2.86—3.12 (2H, m, ring CH_2), 3.39 (1H, t, J=25.0 Hz, NCH), 4.13—4.29 (8H, m, $C\underline{H}_2CH_3$ ×4)	$C_{18}H_{39}NO_6P_2$	50.58 (50.84	9.20 9.35	3.28 3.61)	428, 290, 152	39
90	0.48	0.97—2.07 (6H, m, ring CH_2 ×3), 0.88 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.22 (1H, s, CH_3), 1.30—1.41 (12H, m, $C\underline{H}_3CH_2$ ×4), 2.96—3.00 (2H, m, NCH_2), 3.57 (1H, t, J=25.0 Hz, NCH), 3.58—3.65 (1H, m, $CH_2C\underline{H}N$), 4.10—4.26 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{19}H_{39}NO_6P_2$	51.93 (52.20	8.95 9.18	3.19 3.41)	439 (M^+)	80
93	0.51	1.28—1.40 (12H, m, CH_3 ×4), 1.52—12.12 (15H, m, adamantane ring H), 3.59 (1H, m, J=25.0 Hz, NCH), 4.12—4.31 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{19}H_{26}NO_6P_2$	52.29 (52.36	8.31 8.51	3.21 3.47)	437 (M^+)	20
101	0.19	1.32—1.43 (12H, m, CH_2 ×4), 1.67—2.12 (4H, m, 2-. 6-CH_2), 2.23—2.62 (4H, m, 3-, 5-CH_2), 3.32—3.43 (1H, m, $CH_2C\underline{H}N$), 3.40 (1H, t, J=25.0 Hz, NCH), 4.16—4.30 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{15}H_{30}NO_7P_2$	45.23 (45.46	7.59 7.78	3.52 3.67)	399 (M^+)	26
102	0.47	1.16—1.33 (2H, m, cyclohexane ring CH_2), 1.30—1.40 (12H, m, CH_3 ×4), 1.83—2.40 (6H, m, cyclohexane ring CH_2 ×3), 2.92—3.03 (1H, m, $CH_2C\underline{H}N$), 3.42 (1H, t, J=25.0 Hz, NCH), 4.14—4.29 (8H, m, CH_3CH_2 ×4), 4.62 (2H, s, $=CH_2$)	$C_{16}H_{33}NO_6P_2$	45.34 (45.59	8.37 8.56	3.52 3.74)	397 (M^+)	15
106	0.41	1.31—1.41 (6H, m, CH_3 ×2), 1.53—1.69 (8H, m, 3-, 4-, 5-, 6-CH_2), 1.76 (1H, br s, NH), 2.99—3.07 (4H, m, 2-, 7-CH_2), 3.44 (1H, t, J=25.0 Hz, NCH), 4.14—4.28 (8H, m, $CH_3C\underline{H}_2$ ×4)	$C_{15}H_{33}NO_6P_2$	46.75 (46.99	8.63 8.83	3.63 3.83)	385 (M^+)	7

a) mp (°C). *b*) bp (°C, 1.5 mmHg). *c*) ^{1}H-NMR (in CD_3OD).

TABLE III. Activity to Inhibit the Rise in Serum Calcium Induced by Parathyroid Hormone in Thyroparathyroidectomised Rats (%)

Type	Compd.	Inhibition (%)	Type	Compd.	Inhibition (%)	Type	Compd.	Inhibition (%)
I	**3a**	$-14.0^{a)} \pm 19.41$	III	**31a**	$59.6^{a)} \pm 24.95$	VI	**36**	$78.7^{a)} \pm 9.22$,
	3c	$24.6^{a)} \pm 18.19$		**31b**	$29.5^{a)} \pm 26.40$			$52.1^{b)} \pm 16.54$
	3g	$46.6^{a)} \pm 10.89$		**45a**	$56.1^{b)} \pm 10.73$		**48**	$36.4^{b)} \pm 7.33$
	3d	$-13.6^{b)} \pm 22.90$		**45b**	$1.8^{b)} \pm 14.06$		**52**	$41.5^{a)} \pm 8.83$
	3f	$-24.8^{b)} \pm 39.56$	IV	**34a**	$60.5^{a)} \pm 11.50$,	VII	**55**	$87.7^{a)} \pm 8.43$
II	**8a**	$84.3^{a)} \pm 11.73$,			$48.4^{b)} \pm 13.21$		**61**	$71.0^{a)} \pm 20.14$,
		$65.4^{b)} \pm 4.79$		**34b**	$63.9^{a)} \pm 18.52$			$73.8^{b)} \pm 7.97$
	8b	$89.5^{a)} \pm 8.98$,		**34c**	$3.3^{a)} \pm 7.19$		**63**	$9.1^{b)} \pm 4.82$
		$62.7^{b)} \pm 9.62$		**3b**	$-11.8^{a)} \pm 13.44$		**67**	$13.8^{a)} \pm 18.60$
	8c	$26.2^{b)} \pm 12.06$	V	**37**	$-25.9^{b)} \pm 22.86$		**77**	$90.0^{a)} \pm 6.01$
	8d	$54.0^{b)} \pm 8.84$		**38a**	$11.1^{b)} \pm 12.73$		**82**	$83.5^{a)} \pm 5.66$
	8e	$97.4^{a)} \pm 8.21$,		**38b**	$53.6^{b)} \pm 10.00$	VIII	**85**	$20.6^{a)} \pm 48.36$
		$50.1^{b)} \pm 4.64$		**40b**	—[c]	IX	**88**	$83.1^{a)} \pm 4.52$
	13	$-12.4^{b)} \pm 20.25$		**40c**	$1.5^{b)} \pm 4.45$		**91**	$64.0^{a)} \pm 8.85$
	21	$-26.6^{b)} \pm 16.78$		**40d**	$12.8^{b)} \pm 2.59$	X	**94**	$68.4^{a)} \pm 18.08$
	25	$16.3^{a)} \pm 15.46$		**40e**	$-17.6^{b)} \pm 18.36$		**103**	$27.2^{b)} \pm 7.54$
	27	$-3.3^{b)} \pm 3.24$						

a) 10 mg/kg (s.c.). *b*) 0.2 mg/kg (i.v.). *c*) —, not examined.

