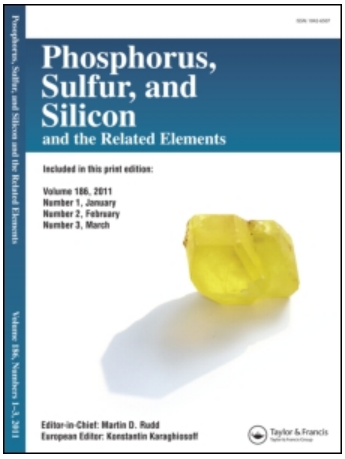

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PHENYLENE-BIS-AMINOMETHANEPHOSPHONIC AND PHOSPHONOUS ACIDS

Józef Barycki[a]; Roman Gancarz[a]; Małgorzata Milewska[a]; Roman Tyka[a]
[a] Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wroclaw, Wroclaw, Poland

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PHENYLENE-BIS-AMINOMETHANEPHOSPHONIC AND PHOSPHONOUS ACIDS

JÓZEF BARYCKI, ROMAN GANCARZ, MAŁGORZATA MILEWSKA and ROMAN TYKA

Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wrocław, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

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The studies on the synthesis of phenylene-bis-aminomethanephosphonic and phosphonous acids are reported. The title compounds were prepared in the reaction of the phenylene di-imine with dialkyl phosphite or hypophosphorous acid. Addition of the second phosphorus nucleophile to the bisimine appears to be stereospecific.

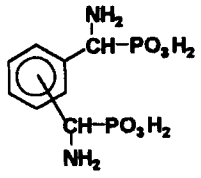
Key words: Phenylene-bis-aminomethanephosphonic and phosphonous acids, phenylene-bis-benzylaminomethanephosphonic and phosphonous acids.

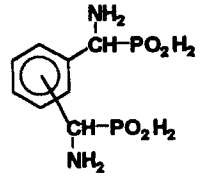
INTRODUCTION

For many years we have been engaged in the synthesis of 1-aminophosphonic acids and their derivatives, a class of compounds which has been studied intensively in both academic and industrial laboratories. This is mostly due to the fact that they display promising biological activity.[1] There are many reports on the synthesis of monoamino-monophosphonic acids[2] but almost no such reports are found for the bis-amino bis phosphonic acids.[3]

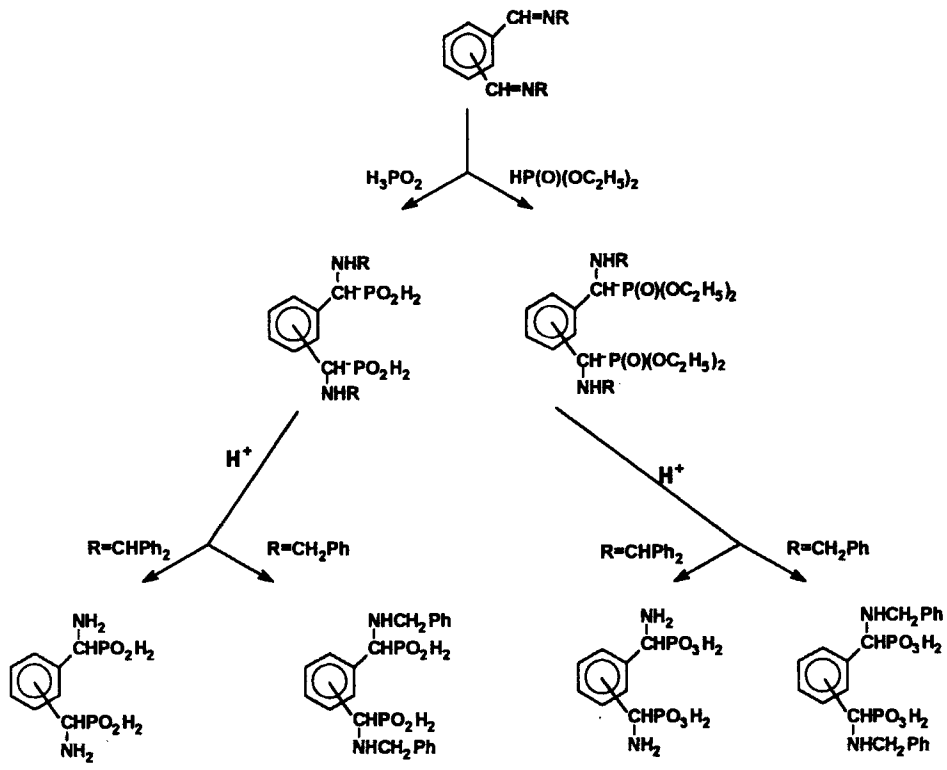
RESULTS AND DISCUSSION

In this paper we report our studies on the synthesis of phenylene-bis-aminomethanephosphonic and phosphonous acids, compounds of the general structure:





