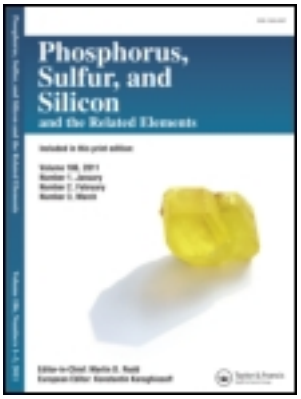

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Characterization of Novel Cycloalkanespiro-5-Hydantoin Phosphonic Acids

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SYNTHESIS AND CHARACTERIZATION OF NOVEL CYCLOALKANESPIRO-5-HYDANTOIN PHOSPHONIC ACIDS

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A series of new cycloalkanespiro-5-hydantoin phosphonic acids have been synthesized and characterized. The mixture of [(2,4-dioxo-1,3-diazaspiro-alkane-3-yl)-methyl]phosphonic acids and [(2,4-dioxo-1,3-diazaspiro-alkane-1,3-diyl)dimethyl]diphospho-nic acids was obtained from cycloalkanespiro-5-hydantoins, formaldehyde, and phosphorus trichloride in a molar ratio of 1:2:2, by a procedure modified by us. Their structures were proved by means of IR, ^{1}H, $^{13}C\{^{1}H\}$ and ^{31}P NMR spectroscopy.

Keywords α-Aminophosphonic acids; cycloalkanespiro-5-hydantoins; phosphorus trichloride

INTRODUCTION

α-Aminophosphonic acids are structurally analogous to aminocarboxylic acids. The structures of aminophosphonic acids are of interest because of the biological role of their derivatives. These compounds possess a variety of biological activities, including anticancer, antiviral, antibacterial, antifungal, and other activities. The established antiproliferative effects, together with the low mammalian toxicity of these agents, has conditioned tremendous interest towards designing novel antineoplastic agents.[1–6] Synthesis of aminophosphonic acids is an active area of research, and many methods are now available.[7–12] Novel α-aminophosphonic acids with moderate clastogenic effect were synthesized reacting 1,3-oxazolidin-2-one derivatives with formaldehyde and phosphorus trichloride.[13, 14] Cyclic or heterocyclic rings, introduced into the molecular skeleton, increase its rigidity and modify the electronic effects. Thus in recent years, many cyclic α-aminophosphonic acids or aminophosphonates have been prepared.[15] A series of α,α-disubstituted cyclic derivatives of *N*-(phosphonomethyl)glycine were obtained from cycloalkaneaminocarboxylic acids, and their biological activity was studied.[16]

Hydantoin derivatives are synthetically valuable, e.g., as precursors to α-amino acid and pyruvic acid derivatives.[17–19] Hydantoins, substituted at C-5, are important medicinal

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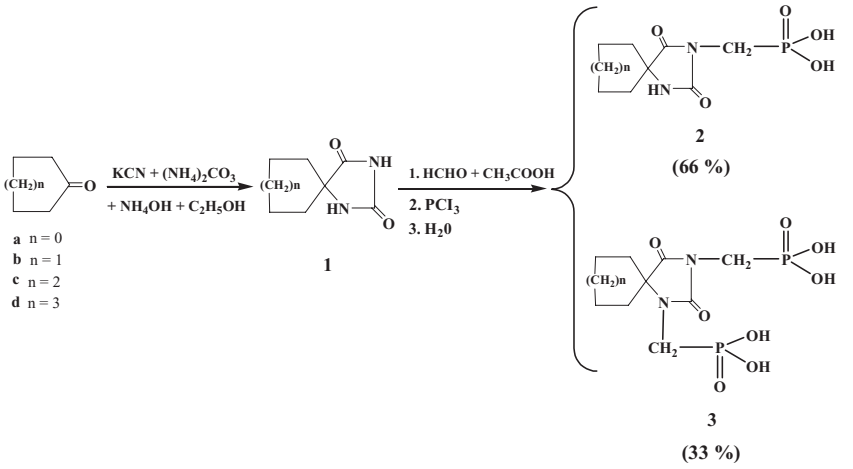
compounds. Numerous applications have been found for hydantoin derivatives due to their antidepressant[20] and antiviral activities,[21] the inhibition of binding of HIV to lymphocytes,[22] as well as their anticonvulsant and cardiac antiarrhythmic effects.[23] Taking into account this fact, we describe in this article the synthesis of novel α-aminophosphonic acids with potential biological activity by reacting phosphorus trichloride with formaldehyde and cycloalkanespiro-5-hydantoins.