TABLE IV. ED_{50} Values of (Piperidinomethylene)bis(phosphonic acid) Derivatives

Compd.	ED_{50} (mg/kg)		Compd.	ED_{50} (mg/kg)	
	i.v.	*p.o.*		i.v.	*p.o.*
8a	0.12 (0.08[a])	9.6	**55**	(0.7[a])	>20.0
8b	0.14	12.8	**61**	0.11	14.1
8d	0.29	>20.0	**77**		>20.0
34a	0.20	20.0	**82**		>20.0
36	0.20	17.7	**88**		>20.0
48	0.36	>20.0	Pamidoronate[b]	0.31	48.2

a) s.c. *b*) Pamidronate[9g] was prepared and evaluated in our laboratory.

36% HCl (150 ml) was stirred at 100 °C for 10 h. The mixture was evaporated to give an oily residue which was recrystallized from MeOH. The compound (**3a**) was obtained as colorless needles. 1.5 g (78%).

Tetraethyl (4-Methylsulfonylpiperidinomethylene)bis(phosphonate) (2e) Methylsulfonyl chloride (0.9 g, 7.8 mmol) was added dropwise to a mixture of **2d** (2.5 g, 6.5 mmol), pyridine (0.5 g), triethylamine (0.65 g) and $CHCl_3$ (10 ml) at 25 °C and the mixture was stirred at 15 °C for 24 h. The mixture was washed with 1 N HCl and dried over Na_2SO_4. The residue obtained from the solution was purified by column chromatography (SiO_2, EtOH : toluene : $CHCl_3$ = 3 : 10 : 90) to give a colorless oil (2.6 g, 86%).

Tetraethyl (4-Azidopiperidinomethylene)bis(phosphonate) (2f) A mixture of **2e** (2.2 g, 4.73 mmol) and sodium azide (3.0 g, 47.3 mmol) in dry DMF (10 ml) was stirred at 65—70 °C for 3 h. The reaction mixture was poured into ice water and extracted with ether. The ether layer was washed with saturated brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, EtOH : toluene : $CHCl_3$ = 1 : 25 : 25) to give **2f** as a colorless oil (0.7 g, 36%).

(4-Azidopiperidinomethylene)bis(phosphonic acid) (3f) Method C: One of the procedures for preparation of bis(phosphonic acids) from their phosphonates: Trimethylsilyl iodide (TMSI) (1.9 g, 9.4 mmol) was added dropwise to a solution of **2f** (0.9 g, 2.3 mmol) in dry $CHCl_3$ (20 ml) at 0 °C under an Ar atmosphere. The mixture was stirred at 0 °C for 0.5 h and the solvent was evaporated off to give a brown oil. Water was added to the oil at 0 °C and the mixture was stirred vigorously for 1 h. MeOH was added to the aqueous solution to give a colorless powder. The powder was purified by column chromatography (SiO_2, $CHCl_3$: MeOH = 12 : 1) to afford **3f** (0.5 g, 81%).

1-Azaspiro[5.5]undecan-1-yl-methylenebis(phosphonic acid) (77) Method D): One of the procedures for preparation of bis(phosphonic acids) from their phosphonates: The phosphonate (**76**) (0.7 g, 2.2 mmol) was dissolved in 10 ml of 25% HBr acetic acid solution at 0 °C. The solution was stirred at 60 °C for 1 h, then concentrated under reduced pressure. The residue (0.7 g) was purified by medium-pressure liquid chromatography with a Lobar column (RP-8, size B) to give 0.3 g (36%) of **77** as a colorless powder.

4-Methylenepiperidine HCl (6a) *n*-BuLi (1.55 M *n*-hexane solution) (47 ml, 72.0 mmol) was added to a solution of methyltriphenylphosphonium bromide (24.6 g, 69.0 mmol) in absolute tetrahydrofuran (THF, 150 ml) at 0 °C under vigorous stirring. An absolute THF solution (50 ml) of 1-benzyl-4-piperidone (12.8 ml, 69.0 mmol) was added to the mixture at 25 °C, and the whole was stirred for 10 h at 25 °C. *n*-Hexane was added to the mixture and the precipitate was filtered off. The filtrate was purified by column chromatography (SiO_2, C_6H_{12} : AcOEt = 9 : 1) to give oily 1-benzyl-4-piperidine (11.3 g, 88%). Rf = 0.79 (TLC on SiO_2, C_6H_{12} : AcOEt = 10 : 1). α-Chloroethyl chloroformate (6.3 ml, 58.0 mmol) was added dropwise to a solution of **5a** (10.5 g, 53.0 mmol) in dry CH_2Cl_2 (500 ml) at 0 °C under vigorous stirring. The mixture was gently refluxed for 2 h. After removal of organic solvent from the mixture, MeOH (300 ml) was added. The solution was stirred at 75 °C for 4 h, then the solvent was evaporated off under reduced pressure. The residue was dissolved in 1/2 N HCl and the solution was washed with Et_2O. The aqueous layer was evaporated under reduced pressure to give **6a** as colorless prisms (6.7 g, 94%). ^{1}H-NMR (D_2O) δ: 2.47—2.55 (4H, m, 3-, 5-CH_2), 3.21—3.29 (4H, m, 2-, 4-CH_2), 4.96 (2H, s, CH_2).

4-Ethylidenepiperidine HCl (6b) The title compound was prepared with ethyl triphenylphosphonium bromide under the conditions used for **6a**. ^{1}H-NMR (D_2O) δ: 1.62 (3H, d, J = 14.0 Hz, CH_3), 1.40—1.56 (4H, m, 3, 5-CH_2), 3.17—3.23 (4H, m, 2-, 6-CH_2), 5.52 (1H, q, J = 7.0 Hz, CH=).