One of the general methods of the synthesis of aminophosphonates is the addition of the dialkyl phosphites to the imines.[4] Replacing the dialkyl phosphite with hypophosphorous acid one can obtain the corresponding aminophonous acids.[5] Thus, both methods for the synthesis of phenylene-bis-aminomethanephosphonic and phosphonous acids were applied. Using benzylamine, benzhydrylamine or phenylcyclopentylamine and meta or para phthalic aldehyde the bis-imines were

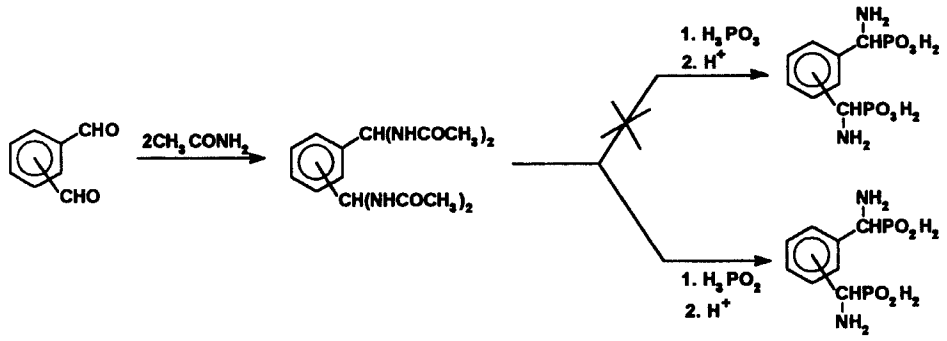


SCHEME 1

easily obtained. After addition of dialkyl phosphite or hypophosphorous acid the expected N-substituted aminophosphonic acid diethyl esters or N-substituted aminophosphonous acids are obtained. The N-substituted derivatives can be easily converted to free aminoacids by hydrogenolysis (for N-benzyl derivatives) or simple acid hydrolysis (Scheme 1).

In this manner we were able to synthesize only the N-substituted meta and para-phenylene-bis-aminophosphonates as well as N-substituted meta and para phenylene-bis-aminophosphonous acids from appropriate imines and diethyl phosphite, or hypophosphorous acid, respectively. In order to obtain the N-substituted aminophosphonic acids directly we tried to replace the diethyl phosphite with phosphorous acid. In this case, however only the imine salt formation instead of addition reaction was observed. After hydrolysis or hydrogenolysis of the N-substituted derivatives the yields of free aminoacids were in the range 25–40%. We did not succeed in the synthesis of ortho bis substituted isomers. This is due to the fact that we were not able to obtain the starting imines. When the amine was added to orthophthalic aldehyde, several coloured products were formed.[6] We have also applied the amidoalkylation reaction[7] as an alternative method as outlined in Scheme 2.

When hypophosphorous acid was caused to react with the pure bisamides the aminophosphonous acids were obtained whereas phosphorous acid did not react.



SCHEME 2

Here again we faced the problem of the synthesis of bisamides from orthophthalaldehyde since we were not able to obtain the appropriate bisamides. Similarly to the formation of bisimines only a mixture of coloured products was formed. We also tried to get the desired ortho-phenylene-bisaminomethanephosphonic and phosphonous acids by several other methods, however all of them failed. For example, the synthesis of aminophosphonates from bis ketophosphonates failed, since we were not able to obtain the last ones. The reaction of bis-acid chlorides with trialkyl phosphite gave only a mixture of different insoluble products, instead of the desired bis-ketophosphonates. Also using the acetals and benzyl carbamates, instead of aldehydes in the reaction with PCl_3, did not give the desired products.[7a]

Syntheses of bisphosphonates by the method outlined in Schemes 1 and 2 were stereocontrolled. After addition of the first molecule of hypophosphorous acid or diethyl phosphite to imines or bisamides or aldehydes, the carbon atom next to phosphorous atom becomes a stereogenic center. The addition of the second phosphorus nucleophile to the stereoisomers leads to the one enantiomeric pair (RR, SS) and one meso form (SR). In the pair RR,SS both carbon stereogenic centers are homotopic, whereas in the meso form they are enantiotopic. It means that for the protons CHP one should expect two doublets in the ^{1}H-NMR due to coupling to the phosphorus atom, (one for meso form and one for enantiomeric pair) and two singlets in the $^{31}P\{^1H\}$ NMR (one for meso form and one for enantiomeric pair) if all stereoisomers are formed. It is also possible that after addition of one molecule of dialkyl phosphite or hypophosphorous acid, the stereogenic center just formed plays an important role influencing the stereochemistry of the addition to the second imine group. If the formation of the second stereogenic center is stereocontrolled and the induction is strong then only enantiomeric pair (RR,SS) or meso form (SR) should be obtained. In this case only one doublet in the ^{1}H-NMR and one singlet in the $^{31}P\{^1H\}$ NMR should be observed.

