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Aminophosphonates in the Synthesis of New Radioprotecting Agents

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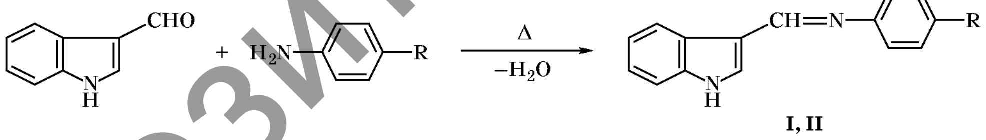
Abstract—Reactions of bis(trimethylsilyl) hydrogen phosphite with Schiff bases derived from indole-3-carbaldehyde and aniline or ethyl *p*-aminobenzoate, as well as of diisopropyl hydrogen phosphite with *N*-benzylideneaniline, gave water-soluble sodium salts of α-aminophosphonic acids which are potential radioprotecting agents.

Search for compounds possessing radioprotective properties constitutes an extensively developing field of chemistry. More than 50 years elapsed since the possibility for chemical protection from ionizing radiation was demonstrated for the first time. During this period, much efforts were made to synthesize and study prophylactic effect of thousands of compounds (including those of natural origin) possessing radioprotective properties. Among these, quite efficient radioprotectors of the indolylalkylamine series have been found [1, 2], which are capable of preventing death of a considerable part of animals exposed to X-ray and γ-radiation. However, high toxicity and narrow range of therapic effect of the known radioprotectors stimulate search for new more efficient compounds.

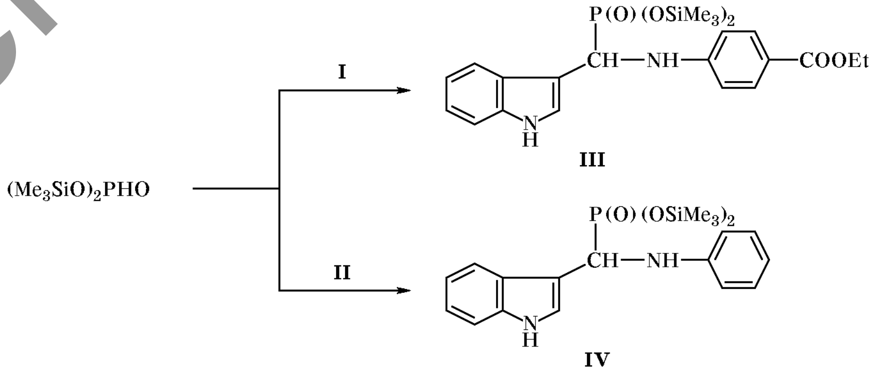
A large group of radioprotecting agents includes aminoalkyl thiophosphoric derivatives (such as Cystaphos and Gammaphos) and also nitrogen-containing heterocycles, in particular indolylalkylamines. With the goal of searching for new efficient radioprotectors we focused on aminophosphonic acid derivatives

Scheme 1.



I, R = COOEt; **II**, R = H.

Scheme 2.



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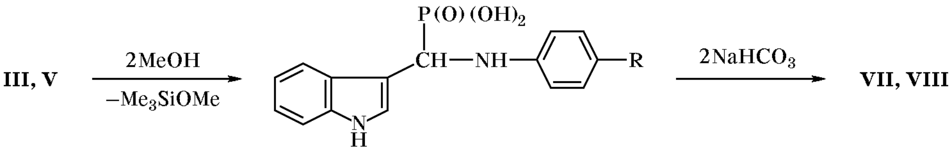
Scheme 3.



V, VI

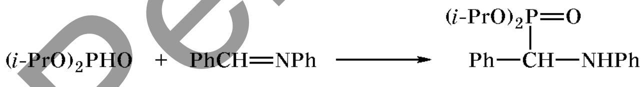
V, **VII**, R = COOEt; **VI**, **VIII**, R = H.

whose structural fragments, specifically, P–C–N and P–C–N–P, are known as carriers of radioprotective properties. As starting compounds we chose Schiff bases **I** and **II** which were synthesized by condensation of indole-3-carbaldehyde with aniline and ethyl *p*-aminobenzoate, respectively, according to standard procedure (Scheme 1). Compounds **I** and **II** are stable crystalline substances. They were brought into reaction with bis(trimethylsilyl) hydrogen phosphite in dry benzene to obtain phosphonates **III** and **IV** (Scheme 2). The progress of the reaction was monitored by ^{31}P NMR and IR spectroscopy. Crystalline phosphonates **III** and **IV** separated from the benzene solution. They were treated with 2 equiv of methanol, and phosphonic acids **V** and **VI** were converted into water-soluble sodium salts **VII** and **VIII** by the action of sodium hydrogen carbonate (Scheme 3).