RESULTS AND DISCUSSION

In our present studies, we used the modified procedure described by Engelmann and Pikl,[24] according to which phosphorus trichloride, formaldehyde, and oxazolidinone derivatives are used as the starting compounds for the preparation of the aminophosphonic acids. The new α-aminophosphonic acids were obtained from cycloalkanespiro-5-hydantoins, formaldehyde, and phosphorus trichloride as shown in Scheme 1. Cycloalkanespiro-5-



Scheme 1

hydantoins **1a–1d**, phosphorus trichloride, and formaldehyde were used as starting compounds in a molar ratio of 1:2:2. The compounds **1a–1d** were prepared by the Bucherer–Lieb reaction.[25] The rate of hydroxymethylation of the two nitrogen atoms is different. Hydroxymethylation at the N-3 atom proceeds faster because of the higher acidity of the NH-bond compared to that of the N-1 atom.[26] In the ^{31}P NMR spectrum of the reaction product, two signals are observed at 20.6 ppm (triplet with $^{2}J_{PH} = 13.5$ Hz) and at 18.1 ppm (triplet with $^{2}J_{PH} = 11.0$ Hz). The signal at 20.6 ppm can be assigned to the phosphorus atom of the fragment connected to N-3, and that at 18.1 ppm to the phosphorus atom of the fragment connected to N-1. The intensity ratio of 2:1 confirms the difference in the reactivity of the two NH-groups in the cycloalkanespiro-5-hydantoins (see Table I).

Unfortunately, the new synthesized compounds could not be separated. The formation of [(2,4-dioxo-1,3-diazaspiro-alkane-3-yl)methyl]phosphonic acids **2a–2d** and [(2,4-dioxo-1,3-diazaspiro-alkane-1,3-diyl)dimethyl]diphosphonic acids **3a–3d** was confirmed by ^{1}H, ^{13}C$\{^{1}$H$\}$, ^{31}P NMR, and IR spectroscopy.

Table I ^{31}P NMR data of the new cycloalkanespiro-5-hydantoin phosphonic acids **2** and **3**

	δ^{31}P (ppm) / $^{2}J_{PH}$ (Hz)
2a	20.6 (t) / 13.5
3a	18.1 (t) / 11.0
2b	19.4 (t) / 15.0
3b	15.5 (t) / 12.0
2c	20.0 (t) / 11.6
3c	17.0 (t) / 12.2
2d	21.1 (t) / 14.5
3d	17.6 (t) / 12.0

In the ^{1}H NMR spectra of all compounds **3a–3d**, doublets with a characteristic $^{2}J_{PH}$ coupling constant of 11–15 Hz are observed for the P—C$\underline{H}_2$ protons. Direct evidence for the formation of the P–C bond in the P–C$\underline{H}_2$ fragment is the doublets that appear in the ^{13}C{^{1}H} NMR spectra of all compounds **3a–3d** with a characteristic $^{1}J_{PC}$ coupling constant of 154–156 Hz (see the Experimental section). In the ^{31}P NMR spectrum of the reaction mixture, an additional signal appears at 22 to 23 ppm, which is characteristic of a phosphonic structure. Further studies to elucidate the structure of these products and their formation are in progress.

CONCLUSION

In this article, the synthesis and characterization of new [(2,4-dioxo-1,3-diazaspiro-alkane-3-yl)methyl]phosphonic acids and [(2,4-dioxo-1,3-diazaspiro-alkane-1,3-diyl)dimethyl] diphosphonic acids, prepared by reacting cycloalkanespiro-5-hydantoins with formaldehyde and phosphorus trichloride, is described.

EXPERIMENTAL

Instruments and Reagents

Cycloalkanones, phosphorus trichloride, paraformaldehyde, and the solvents were purchased from Fluka and Merck, and were used without further purification.