Indeed we have observed that the obtained amino acids are pure stereoisomers. We, however, do not know whether they are a mixture of enantiomers (RR,SS) or the meso forms (RS). The studies in this direction are in progress. For now we want to stress that there is a very strong chiral discrimination in the formation of the second stereocenter. Since the yields of aminoacids were close to 50% or even less, we decided to examine the reaction mixture obtained just after addition of

dialkyl phosphites to imines, without further purification. In this case we also found that only one diastereomer is obtained in excess of 95%. When diethyl phosphite was added to phthalic aldehyde, both diastereomeric hydroxyphosphonates were formed in the ratio 1:3. In the last case, however, the chiral discrimination could be explained as thermodynamically controlled. The formation of hydroxyphosphonates under this condition is reversible[8] and several equilibria are established in the reaction mixture. The most favored diastereoisomer is the one which is the product. The reversibility of the aminophosphonate formation however is also possible but it requires a stronger base.[9] Thus we postulate that in this case the first formed stereogenic center arranges the second imine group in such a position that only one of the diastereotopic faces of the imine group is exposed to the attack of the second phosphorus nucleophile. The investigations in this area are in progress and will be a subject of a separate paper.

EXPERIMENTAL

Starting materials were obtained commercially and were used as received from the suppliers. NMR spectra were recorded on AMX 300 MHz Brucker instrument, operating at 300.13 MHz (^{1}H) and 121.499 (^{31}P). Measurements were made in D_2O/NaOD. IR spectra and elemental analysis were performed in the Institute of Organic Chemistry, Biochemistry and Biotechnology.

In all cases, products were characterized by IR, ^{1}H and ^{31}P NMR spectroscopy and microanalysis.

Bisamides

Bisamides were obtained by refluxing an appropriate aromatic aldehyde and acetamide in glacial acetic acid and acetic anhydride as described earlier.[7a]

Schiff's bases

Schiff's bases were synthesized by reaction of amine with the corresponding dicarbonyl-compounds in absolute ethanol containing a small quantity of K_2CO_3. The reaction mixture was refluxed for 1 hour then the K_2CO_3 and solvent were removed.

Phenylene-bis-aminomethane phosphonic acids and their esters

Method A

Schiff base (0.1 mole) was heated with diethyl phosphite (0.21 mole) for 1 hour at 110–130°C. After cooling the mixture was diluted with ether, washed with 3% NaOH, dried over $MgSO_4$. The solvent was evaporated and the crude ester was obtained as an oil.

The esters were refluxed with 20% HCl for 3 hours, decolourized with charcoal, filtered and evaporated on a rotatory evaporator. The residue was treated with ethanol, collected by filtration and the product was purified by dissolution in diluted NaOH followed by precipitation by acidification with HCl. Free aminoacids were obtained from N-benzhydryl esters by hydrolysis. In the case of the N-benzyl derivatives the free aminoacids were obtained after hydrogenolysis. It is worth mentioning that addition of diethyl phosphite to the imines derived from monoaromatic aldehydes gives markedly higher yields than in the case of diaromatic aldehydes.[10]

Method B

To an ethanolic solution of the Schiff base (0.1 mole) obtained from aldehyde and benzylamine 0.2 mole of anhydrous hypophosphorous acid in absolute ethanol was added. Then the mixture was refluxed for 3 hours. A crude crystalline product was obtained upon evaporation of solvent. Its recrystallization from a mixture of ethanol and water afforded a white powder.

Method C

A mixture of 0.1 mole of bisamide and 0.2 mole of anhydrous hypophosphorous acid was refluxed in 50 ml of acetic acid for 1 hour. The solvent was evaporated on a rotatory evaporator and the residue was dissolved in 50 ml of 36% HCl and refluxed for 2 hours. After evaporation of the solvent the residue was dissolved in ethanol and treated with propylene oxide. The crude acid was filtered and recrystallized from ethanol or purified on a Dowex WX-8 in H-form column.