The IR spectra of sodium salts **VII** and **VIII** contain absorption bands typical of P–C (750 cm^{-1}), P=O (1100 cm^{-1}), C–O–C (1280–1290 cm^{-1}), C–C$_{arom}$ (1460–1470 cm^{-1}), C–N (1550–1570 cm^{-1}), C=O (1695 cm^{-1}), O–H (2700–2500 cm^{-1}, br), and NH (3300 cm^{-1}) groups and bonds. In the ^{31}P NMR spectra of aqueous solutions of **VII** and **VIII** signals at δ_P 40.75 and 40.47 ppm were observed, which correspond to phosphonate groups.

In order to synthesize compounds having a potentially radioprotective P–N–C–P fragment we performed the reaction of *N*-benzylideneaniline with diisopropyl hydrogen phosphite (Scheme 4).

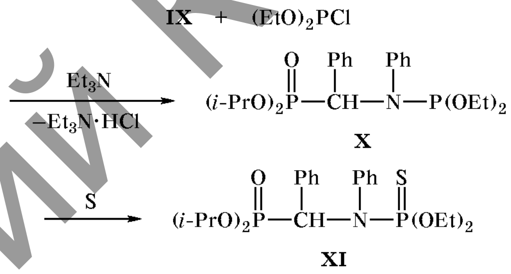
Scheme 4.



IX

The product was aminophosphonate **IX** which showed a signal at δ_P 22 ppm in the ^{31}P NMR spectrum. Its IR spectrum contained the following bands, ν, cm^{-1}: 760 (P–C), 1030 (P–O–C), 1240 (P=O), 1510 (C–N), 1500 and 1530 (C–C$_{arom}$), 3300 (NH). We failed to obtain the desired phosphonic acid by hydrolysis of phosphonate **IX** in 5 M hydrochloric acid. Phosphorylation of **IX** with diethyl phosphorochloridite in the presence of triethylamine as hydrogen chloride acceptor afforded phosphonate **X** having a P–C–N–P fragment. Compound **X** was treated with molecular sulfur to obtain thiophosphonate **XI** (Scheme 5).

Scheme 5.



X

XI

The ^{31}P NMR spectrum of diethyl *N*-(α-diisopropoxyphosphinoylbenzyl)-*N*-phenylamidophosphorothioate (**XI**) contained signals at δ_P 26 and 80 ppm, which were split with a constant $J_{P,P}$ of 20 Hz.

EXPERIMENTAL

The ^{31}P NMR spectra were recorded on a KGU-4 instrument at 10.2 MHz; the chemical shifts were measured relative to 85% H_3PO_4. The IR spectra were obtained on a UR-20 spectrometer in KBr.

Reaction of indole-3-carbaldehyde with ethyl *p*-aminobenzoate. An Arbuzov flask was charged with 7.5 g of indole-3-carbaldehyde and 8.25 g (5% excess) of ethyl *p*-aminobenzoate, and the mixture was heated at 90–100°C under reduced pressure (water-jet pump). Liberation of water was observed. When the reaction was complete (~2 h), excess ethyl *p*-aminobenzoate was removed at 78–80°C (1 mm), and the residue was washed with petroleum ether. The precipitate was filtered off and recrystallized from benzene. We thus obtained 8.74 g (65%) of ethyl *N*-(3-indolylmethylene)-*p*-aminobenzoate (**I**), mp 176–177°C. Found, %: C 73.42; H 5.71; N 9.41. $C_{18}H_{16}N_2O_2$. Calculated, %: C 73.97; H 5.48; N 9.59.

Reaction of indole-3-carbaldehyde with aniline. An Arbuzov flask was charged with 4.32 g of indole-3-carbaldehyde and 15.33 g (5 equiv) of aniline. The mixture was heated under reduced pressure (10 mm). The reaction was accompanied by liberation of water. After 2 h, the mixture was treated with petroleum ether, and light yellow crystals separated from the dark mixture. The crystals were filtered off and recrystallized from benzene to obtain 3.67 g (59%) of *N*-(3-indolylmethylene)aniline (**II**), mp 127–128°C. Found, %: C 81.24; H 5.98; N 12.38. $C_{15}H_{12}N_2$. Calculated, %: C 81.82; H 5.45; N 12.73.

Reaction of Schiff base I with bis(trimethylsilyl) hydrogen phosphite. A mixture of 3.21 g of Schiff base **I** and 2.49 g of bis(trimethylsilyl) hydrogen phosphite in 50 ml of benzene was heated for 4–5 h at 70–80°C. The mixture was treated with petroleum ether to isolate 2.22 g (59%) of bis(trimethylsilyl) 3-indolyl(*p*-ethoxycarbonylphenylamino)methylphosphonate (**III**), mp 109–110°C. Found, %: C 55.43; H 6.37; N 5.28; P 6.02. $C_{24}H_{35}N_2O_5PSi_2$. Calculated, %: C 55.60; H 6.76; N 5.41; P 5.98.