4-Propylidenepiperidine HCl (6c) The title compound was prepared with propyl triphenylphosphonium bromide under the conditions used for **6a**. MS m/z: 125 (M^+). ^{1}H-NMR (D_2O) δ: 0.95 (3H, t, J = 7.0 Hz, CH_3), 1.98—2.12 (2H, m, $CH_3C\underline{H}_2$), 2.41—2.47 (2H, m, 3- or 5-CH_2), 2.47—2.57 (2H, m, 3- or 5-CH_2), 3.16—3.27 (4H, m, 2-, 6-CH_2), 5.47 (1H, t, J = 7.0 Hz, CH=).

4-Butylidenepiperidine HCl (6d) The title compound was prepared with butyl triphenylphosphonium bromide under the conditions used for **6a**. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.0 Hz, CH_3), 1.28—1.44 (2H, m, $CH_3C\underline{H}_2$), 1.92—2.05 (2H, m, $CH_3CH_2C\underline{H}_2$), 2.47—2.62 (4H, m, 3-, 5-CH_2), 3.12—3.23 (4H, m, 2-, 6-CH_2), 5.34 (1H, t, J = 7.0 Hz, CH=), 9.66 (2H, br s, NH_2^+).

4-Hexylidenepiperidine HCl (6e) The title compound was prepared with hexyl triphenylphosphonium bromide under the conditions used for **6a**. ^{1}H-NMR (D_2O) δ: 0.89 (3H, t, J = 17.0 Hz, CH_3), 1.22—1.45 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.98—2.11 (2H, m, $C\underline{H}_2CH$=), 2.38—2.55 (4H, m, 3-, 5-CH_2), 5.15—3.26 (4H, m, 2-, 6-CH_2), 5.42 (1H, t, J = 17.0 Hz, CH=).

3-Methylenepiperidine HCl (11) The title compound was prepared from 1-benzyl-3-piperidone with methyl triphenylphosphonium bromide under the conditions used for **6a**. ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.04 (2H, m, 5-CH_2), 2.32—2.38 (2H, m, 4-CH_2), 3.18—3.28 (2H, m, 6-CH_2), 3.62—3.69 (2H, m, 2-CH_2), 5.08 (1H, br s, one of =CH_2), 5.12 (1H, br s, one of CH_2=), 9.65 (1H, br s, NH).

3-Methylenepyrrolidine HCl (17) The alcohol (**14**) was converted to the ketone (**15**) by means of Swern oxidation. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (2H, t, J=6.9 Hz, 4-CH_2), 2.93 (2H, t, J=6.9 Hz, 5-CH_2), 2.95 (2H, s, 2-CH_2), 3.72 (2H, s, $C_6H_5C\underline{H}_2$), 7.26—7.36 (5H, m, $C_6\underline{H}_5CH_2$). MS m/z: 175 (M^+). The ketone (**15**) was treated with methyltriphenylphosphonium bromide under the conditions used for **5a** to afford **16**. ^{1}H-NMR ($CDCl_3$) δ: 2.43—2.52 (2H, m, 4-CH_2), 2.66 (2H, t, J=6.9 Hz, 5-CH_2), 3.13 (2H, br s, 2-CH_2), 3.63 (2H, s, $C_6H_5CH_2$), 4.83 (2H, br s, CH_2=), 7.23—7.35 (5H, m, $C_6\underline{H}_5CH_2$). MS m/z: 173 (M^+). Treatment of **16** with α-chloroethyl chloroformate under the conditions used for **11** gave **17**. ^{1}H-NMR (D_2O) δ: 2.67—2.76 (2H, m, 4-CH_2), 3.45 (2H, t, J=7.6 Hz, 5-CH_2), 3.91 (2H, br s, 2-CH_2), 5.17—5.22 (2H, m, CH_2=). MS m/z: 83 (M^+ − HCl).

4-(5*H*-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine HCl (19) Cyproheptadine HCl·1.5 H_2O was treated with α-chloroethyl chloroformate under conditions similar to those used for **6a**. ^{1}H-NMR ($CDCl_3$) δ: 2.03—2.32 (4H, m, $NCH_2C\underline{H}_2\times$2), 2.59—2.94 (4H, m, $NCH_2\times$2), 6.92 (2H, s, CH=CH), 7.16—7.35 (8H, m, aromatic H).

Tetraethyl (4-Oxopiperidinomethylene)bis(phosphonate) (24) 1,4-Dioxa-8-azaspiro[4.5]decane (**22**) (50.0 g, 350.0 mmol) was converted to 1,4-dioxa-8-azaspiro[4.5]decan-8-yl-methylenebis(phosphonate) (**23**) as an oily residue (130 g) by the use of method A. The crude **23** was stirred in 80% acetic acid (500 ml) at 110 °C for 12 h. Removal of the solvent left an oily residue which was purified by column chromatography (SiO_2, EtOH : $CHCl_3$ = 2 : 98). The title compound was obtained as a colorless oil (95 g, 70%).

Tetraethyl (4-Hexylidenepiperidinomethylene)bis(phosphonate) (7e) *n*-BuLi (1.55 M *n*-hexane solution) (7.5 ml, 12.0 mmol) was added to the solution of *n*-hexyltriphenylphosphonium bromide (5.0 g, 12 mmol) in absolute THF (30 ml) at 0 °C under vigorous stirring. An absolute THF solution (5 ml) of **24** (3.9 g, 10 mmol) was added to the above solution at 24 °C, and the mixture was stirred for 15 h at 24 °C. *n*-Hexane was added to the mixture and the precipitate was removed. The solution was purified by column chromatography (SiO_2, $CHCl_3$: C_6H_6 = 1 : 6) to give **7e** as a colorless oil (1.9 g, 36%).

Tetraethyl (4-Ethylidenepiperidinomethylene)bis(phosphonate) (7b) The title compound was prepared with ethyltriphenyl phosphonium bromide by the same procedure as above (45%).