The infrared (IR) spectra were recorded in KBr pellets with a Perkin-Elmer Model 1600 Series FT-IR instrument. Melting points (mp) were determined on a Koffler microscope and were uncorrected. The purity of the products was checked by TLC on precoated plates of silica gel 60 F254 (Merck) using as the mobile phase a 3:1:1 mixture of *n*-BuOH, AcOH, and H_2O. Spots on TLS chromatograms were detected by chlorine/*o*-tolidine reaction. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained with a Bruker DRX 400 spectrometer at 400.13, 100.61, and 161.97 MHz, respectively. ^{13}C NMR spectra were fully ^{1}H decoupled. Chemical shifts are reported in δ values (ppm), and J values are reported in hertz (Hz).

The compounds **1a–1d** were prepared by the Bucherer–Lieb reaction.[25,27]

Preparation of Cycloalkanespiro-5-hydantoins (1a–1d) by Bucherer–Lieb Synthesis

To a solution of the cycloalkanone (0.0594 mol) in ethanol (55 mL) and water (50 mL), sodium cyanide (6.63 g, 0.1 mol) and ammonium carbonate (34.6 g, 0.36 mol) were

added. The mixture was refluxed for 6 h with stirring. After dilution with water, the cooled mixture was acidified with concentrated hydrochloric acid. The crude cycloalkanespiro-5-hydantoin precipitated overnight upon cooling at 5°C. The pure compound was crystallized from water as colorless crystals.

1,3-Diazaspiro[4.4]nonane-2,4-dione (1a). Yield 96.0% (8.79 g), $R_f = 0.74$, mp = 204–205°C; IR (KBr, cm^{-1}): 3215 (^{3}N—H), 3074 (^{1}N—H), 1788 (^{2}C=O), 1737 (^{4}C=O). ^{1}H NMR (d^6-DMSO): δ = 1.8–2.1 (m, 8H, C$\underline{H}_2$), 7.3 (s, 1H, NH), 10.4 (s, 1H, NH). ^{13}C{^{1}H} NMR (d^6-DMSO): δ = 23.8 (C-3,4), 35.8 (C-2,5), 69.9 (—C—), 157.4 2-C=O, 168.9 4-C=O.

1,3-Diazaspiro[4.5]decane-2,4-dione (1b). Yield 88.2% (8.81 g), $R_f = 0.87$, mp = 219–220°C; IR (KBr, cm^{-1}): 3198 (^{3}N—H), 3070 (^{1}N—H), 2951–2858 (C—H), 1775 (^{2}C=O), 1727 (^{4}C=O). ^{1}H NMR (d^6-DMSO): δ = 1.6–1.9 (m, 10H, C$\underline{H}_2$), 8.2 (s, 1H, NH), 10.3 (s, 1H, NH). ^{13}C{^{1}H} NMR (d^6-DMSO): δ = 23.1 (C-3,5), 25.4 (C-4), 36.0 (C-2,6), 68.7 (—C—), 157.0 2-C=O, 167.7 4-C=O.

1,3-Diazaspiro[4.6]undecane-2,4-dione (1c). Yield 76.2% (8.23 g), $R_f = 0.87$, mp = 213–215°C; IR (KBr, cm^{-1}): 3282 (^{3}N—H), 3055 (^{1}N—H), 2941–2852 (C—H), 2347 (NH), 1770 (^{2}C=O), 1709 (^{4}C=O). ^{1}H NMR (d^6-DMSO): δ = 1.5–1.8 (m, 12H, C$\underline{H}_2$), 8.2 (s, 1H, NH), 10.4 (s, 1H, NH). ^{13}C{^{1}H} NMR (d^6-DMSO): δ = 21.9 (C-3,6), 26.8 (C-4,5), 35.9 (C-2,7), 66.7 (—C—), 157.3 2-C=O, 172.7 4-C=O.

1,3-Diazaspiro[4.7]dodecane-2,4-dione (1d). Yield 91.0% (10.59 g), R_f = 0.79, mp = 240–241°C; IR (KBr, cm^{-1}): 3250 (^{3}N—H), 3183 (^{1}N—H), 1765 (^{2}C=O), 1713 (^{4}C=O). ^{1}H NMR (d^6-DMSO): δ = 1.5–2.1 (m, 14H, C$\underline{H}_2$), 8.2 (s, 1H, NH),10.4 (s, 1H, NH). ^{13}C{^{1}H} NMR (d^6-DMSO): δ = 20.0 (C-3,7), 24.2 (C-5), 26.8 (C-4,6), 38.1 (C-2,8), 68.0 (—C—), 158.1 2-C=O, 176.0 4-C=O.

