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SHORT COMMUNICATIONS

Synthesis of (Pyrrolidin-1-yl- and Morpholinoalkyl)phosphonic Acids

A.E. Baltser, I.V. Shukan, and E.N. Barskova

Russian Scientific Center "Applied Chemistry," St. Petersburg,197198 Russia
e-mail: fominarscac@mail.ru

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A fragment of phosphonous acid combined with an aminoalkyl group underlies the structure of a series of organic compounds endowed with a high biological activity without high toxicity, and also anticorrosion properties with respect to carbon and low-alloy steels [1–4].

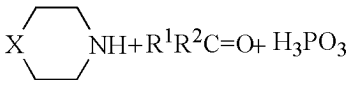
Convenient synthons for introduction of this fragment are phosphonic acid and its esters whose aminoalkylation provided a wide series of nitrogen-containing phosphonous acids, also with nitrogen heterocyclic substituents involved into the composition of the amino component in the condensation reaction and linked to the reacting primary amino group through an amino-hydrocarbon bridge [5].

Although in patent [5] in the general claim was declared a possibility to synthesize N-heterylalkylphos-phonic acids where the heterocyclic nitrogen is linked to the phosphonic group through a single-carbon bridge (at m = 0), these compounds, e.g., with a pyrrolidine or morpholine fragments were not described in the given examples, and their properties were not characterized. Moreover the reactivity of secondary alicyclic amines can considerably differ from that of primarily linear ana-logs. It is known that the appearance of steric hindrances at the secondary nitrogen in the amine component considerably reduces its reactivity and the acid properties of the resulting aminoalkylphosphonic acids [6].

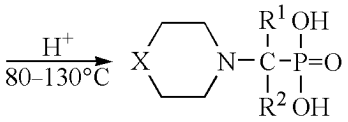
$$Ht(CH_2CH_2NH_n)_m[CR^1R^2P{=}O(OH)_2]_p$$

$$n = 0, 1; m = 0–3; p = 1, 2.$$

In this study we perfomed the aminoalkylation of phosphonic acid with pyrrolidine and morpholine along Mannich reaction using formaldehyde, acetone, or methyl ethyl ketone as carbonyl component.



I, II

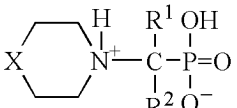


IIIa–IIIc, IVa, IVb

$R^1 = R^2 = H$ (**a**), CH_3 (**b**); $R^1 = CH_3$, $R^2 = C_2H_5$ (**c**); No X (**I, III**), X = O (**II, IV**).

It turned out that at employing the mentioned amines the plausible yields (50–85%) of the target products were attained only at a prolonged heating of the reaction mixture for 10–12 h.

The synthesized compounds **IIIa–IIIc**, **IVa**, and **IVb** are lightly colored oily substances, well soluble in water and poorly soluble in organic solvents. Like all known aminoalkylphosphonic acids [6, 7] the obtained compounds exist in solution in zwitter-ionic betaine-like structure **A**.



A

This fact is confirmed by the downfield shift by 0.2–0.5 ppm of the signals of methylene protons in the ^1H NMR spectra as compared to the analogous signals

of pyrrolidine and morpholine substituents nonprotonated at the nitrogen atom.

(Pyrrolidin-1-ylmethyl)phosphonic acid (IIIa). To 35.5 g (0.5 mol)of pyrrolidine at 20–25°C was added while stirring 41 g (0.5 mol) of phosphonic acid obtained from an appropriate amount of PCl_3 by procedure [8], 18 g of 35% hydrochloric acid, and 18 g of water. The mixture was heated at 100°C and within 1 h was added 38 g (0.5 mol) of 40% aqueous formaldehyde, and the stirring at this temperature was continued for 12 h. Afterwards the volatile products were distilled off. The residue was thrice washed with chloroform and dried in a vacuum. Yield 65 g (80%). IR spectrum, ν, cm^{-1}: 3390 br, 2995 br (NH, OH), 2760, 1630, 1160 (P=O, P–O), 1450, 1375 (CH). ^1H NMR spectrum, δ, ppm: 2.24 m, 2.31 m (4H, $2CH_2$), 2.65 m (2H, CH_2N), 2.91 m (2H, CH_2N), 3.56 d.d (2H, CH_2P). Found, %: C 36.12; H 7.01; N 8.18; P 18.02. $C_5H_{12}NO_3P$. Calculated, %: C 36.36; H 7.21; N 8.48; P 18.79.

Compounds **IIIa** and **IIIb, IVa** and **IVb** were prepared similarly.

(1-Methyl-1-pyrrolidin-1-ylethyl)phosphonic acid (IIIb). Yield 72%. IR spectrum, ν, cm^{-1}: 3380 br, 2980 br (NH, OH), 2767, 1638, 1180 (P=O, P–O), 1461, 1390 (CH). ^1H NMR spectrum, δ, ppm: 1.39 d (6H, $2CH_3$), 2.32 m (4H, $2CH_2$), 2.82 m (2H, CH_2N), 3.13 m (2H, CH_2N). Found, %: C 43.11; H 7.90; N 7.02; P 15.89. $C_7H_{16}NO_3P$. Calculated, %: C 43.52; H 8.29; N 7.25; P 16.06.

(1-Methyl-1-pyrrolidin-1-ylpropyl)phosphonic acid (IIIc). Yield 52%. IR spectrum, ν, cm^{-1}: 3385 br, 2980 br (NH, OH), 2760, 1640, 1180 (P=O, P–O), 1465, 1395 (CH). ^1H NMR spectrum, δ, ppm: 1.36 m (3H, CH_3), 1.56 d (3H, CH_3CH_2), 1.82 m, 1.92 m (2H, CH_3CH_2), 2.36 m (4H, $2CH_2$), 2.79 m (2H, CH_2N), 3.09 m (2H, CH_2N). Found, %: C 46.01; H 8.40; N 6.32; P 15.99. $C_8H_{18}NO_3P$. Calculated, %: C 46.38; H 8.70; N 6.76; P 14.98.

Morpholinomethylphosphonic acid (IVa). Yield 73%. IR spectrum, ν, cm^{-1}: 3380 br, 2980 br, 2767, 2450, 1638, 1460, 1390, 1180, 1024. ^1H NMR spectrum, δ, ppm: 3.01 m (2H, CH_2N), 3.28 m (2H, CH_2N), 3.59 d.d (2H, CH_2P), 4.07 m (4H, $2CH_2O$). Found, %: C 32.82; H 7.04; N 7.28; P 18.05. $C_5H_{12}NO_4P$. Calculated, %: C 33.15; H 6.63; N 7.73; P 17.13.

(1-Methyl-1-morpholinoethyl)phosphonic acid (IVb). Yield 65%. IR spectrum, ν, cm^{-1}: 3370 br, 2930 br, 2460, 1611, 1456, 1310, 1180, 1105. ^1H NMR spectrum, δ, ppm: 1.41 t (6H, $2CH_3$), 3.15 m (2H, CH_2N), 3.39 m (2H, CH_2N), 4.03 m (4H, $2CH_2O$). Found, %: C 40.01; H 7.20; N 6.32; P 15.99. $C_7H_{16}NO_4P$. Calculated, %: C 40.19; H 7.65; N 6.70; P 14.83.

IR spectra were recorded on a spectrophotometer Shimadzu FTIR 8400 from thin films. ^1H NMR spectra were registered on a spectrometer Varian 60A in D_2O with respect to TMS.

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