Tetraethyl [4-(Dicyanomethylidene)piperidinomethylene]bis(phosphonate) (26b) A mixture of **24** (3.1 g, 8.1 mmol), malononitrile (1.0 g, 15 mmol), and piperidine (0.16 g, 2 mmol) in benzene (200 ml) was stirred at 80 °C for 3 h. Removal of the solvent left an oily residue, which was purified by column chromatography (SiO_2, EtOH : C_6H_6 = 2 : 98). The compound (**26b**) was obtained as a colorless oil (1.5 g, 43%).

Tetraethyl [4-(Ethoxycarbonylcyanomethylidene)piperidinomethylene]-bis(phosphonate) (26a) A mixture of **24** (2.0 g, 5.2 mmol), ethyl cyanoacetate (1.0 g, 8.8 mmol) and piperidine (0.09 g, 1 mmol) in benzene (30 ml) was stirred at 65 °C for 2 h. Removal of the solvent left an oily residue, which was purified by column chromatography (SiO_2, EtOH : C_6H_6 = 3 : 97). The compound (**26a**) was obtained as a colorless oil (1.6 g, 64%).

Tetraethyl (4-Chloro-3,4-dehydropiperidinomethylene)bis(phosphonate) (30c) A mixture of **24** (1.9 g, 5 mmol), triphenyl phosphine (2.6 g, 10 mmol) and CCl_4 (10 ml) was stirred at 23 °C for 6 h. After usual work-up, the residue was purified by column chromatography (SiO_2, $CHCl_3$: C_6H_6 = 1 : 1) to give **30c** as a colorless oil (0.26 g, 34%).

4,4-Dimethylpiperidine HCl (32a) A solution of 3,3-dimethylglutarimide (120 g, 850 mmol) in dry THF (1000 ml) was added dropwise to a suspension of $LiAlH_4$ (87 g, 2.29 mol) in dry THF (1000 ml) at 0 °C and the whole was stirred at 65 °C for 3 h. After the usual work-up, 4,4-dimethylpiperidine was treated with 2 N HCl to give **32a** as colorless prisms (126.7 g, 99%). ^{1}H-NMR (D_2O) δ: 1.02 (6H, s, $CH_3\times$2), 1.54—1.62 (4H, m, 3-, 5-CH_2), 3.15—3.24 (4H, m, 2-, 6-CH_2).

(4-Chloro-4-methylpiperidinomethylene)bis(phosphonic acid) (36) Dry HCl gas was introduced into a solution of **7a** (3.8 g, 10 mmol) in dry CH_2Cl_2 (50 ml) and dry $CHCl_3$ (50 ml) at 0 °C. The mixture was stirred at 25 °C for 2 h and then at 100 °C for 0.5 h. Removal of the solvent gave the crude phosphate (**35**) (4.0 g).[31] TMSI (7.6 g, 36 mmol) was added dropwise to a mixture of **35** and dry CCl_4 (40 ml) under an Ar atmosphere at 0 °C and the whole was stirred at 0 °C for 2 h. Removal of the solvent left an oily residue, which was stirred in aqueous methanol solution (20 ml) (H_2O : MeOH = 1 : 1) at 25 °C for 2 h. The precipitates were collected by filtration and recrystallized from CH_3OH–Et_2O to give **36** (1.5 g, 47%).

(4-Hydroxy-4-methylpiperidinomethylene)bis(phosphonic acid) (37) A mixture of **8a** (1.5 g, 6 mmol) and 5% H_2SO_4 (100 ml) was stirred at 100 °C for 15 h. The reaction mixture was evaporated under reduced pressure to give crude prisms, which were recrystallized from EtOH. The compound (**37**) was obtained as colorless prisms (1.2 g, 75%). The hydroxy compound (**37**) was also prepared from **7a** as follows. A mixture of **7a** (3.8 g, 10 mmol) and 37% HCl (20 ml) was stirred at 80 °C for 50 h. The mixture was concentrated under reduced pressure to give an oily residue. An aqueous solution of the residue was decolorized with charcoal and EtOH was added to the solution to produce **37** as colorless prisms (1.7 g, 83%).

(4-Ethyl-4-hydroxypiperidinomethylene)bis(phosphonic acid) (38a) The title compound was prepared from **7b** by a similar procedure (using HCl) to that used for the preparation of **37**. Recrystallized from CH_3OH–H_2O (1 : 1) (99%).

(4-Hexyl-4-hydroxypiperidinomethylene)bis(phosphonic acid) (38b) The title compound was prepared from **7e** by a similar procedure (using HCl) to that used for the preparation of **37**. Recrystallized from CH_3OH–H_2O (1 : 1) (78%).

Tetraethyl (4-Hydroxy-4-methylpiperidinomethylene)bis(phosphonate) (39a) Methylmagnesium bromide (1.0 M THF solution, 21 ml) was added to a mixture of **24** (3.8 g, 10 mmol) and absolute THF (50 ml) at 0 °C under an Ar atmosphere and the whole was stirred at 25 °C for 2 h, then poured into ice-water and adjusted to pH 4 with 0.1 N HCl. The solution was extracted with $CHCl_3$ and the $CHCl_3$ layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, C_6H_{12} : $CHCl_3$: MeOH = 6 : 12 : 1) to give **39a** as a colorless oil (2.7 g, 67%). The oil (**39a**) afforded **37** when treated according to method C.

Tetraethyl (4-Hydroxy-4-isopropylpiperidinomethylene)bis(phosphonate) (39b) The title compound was prepared from **24** with isopropylmagnesium bromide under conditions similar to those used for **39a** (39%).

Tetraethyl (4-Hydroxy-4-vinylpiperidinomethylene)bis(phosphonate) (39c) The title compound was prepared from **24** with vinylmagnesium bromide under conditions similar to those used for **39a** (37%).

Tetraethyl (4-Allyl-4-hydroxypiperidinomethylene)bis(phosphonate) (39d) The title compound was prepared from **24** with allylmagnesium bromide under conditions similar to those used for **39a** (44%).