Preparation of [(2,4-Dioxo-1,3-diazaspiro-alkane-3-yl)methyl]-phosphonic Acids (2a–2d), [(2,4-Dioxo-1,3-diazaspiro-alkane-1,3-diyl) dimethyl]diphosphonic Acids (3a–3d) in Ratio of 2:1: General Procedure

The respective cycloalkanespiro-5-hydantoins (0.0059 mol) and paraformaldehyde (0.36 g, 0.0119 mol) were placed under argon in a four-necked round-bottomed flask equipped with a magnetic stirrer, reflux condenser, thermometer, dropping funnel, and argon inert. Under vigorous stirring glacial acetic acid (5.95 mL) was added dropwise. A white suspension formed. The reaction mixture was refluxed (~115°C) for 12.5 h, after which it became a clear solution. Then the temperature was lowered to 20°C and 1.04 mL (1.63 g, 0.0119 mol) of phosphorus trichloride was added dropwise. During and after the addition hydrogen chloride evolved. The reaction mixture was refluxed (~118°C) for 6 h. Subsequently 6.80 mL of distilled water was added. After 4 h further refluxing, the reaction mixture was concentrated under reduced pressure.

The solvent was evaporated, and the product left was dissolved in a large excess of methanol. After filtration, the filtrate was evaporated to give a residue, which was purified by precipitation in methanol/ethyl acetate and collected by filtration. The purification step was repeated several times to give compounds (**2a–2d** and **3a–3d**).

[(2,4-Dioxo-1,3-diazaspiro[4.4]nonane-3-yl)methyl]phosphonic Acid (2a), [(2,4-Dioxo-1,3-diazaspiro[4.4]nonane-1,3-diyl)dimethyl]diphosphonic Acid (3a). Yellow oil, yield 45.0% (0.66 g), $R_f = 0.45$; IR (KBr, cm^{-1}): 3424 (OH), 2942–2854 (C—H), 1730 (^{2}C=O), 1708 (^{4}C=O), 1156 (P=O), 1114, 1012 (P—O—H). ^{1}H NMR (400.13 MHz, CD_3OD): δ = 1.1—1.9 (m, 8H, C$\underline{H}_2$), 3.2 (d, $^2J_{PH}$ = 11.5 Hz, 2H, P—C$\underline{H}_2$),

3.3 (d, $^2J_{PH}$ = 10.0 Hz, 2H, P—C$\underline{H}_2$), 5.6 (br.s., 2H, P—O$\underline{H}$), 8.2 (br.s., 2H, P—O$\underline{H}$). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD): δ = 21.5 (CH_2), 24.2 (CH_2), 25.2 (CH_2), 34.5 (d, $^1J_{PC}$ = 149.6 Hz, P—$\underline{C}H_2$), 59.0 (d, $^1J_{PC}$ = 154.1 Hz, P—$\underline{C}H_2$), 63.4 (–C—), 156.4 (2-C=O), 177.7 (4-C=O). ^{31}P NMR (161.97 MHz, CD_3OD): = 18.1 (t, $^2J_{PH}$ = 11.0 Hz), 20.6 (t, $^2J_{PH}$ = 13.5 Hz) intensity integral ratio of 2:1.

[(2,4-Dioxo-1,3-diazaspiro[4.5]decane -3-yl)methyl]phosphonic Acid (2b), [(2,4-Dioxo-1,3-diazaspiro[4.5]decane-1,3-diyl)dimethyl]diphosphonic Acid (3b). Yellow oil, yield 48.0% (0.74 g), R_f = 0.41; IR (KBr, cm^{-1}): 3397 (OH), 2942–2854 (C—H), 1740 (^{2}C=O), 1713 (^{4}C=O), 1150 (P=O), 1036, 914 (P—O—H). ^{1}H NMR (400.13 MHz, CD_3OD): δ = 1.5—2.1 (m, 10H, C$\underline{H}_2$), 3.5 (d, $^2J_{PH}$ = 11.0 Hz, 2H, P—C$\underline{H}_2$), 3.8 (d, $^2J_{PH}$ = 9.0 Hz, 2H, P—C$\underline{H}_2$), 5.7 (br.s., 2H, P—O$\underline{H}$), 8.1 (br.s., 2H, P—O$\underline{H}$). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD): δ = 21.0 (C-4), 22.0 (C-3,5), 26.0 (C-2,6), 38.5 (d, $^1J_{PC}$ = 150.5 Hz, P—$\underline{C}H_2$), 60.0 (d, $^1J_{PC}$ = 156.6 Hz, P—$\underline{C}H_2$), 68.0 (–C—), 156.7 (2-C=O), 176.7 (4-C=O). ^{31}P NMR (161.97 MHz, CD_3OD): δ = 15.5 (t, $^2J_{PH}$ = 12.0 Hz), 19.4 (t, $^2J_{PH}$ = 15.0 Hz) intensity integral ratio of 2:1.