Reaction of Schiff base II with bis(trimethylsilyl) hydrogen phosphite. A mixture of 3.28 g of bis(trimethylsilyl) hydrogen phosphite and 3.2 g of Schiff base **II** in 50 ml of benzene was heated for 2 h at 70–80°C. The precipitate was washed with petroleum ether. Yield 4.5 g (69%) of bis(trimethylsilyl) 3-indolyl(phenylamino)methylphosphonate (**IV**), mp 201–202°C. Found, %: C 56.23; H 6.48; N 6.08; P 7.15. $C_{21}H_{31}N_2O_3PSi_2$. Calculated, %: C 56.50; H 6.95; N 6.28; P 6.95.

Reaction of phosphonate III with methanol. Methanol, 10 ml, was added to 2.12 g of phosphonate **III**, and the mixture was heated for 5–6 h at 60–70°C. Excess methanol and liberated methyl trimethylsilyl ether were distilled off to obtain 1.4 g (93%) of 3-indolyl(*p*-ethoxycarbonylphenylamino)methylphosphonic acid (**V**), mp 79–80°C. Found, %: C 57.48; H 5.33; N 7.81; P 8.11. $C_{18}H_{19}N_2O_5P$. Calculated, %: C 57.75; H 5.08; N 7.49; P 8.29.

Reaction of phosphonate IV with methanol. Methanol, 50 ml, was added to 4.0 g of compound **IV**, and the mixture was heated for 2 h at 80–90°C. Excess methanol and liberated methyl trimethylsilyl ether were distilled off to obtain 2.5 g (93%) of 3-indolyl(phenylamino)methylphosphonic acid (**VI**), mp 209–210°C. Found, %: C 59.23; H 5.12; N 9.12; P 10.48. $C_{15}H_{15}N_2O_3P$. Calculated, %: C 59.60; H 4.97; N 9.27; P 10.26.

Reaction of phosphonic acid V with sodium hydrogen carbonate. Water, 10 ml, was added to 1.4 g of phosphonic acid **V**, and a solution of 0.62 g of $NaHCO_3$ in 30 ml of water was added dropwise under vigorous stirring, maintaining the pH at a value of 7. After 2 h, the mixture was filtered, and the filtrate was evaporated to obtain 1.2 g (76%) of disodium 3-indolyl(*p*-ethoxycarbonylphenylamino)methylphosphonate (**VII**), mp 71–72°C. Found, %: C 51.98; H 4.33; N 6.42; P 7.66. $C_{18}H_{17}N_2Na_2O_5P$. Calculated, %: C 51.67; H 4.07; N 6.70; P 7.42.

Reaction of phosphonic acid VI with sodium hydrogen carbonate. Water, 10–15 ml, was added to 2.14 g of acid **VI**, and a solution of 1.2 g of $NaHCO_3$ in 50 ml of water was added dropwise. The mixture was treated as described above to obtain 2.1 g (87%) of disodium 3-indolyl(phenylamino)methylphosphonate (**VIII**), mp 219–220°C. Found, %: C 52.62; H 3.78; N 8.41; P 8.71. $C_{15}H_{13}N_2Na_2O_3P$. Calculated, %: C 52.02; H 3.76; N 8.09; P 8.96.

Reaction of *N*-benzylideneaniline with diisopropyl hydrogen phosphite. A mixture of 5.4 g of *N*-benzylideneaniline and 5.2 g (5% excess) of diisopropyl hydrogen phosphite was heated for 2–3 h on a water bath. After cooling, the colorless crystals were filtered off and washed with ether. Yield 6.2 g (59%) of diisopropyl α-(phenylamino)benzylphosphonate (**IX**), mp 96°C. Found, %: C 65.28; H 7.23; N 4.48; P 8.71. $C_{19}H_{26}NO_3P$. Calculated, %: C 65.71; H 7.49; N 4.03; P 8.93.

Reaction of phosphonate IX with diethyl phosphorochloridite. Diethyl phosphorochloridite, 0.86 g, was added dropwise with stirring to a mixture of 1.9 g of phosphonate **IX** and 1.04 g of triethylamine in dry diethyl ether. The precipitate of triethylamine hydrochloride was filtered off, and the solvent was removed from the filtrate to obtain 1.7 g (65%) of diisopropyl α-(*N*-diethoxyphosphino-*N*-phenylamino)benzylphosphonate (**X**), mp 99°C. Found, %: C 59.67; H 7.89; N 2.75; P 13.59. $C_{23}H_{35}NO_5P_2$. Calculated, %: C 59.10; H 7.49; N 2.99; P 13.28.

Reaction of phosphonate X with elemental sulfur. A mixture of 1.5 g of compound **X** and 0.1 g of powdered sulfur was heated for 3 h at 80°C. The mixture was dissolved in ether, and the solvent was distilled off to obtain 0.9 g of diethyl *N*-(α-diisopropoxyphosphinoylbenzyl)-*N*-phenylamidophosphorothioate (**XI**), mp 115°C. Found, %: C 55.78; H 7.49; N 2.47; P 12.88; S 6.22. $C_{23}H_{35}NO_5P_2S$. Calculated, %: C 55.31; H 7.01; N 2.81; P 12.42; S 6.41.

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