Tetraethyl (4-*tert*-Butyl-4-hydroxypiperidinomethylene)bis(phosphonate) (43) and Tetraethyl (4-*tert*-Butyl-3,4-dehydropiperidinomethylene)bis(phosphonate (44) A mixture of 1-benzyl-4-hydroxy-4-*tert*-butylpiperidine (**41**) (12.4 g, 50 mmol), 10% Pd–C (2.3 g) and MeOH (150 ml) was vigorously shaken under an H_2 atmosphere at 25 °C for 50 h. After usual work-up, oily **42** was obtained. (6.2 g, 79%). Rf=0.49 (TLC on SiO_2, $CHCl_3$: MeOH = 10 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.92. (9H, s, $CH_3\times$3), 1.49—1.72 (6H, m, 3-, 5-CH_2, NH, OH), 2.88—2.97 (4H, m, 2-, 6-CH_2). The amine (**42**) gave a mixture of **43** and **44** when treated by method A. The two phosphonates (**43**, **44**) were separated by column chromatography (C_6H_{12} : $CHCl_3$: MeOH = 20 : 40 : 1). **43**: Rf=0.49 (TLC on SiO_2), 0.7 g, 16%. **44**: Rf=0.65 (TLC on SiO_2), 0.8 g, 19%.

Tetraethyl (4-Fluoro-4-methylpiperidinomethylene)bis(phosphonate) (46) and Tetraethyl (4-Methyl-3,4-dehydropiperidinomethylene)bis(phosphonate (47) A solution of **39a** (31.6 g, 78.7 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise to a mixture of diethylaminosulfur trifluoride (15.2 g, 94.4 mmol) and dry CH_2Cl_2 (300 ml) at −78 °C. The reaction mixture was stirred at 25 °C for 5 h and the solvent was evaporated off. The residue was extracted with ethyl acetate. The extract was dried over Na_2SO_4 and the solvent was evaporated off to give a mixture of **46** and **47** as a yellow oil (25 g). The mixture was purified by column chromatography (SiO_2, C_6H_{12} : isopropyl ether : MeOH = 10 : 2 : 0.5) to give **46** (11.6 g, 31%) and **47** (7.7 g, 21%).

4,4-Difluoropiperidine HCl (50) DAST (9.5 g, 58 mmol) was added dropwise to a solution of **4** (5.9 g, 24 mmol) in benzene (290 ml) at 0 °C. The mixture was stirred at 80 °C for 20 h, then washed with aqueous $NaHCO_3$ solution and water, and dried over Na_2SO_4. The solvent was evaporated off to afford an oil. The oil was purified by column chromatography to give oily **49** (4.3 g, 71%). Rf=0.69 (C_6H_{12} : AcOEt = 2 : 1). α-Chloroethyl chloroformate (1.7 ml, 17 mmol) was added dropwise to a solution of **49** (3.1 g, 15 mmol) in CH_2Cl_2 (150 ml) at 0 °C under an Ar atmosphere. The mixture was stirred at 55 °C for 2 h. Removal of the solvent from the mixture gave a residue, which was treated with MeOH (80 ml) at 75 °C for 4 h. The mixture was concentrated to give a residue, which gave colorless prisms (**50**) on treatment with MeOH (2.1 g, 88%). ^{1}H-NMR (D_2O) δ: 2.26—2.43 (4H, m, 3-, 5-CH_2), 3.39—3.49 (4H, m, 2-, 6-CH_2). MS m/z: 120 (M^+).

8-Azaspiro[4.5]decane HCl (59) 3,3-Tetramethyleneglutaric anhydride (**56**) (50 g, 297 mmol) was added to benzylamine (32.5 ml, 297 mmol) at 0 °C. The mixture was stirred at 22 °C for 10 h, then extracted with AcOEt.

The extract was concentrated to afford a residue, which was purified by column chromatography (SiO_2, Et_2O: C_6H_{14} = 1 : 2) to give **57** (55.4 g, 73%). A solution of **57** (55 g, 214 mmol) in absolute THF (300 ml) was added dropwise to a suspension of $LiAlH_4$ (25 g, 659 mmol) in absolute THF (1000 ml) at 0 °C. The mixture was stirred at 50 °C for 12 h. After usual work-up, the product was purified by column chromatography (SiO_2, Et_2O) to give **58** (40.1 g, 82%). Treatment of **58** (35.6 g, 155 mmol) with α-chloroethyl chloroformate (18.4 ml, 171 mmol) under conditions similar to those used for **50** gave **59** (24.9 g, two-step yield 22%). ^{1}H-NMR ($CDCl_3$) δ: 1.34—1.72 (12H, m, 1-, 2-, 3-, 4-, 6-, 10-CH_2), 2.83—2.94 (4H, m, 7-, 9-CH_2), 5.20 (1H, br s, NH). MS *m/z*: 228 ($M^+ - 1$), 152.

Tetraethyl 1,1-Difluoro-6-azaspiro[2.5]octan-6-yl-methylenebis(phosphonate) (62) CBr_2F_2 (3 ml, 33 mmol) was added to a mixture of **7a** (4.2 g, 11.0 mmol), diethylzinc (34 ml, 33 mmol) and THF (20 ml) at −60 °C. The mixture was stirred at 25 °C for 15 h, poured into water and extracted with $CHCl_3$. A residue obtained from the extract was purified by column chromatography (SiO_2, $CHCl_3$: CH_3OH = 10 : 1) to give **62** (0.65 g, 14%).

2-Azaspiro[5.5]undecane (65) The title compound was prepared from **64** by use of the procedure reported by Liebowitz,[22] ^{1}H-NMR ($CDCl_3$) δ: 1.11—1.63 (14H, m, 4-, 5-, 7-, 8-, 9-, 10-, 11-CH_2), 2.57 (2H, s, 1-CH_2), 2.73—2.79 (2H, m, 3-CH_2), 3.23 (1H, br s, NH). MS *m/z*: 153 (M^+), 110.