[(2,4-Dioxo-1,3-diazaspiro[4.6]undecane-3-yl)methyl]phosphonic Acid (2c), [(2,4-Dioxo-1,3-diazaspiro[4.6]undecane-1,3-diyl)dimethyl]diphosphonic Acid (3c). Yellow oil, yield 42.0% (0.68 g), R_f = 0.43; IR (KBr, cm^{-1}): 3348 (OH), 2955–2859 (C—H), 1745 (^{2}C=O), 1710 (^{4}C=O), 1171 (P=O), 1013, 965 (P—O—H). ^{1}H NMR (400.13 MHz, CD_3OD): δ = 1.2—1.9 (m, 12H, C$\underline{H}_2$), 3.3 (d, $^2J_{PH}$ = 12.0 Hz, 2H, P—C$\underline{H}_2$), 3.5 (d, $^2J_{PH}$ = 11.0 Hz, 2H, P—C$\underline{H}_2$), 5.2 (br.s., 2H, P—O$\underline{H}$), 8.4 (br.s., 2H, P—O$\underline{H}$). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD): δ = 20.0 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 34.0 (CH_2), 37.0 (d, $^1J_{PC}$ = 156.6 Hz, P—$\underline{C}H_2$), 57.6 (d, $^1J_{PC}$ = 152.1 Hz, P—$\underline{C}H_2$), 61.0 (–C—), 159.7 (2-C=O), 176.0 (4-C=O). ^{31}P NMR (161.97 MHz, CD_3OD): δ = 17.0 (t, $^2J_{PH}$ = 12.2 Hz), 20.0 (t, $^2J_{PH}$ = 11.6 Hz) intensity integral ratio of 2:1.

[(2,4-Dioxo-1,3-diazaspiro[4.7]dodecane-3-yl)methyl]phosphonic Acid (2d), [(2,4-Dioxo-1,3-diazaspiro[4.7]dodecane-1,3-diyl)dimethyl]diphosphonic Acid (3d). Yellow oil, yield 45.8% (0.79 g), R_f = 0.47; IR (KBr, cm^{-1}): 3261 (OH), 2925–2855 (C—H), 1765 (^{2}C=O), 1710 (^{4}C=O), 1180 (P=O), 1012, 969 (P—O—H). ^{1}H NMR (400.13 MHz, CD_3OD): δ = 1.1—1.9 (m, 8H, C$\underline{H}_2$), 3.2 (d, $^2J_{PH}$ = 11.5 Hz, 2H, P—C$\underline{H}_2$), 3.3 (d, $^2J_{PH}$ = 10.0 Hz, 2H, P—C$\underline{H}_2$), 5.8 (br.s., 2H, P—O$\underline{H}$), 8.0 (br.s., 2H, P—O$\underline{H}$). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD): δ = 21.8 (C-5), 24.4 (C-4,6), 27.7 (C-3,7), 33.0 (C-2,8), 38.5 (d, $^1J_{PC}$ = 153.2 Hz, P—$\underline{C}H_2$), 58.7 (d, $^1J_{PC}$ = 155.5 Hz, P—$\underline{C}H_2$), 64.6 (–C—), 155.9 (2-C=O), 178.9 (4-C=O). ^{31}P NMR (161.97 MHz, CD_3OD): δ = 17.6 (t, $^2J_{PH}$ = 12.0 Hz), 21.1 (t, $^2J_{PH}$ = 14.5 Hz) intensity integral ratio of 2:1.

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