1-Azaspiro[5.5]undecane (75) Ethyl acrylate (83.4 ml, 770 mmol) was added to a mixture of nitrocyclohexane (99.5 g, 770 mmol), *tert*-BuOH (40 ml) and 40% Triton B (7 ml), and the mixture was stirred at 25 °C for 10 h. After usual work-up, the ester (**69**) was obtained (153 g, 87%). The ester (**69**) (30 g, 130 mmol) was treated with 3 N NaOH (300 ml) to give the acid (**70**) (20 g, 95%). A mixture of **70** (20 g) and thionyl chloride (200 ml) was stirred at 50 °C for 2 h to give the chloride (**71**) (20 g). A mixture of **71** (20 g, 85 mmol), diazomethane (14.5 g, 15% Et_2O solution) and Et_2O (60 ml) was stirred at 25 °C for 5 h. After usual work-up, the oily residue was treated with silver oxide (10 g, 43.2 mmol) in EtOH (100 ml) at 75 °C for 3 h to give the ester **72** (6.5 g, two steps yield 27%). The ester (**72**) was converted to the amine (**73**) by catalytic reduction (H_2: 65 kg/cm^2, Raney Ni, in EtOH). The amine (**73**) was heated at 75 °C in EtOH to give the amide (**74**) (1.7 g, two steps yield 39%). The amide (**74**) (1.7 g, 10.2 mmol) was treated with $LiAlH_4$ (1.1 g, 28.9 mmol) in THF (50 ml) to give the spiro amine (**75**) (1.0 g, 65%). ^{1}H-NMR ($CDCl_3$) δ: 1.31—1.58 (16H, m, 3-, 4-, 5-, 7-, 8-, 9-, 10-, 11-CH_2), 2.74—2.83 (2H, m, 2-CH_2), 3.31 (1H, br s, NH). MS *m/z*: 153 (M^+), 110.

1-Azaspiro[4.5]decane (80) The nitro compound (**69**) (20.0 g, 87.3 mmol) was converted to the amine (**78**) at 25 °C by catalytic reduction (H_2: 70 kg/cm^2, Raney Ni, in EtOH). After removal of the Raney Ni, the solution was stirred at 75 °C for 5 h. Removal of the solvent from the mixture gave the amide (**79**) (8.0 g, 69%). The amide (**79**) (8.0 g, 52.3 mmol) was treated with $LiAlH_4$ (3.6 g, 94.7 mmol) in THF (30 ml) at 25 °C for 15 h to give **80** (7.4 g, 83%). ^{1}H-NMR ($CDCl_3$) δ: 1.27—1.81 (14H, m, 3-, 4-, 6-, 7-, 8-, 9-, 10-CH_2), 2.93 (2H, t, *J* = 7.0 Hz, 2-CH_2). MS *m/z*: 139 ($M^+ + 1$), 96.

Tetraethyl 4-Oxocyclohexylaminomethylenebis(phosphonate) (101) A mixture of the ketone (**95**) (25 g, 160 mmol), $NaBH_4$ (6.0 g, 158 mmol) and MeOH (250 ml) was stirred at 28 °C for 3 h. After work-up, the alcohol (**96**) was obtained as a colorless oil (23.7 g, 94%). Methanesulfonyl chloride (26.0 g, 224 mmol) was added to a mixture of the alcohol (**96**) (23.7 g, 150 mmol), pyridine (25 ml) and CH_2Cl_2 (200 ml) at 5 °C and the solution was stirred at 27 °C for 10 h. After work-up, **97** was obtained as a colorless powder (31.0 g, 87%). ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.05 (8H, m, cyclohexane CH_3 × 4), 3.04 (3H, s, CH_3), 3.90—4.03 (4H, m, OCH_2CH_2O), 4.80—4.92 (1H, m, CH). MS *m/z*: 236 (M^+), 206. A mixture of **97** (13.9 g, 59 mmol), NaN_3 (26.5 g, 410 mmol) and DMF (110 ml) was stirred at 75 °C for 7 h. The mixture was poured into H_2O and extracted with Et_2O. The residue obtained from the extract was purified by column chromatography (SiO_2, C_6H_{12}: AcOEt = 10 : 1) to give the azide (**98**) (6.9 g, 64%) as an oil. The azide (**98**) (5.9 g, 32 mmol) was treated with $LiAlH_4$ (3.2 g) in Et_2O (310 ml) at 25 °C for 5 h. After work-up, the amine (**99**) was obtained as colorless prisms (4.9 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.86 (8H, m, cyclohexane CH_2 × 4), 2.72—2.84 (1H, m, CH), 3.93 (4H, s, OCH_2CH_2O). MS *m/z*: 157 (M^+). A mixture of **99** (4.9 g, 31 mmol), triethyl orthoformate (5.7 g, 39 mmol) and triethyl phosphite (14.1 g, 102 mmol) was stirred at 140 °C for 12 h. The mixture was extracted with Et_2O and the extract was washed with 2 N NaOH and brine, and dried over Na_2SO_4. Removal of the solvent gave the phosphonate (100) (8.7 g). ^{1}H-NMR ($CDCl_3$) δ: 1.29—1.39 (12H, t, *J* = 7.0 Hz, CH_3 × 4), 1.36—1.87 (8H, m, cyclohexane CH_2 × 4), 2.85—2.96 (1H, m, $CH_2\underline{C}HCH_2$), 3.38 (1H, t, *J* = 22.0 Hz, CHP), 3.93 (4H, s, OCH_2CH_2O), 4.14—4.29 (8H, m, $CH_3\underline{C}H_2$ × 4). Treatment of **100** (8.7 g) with 80% AcOH (100 ml) at 85 °C for 5 h afforded the crude ketone (**101**), which was purified by column chromatography (SiO_2, AcOEt : C_6H_6 : MeOH = 9 : 1 : 1) (3.2 g, 20% from **99**).

Tetraethyl 4-Methylenecyclohexylaminomethylenebis(phosphonate) (102) *n*-BuLi (1.55 M *n*-hexane solution, 9 ml, 7.4 mmol) was added to a solution of methyltriphenylphosphonium bromide (2.8 g, 7.8 mmol) in absolute THF (13 ml) at 0 °C. An absolute THF solution (4.2 ml) of the ketone (**101**) (2.1 g, 5.3 mmol) was added to the mixture at 25 °C and stirred for 3 h. *n*-Hexane (150 ml) and Et_2O (100 ml) were added to the mixture, and the precipitate that formed was removed. The solution was washed with H_2O and dried over Na_2SO_4. The residue obtained from the solution was purified by column chromatography (SiO_2, AcOEt : C_6H_6 : MeOH = 20 : 1 : 1) to give the oily phosphonate (**102**) (0.47 g, 15%).

Tetraethyl 1-(Homopiperidino)methylenebis(phosphonate) (106) and *N*-(Diethylphosphorylmethylene)-1-aminohomopiperidine (107) A mixture of 1-aminohomopiperidine (**104**) (1.0 g, 8.8 mmol), triethyl orthoformate (1.6 g, 11 mmol) and triethyl phosphite (3.9 g, 28 mmol) was stirred at 140 °C for 10 h. The mixture was extracted with $CHCl_3$ (200 ml) and the extract was washed with 2 N NaOH and brine, then dried over Na_2SO_4. An oily residue was obtained from the extract. Two compounds (**106**, **107**) were isolated from the residue by column chromatography (SiO_2, AcOEt : CH_3OH = 25 : 1). **106**: 0.25 g, 7.0%, *Rf* = 0.41 (TLC on SiO_2, AcOEt : CH_3OH = 20 : 1). **107**: 0.34 g, 15.0%, *Rf* = 0.53 (TLC on SiO_2, AcOEt : CH_3OH = 20 : 1), ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.38 (6H, t, *J* = 7.0 Hz, CH_3 × 2), 1.53—1.83 (8H, m, 3-, 4-, 5-, 6-CH_2), 2.43—2.56 (4H, m, 2-, 7-CH_2), 4.06—4.19 (4H, m, $CH_3\underline{C}H_2$ × 2), 6.19 (1H, d, *J* = 45.0 Hz, PCH). *Anal.* Calcd for $C_{11}N_{23}N_2O_3P$: C, 50.37; H, 8.84. Found: C, 50.63; H, 9.12.

Inhibitory Activity for Rise in Serum Calcium Induced by Parathyroid Hormone Male Wistar rats, weighing 160—180 g, were thyroparathyroidectomised surgically. On the 4th day after the operation, animals below 80 μg/ml in serum calcium were divided into groups at random and allocated to the various treatments with test compounds and controls. All compounds were dissolved in 2% $NaHCO_3$ or suspended in 0.5% CMC for intravenous and subcutaneous or oral administration, respectively. On the 5th day after the operation, test compounds were given. All animals were maintained on a diet low in calcium (low calcium diet, Oriental Yeast Co., Ltd.) from the 7th day to the 9th day after the operation. On the 8th day, all animals were injected once subcutaneously with PTH emulsion (PTH: 40 μg/animal). [The PTH emulsion was prepared with PTH (Peptide Inst.), aqueous 1.5% cysteine HCl solution and Freund's incomplete adjuvant.]. Twenty hours after the injection, a blood sample was taken and calcium in serum was determined by atomic absorption spectroscopy (Hitachi 173-30 instrument).

Acknowledgement The authors wish to thank Professor Shunsaku Ohta of Kyoto Pharmaceutical University for his valuable advice and also Professor Kazumoto Miyahara of Setsunan University for FAB-MS measurements.

References and Notes

1) P. Cartier, *Bull. Soc. Chim. Biol.* (Paris), **39**, 169 (1957); H. R. Perkins, P. G. Walker, *J. Bonet Jt Sung. B*, **40**, 333 (1958).
2) H. Fleisch, J. Maerki, R. G. G. Russell, *Proc. Soc. Exp. Biol.* (*N.Y.*), **122**, 317 (1966).
3) W. F. Neuman, *Amer. J. Physiol.*, **200**, 1296 (1961); H. Fleisch, F. Straumann, *Nature* (London), **212**, 901 (1966).
4) J. A. Boezi, *Pharm. Ther.*, **4**, 231 (1979); D. W. Hutchinson, *Antiviral Res.*, **5**, 193 (1985).
5) D. W. Hutchinson, M. Naylor, G. Semple, *Chem. Scripta.*, **26**, 91 (1986).
6) *a*) R. G. G. Russell, R. C. Muhlbauer, S. Bisaz, D. A. Williams, H.b:g1 A. Fleisch, *Calc. Tiss. Res.*, **6**, 183 (1970); *b*) M. D. Francis, R. G. G. Russell, H. A. Fleisch, *Science*, **165**, 1264 (1969); *c*) H. A. Fleisch, R. G. G. Russell, S. Bisaz, R. C. Muhlbauer, D. A. Williams, *Europ. J. Clin. Invest.*, **1**, 12 (1970); *d*) C. E. McKenna, L. A. Khawli, W. Y. Ahmad, P. Pham, J. P. Bongartz, *Phosphorus Sulfur*, **37**, 1 (1988).
7) H. Fleisch, "Handbook of Experimental Pharmacology," Vol. 83, ed. by P. F. Baker, Springer, Berlin, Hidelberg, 1988, p. 441.
8) M. D. Francis, R. Martodam, "The Role of Phosphonates in Living Systems," ed. by R. L. Hiderbrand, CRC Press, Boca Raton, Fla., 1983, p. 55 ; J. J. Benedict, C. M. Perkins, European Patent 186405 [*Chem. Abstr.*, **105**, 232453*q* (1986)].
9) *a*) F. H. Ebetino, C. R. Degenhardt, L. A. Jamieson, D. C. Burdall,

Heterocycles, **30**, 855 (1990); *b*) D. W. Hutchinson, D. M. Thornton, *Synthesis*, **1990**, 135; *c*) G. Sturtz, J. Guervenous, *ibid.*, **1991**, 661; *d*) C. Yuan, C. Li, Y. Ding, *ibid.*, **1991**, 854; *e*) J. P. Bjorkroth, T. A. Pakkanen, J. Lindroos, *J. Med. Chem.*, **34**, 2338 (1991); *f*) M. Menge, K. J. Munzenberg, E. Reimann, *Arch. Pharm.*, **314**, 218 (1981); *g*) P. Burckhardt, "Disodium Pamidoronate (APD) in the Treatment of Malignancy-Related Disorders," Hans Huber Publisher, Tront, 1989.

10) M. D. Francis, *Calc. Tiss. Res.*, **3**, 151, (1969); M. D. Francis, R. L. Gentner, *J. Chem. Ed.*, **55**, 760 (1978); M. D. Francis, U.S. Patent 3584125 [*Chem. Abstr.*, **75**, 52779*d* (1971)].
11) All of the tetraethyl phosphonates were prepared by the use of this method.
12) It was reported that introduction of an *exo*-double bond into biologically active molecules occasionally enhances the activity. [F. Zutterman, H. De Wilde, R. De Clercq, M. Vandewalle, *Tetrahedron*, **35**, 2389 (1979)].
13) R. A. Olofson, J. T. Martz, Jean-Pierre Senet, M. Piteau, T. Malfroot, *J. Org. Chem.*, **49**, 2081 (1984).
14) The *exo*-double bond reduction was faster than debenzylation during catalytic reduction in the presence of 5% Pd–C.
15) Reaction of **24** with other Wittig reagents such as 2-dimethylaminoethyl-, 3-dimethylaminopropyl- and α-(γ-butyrolactone)triphenylphosphonium bromide and ethoxycarbonylmethyl(triphenyl)phosphonium bromide was unsuccessful. But, it was reported that 1-benzyl-4-piperidone gave 1-benzyl-4-dimethylaminoethylideno piperidine on treatment with dimethylaminoethyltriphenylphosphonium bromide, in good yield. [F. D. Bellamy, J. B. Chazan, P. Dodey, P. Dutartre, K. Ou, M. Pascal, J. Robin, *J. Med. Chem.*, **34**, 1545 (1991); A. Marxer, T. Leutert, *Helv. Chim. Acta*, **61**, 1708 (1978)]. These results suggest that reactivity of **24** with Wittig reagents may be limited.
16) A. Ando, T. Shinada, S. Kinoshita, N. Arimura, M. Koyama, T. Nagai, T. Miki, I. Kumadaki, H. Sato, *Chem. Pharm. Bull.*, **38**, 2175 (1990).
17) N. S. Isaaks, *Chem. Commun.*, **1972**, 443.
18) L. N. Markovskij, V. E. Pashinnik, A. V. Kirsanov, *Synthesis*, **1973**, 787; W. Middleton, *J. Org. Chem.*, **40**, 574 (1975).
19) Attempts to prepare **46** selectively from **39a** or **7a** by using HF in piperidine were unsuccessful. N. Mongelli, F. Animati, R. D. Alessiol, L. Zuliani, C. Gandolfi, *Synthesis*, **1988**, 311; A. I. Ayi, M. Remli, R. Guedj, *Tetrahedron Lett.*, **22**, 1505 (1981).
20) L. M. Rice, C. F. Geschickter, C. H. Grogan, *J. Med. Chem.*, **6**, 388 (1963).
21) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, G. Tosi, *J. Am. Chem. Soc.*, **92**, 7428 (1970); L. K. Bee, J. Beeby, J. W. Everett, P. J. Garratt, *J. Org. Chem.*, **40**, 2212 (1975); C. Filliatre, C. Gueraud, *C. R. Acad. Sci. C*, **273**, 1186 (1971).
22) S. M. Liebowitz, E. J. Belair, D. T. Witiak, D. Ledenicer, *Eur, J. Med. Chem.-Chim. Ther.*, **21**, 439 (1986).
23) M. R. Bryce, J. M. Gardiner, P. J. Horton, S. A. Smith, *J. Chem. Research (S)*, **1989**, 1; R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957).
24) The azaspiro[5.5]undecane compound (**77**) was obtained by treatment of **76** with 25% HBr–AcOH at 50 °C in 36% yield (method D).
25) R. G. G. Russell, R. C. Muhlbauer, S. Bisaz, D. A. Williams, *Calc. Tiss. Res.*, **6**, 183 (1970).
26) J. J. Benedict, K. Y. Johnson, J. A. Bevan, C. M. Perkins, *Calc. Tiss. Int.*, **38**, Suppl., S31 (1985); J. A. Bevan, A. F. Franks, J. E. McOsker, R. W. Boyce, K. W. Buckingham, *Min. Res.*, **3** Suppl., Abstract 498 (1988).
27) H. Shinoda, G. Adamek, R. Felix, H. Fleisch, R. Schenk, P. Hagan, *Calc. Tiss. Int*, **35**, 87 (1983); P. H. Reitsma, O. L. M. Bijvoet, H. Verlinden-Ooms, L. J. A. van der Wee-Pals, *ibid.*, **32**, 145 (1980); R. Schenk, P. Eggli, H. Fleisch, S. Rosini, *ibid.*, **38**, 342 (1986); P. M. Boonekamp, C. W. G. M. Lowik, L. J. A. van der Wee-Pals, M. L. L. van Wijk-van Lennep, O. L. M. Bijvoet, *Bone Mineral*, **2**, 29 (1987).
28) The 50% inhibitory dose against the rise in serum calcium of control animals.
29) Though **48** showed low activity in the iv screening test, uility on administration *via* the peroral route was expected.
30) A part of the results was presented at the 10th Annual Meeting of the Japanese Society for Bone and Mineral Research, Tokyo, Japan, July 1992.
31) The structure of **35** was presumed on the basis of that of **36**. Crude **35** was also detected in the reaction mixture of **7a** and 37% HCl by ^{1}H-NMR spectroscopy.