1,3-Phenylene bis-N-benzylaminomethane phosphonic acid

This compound was obtained (method A) from 10 g Schiff's base and 8.9 g diethylphosphite. Yield 7 g (45.9%) m.p. 267–272°C, microanalysis calculated for: $C_{22}H_{26}N_2O_6P_2 \cdot HCl$, Mol. Weight 512.87, P 12.08%, N 5.46%, found: P 12.6%, N 5.38%. ^{1}H-NMR 7.27–7.03 (m, 4H, ArH); 6.83 (m, 10H, NCH_2Ar—H); 3.57 (d × d, 2H, NCHP, J_{PH} = 17.6, J_{HH} = 10.9 Hz); 3.31 (d, 2H, NCH_ACH_BAr, J_{HH} = 12.3 Hz); 3.09 (d, 2H, NCH_ACH_BAr, J_{HH} = 12.3 Hz); $^{31}P\{^1H\}$ 16.27; IR (KBr) 3000–2600 (vb), 1612, 1460, 1420, 1018, 944 cm^{-1}.

1,4-Phenylene bis-N-benzylaminomethane phosphonic acid

This compound was obtained from 3.12 g Schiff's base (method A) and 2.76 g diethylphosphite to give 1.8 g (38%) as a white powder. m.p. 258–261°C, microanalysis calculated for: $C_{22}H_{26}N_2O_6P_2 \cdot HCl$, Mol. Weight 512.87, P 12.08%, N 5.46%, found: P 12.07%, N 5.46%. ^{1}H-NMR 7.27 (s, 4H, ArH); 7.18–7.00 (m, 10H, NCH_2ArH); 3.61 (d, PCHN, J_{HP} = 16.9 Hz), 3.48 (d, 1H, NCH_ACH_BAr, J_{HH} = 13.0 Hz), 3.35 (d, 1H, NCH_ACH_BAr, J_{HH} = 13.0 Hz); $^{31}P\{^1H\}$ 19.82; IR (KBr) 3100–2800 (vb), 1620, 1460, 1168, 1084, 920 cm^{-1}.

1,3-Phenylene bis-aminomethanephosphonic acid

This compound was obtained from 2.3 g Schiff's base and 1.5 g diethylphosphite (method A), yield 0.6 g (37.03%) as a white powder. m.p. 312–316°C, microanalysis calculated for: $C_8H_{14}N_2O_6P_2 \cdot HCl$, Mol. Weight 332.64, P 18.62%, N 8.42%, found: P 18.4%, N 8.32%. ^{1}H-NMR 7.20–7.15 (m, 4H, ArH); 3.68 (d, 2H, NCHP, J = 15.5 Hz); $^{31}P\{^1H\}$ 18.38; IR (KBr) 2950, 1624, 1554, 1164, 1082, 1032, 938 cm^{-1}.

1,4-Phenylene bis-aminomethanephosphonic acid

This compound was obtained from 4.6 g Schiff's base and 4.2 g diethylphosphite (method A), yield 0.8 g (25%) of a white powder. m.p. 309–312°C, (lit[3a] 262–265°C), microanalysis calculated for: $C_8H_{14}N_2O_6P_2 \cdot HCl$, Mol. Weight 332.64, P 18.62%, N 8.42%, found: P 18.65%, N 8.27%. ^{1}H-NMR 7.04–7.00 (s, 4H, ArH); 3.50 (d, 2H, NCHP, J = 14.7 Hz); $^{31}P\{^1H\}$ 18.30; IR (KBr) (3200), 1640, 1548, 1156, 1082, 936 cm^{-1}.

1,3-Phenylene bis-N-benzylaminomethanephosphonous acid

This compound was obtained from 9 g Schiff's base and 3.98 g anhydrous H_3PO_2 (method B), yield 4 g (31%) of a white powder. m.p. 237–240°C, microanalysis calculated for: $C_{22}H_{26}N_2O_4P_2$, Mol. Weight 444.41, P 13.93%, N 6.30%, found: P 14.05%, N 6.33%. ^{1}H-NMR 6.69 (d, 2H, PH, J_{PH} = 522.5 Hz); 7.40–6.20 (m, 14H, ArH), 3.46 (d, 2H, PCHN, J = 14.6 Hz), 3.26 (d, 2H, NCH_ACH_BAr, J = 10.8 Hz), 3.01 (d, 2H, NCH_ACH_BAr, J = 10.8 Hz); $^{31}P\{^1H\}$ 27.07; IR (KBr) 3460 (broad), 2324, 1608, 1458, 1204, 1054 cm^{-1}.

1,4-Phenylene bis-N-benzylaminomethanephosphonous acid

This compound was obtained from 3.12 g Schiff's base and 1.32 g of anhydrous H_3PO_2 (method B), yield 1.49 g (31.53%) of a white powder. m.p. 243–246°C, microanalysis calculated for: $C_{22}H_{26}N_2O_4P_2 \cdot HCl$, Mol. Weight 480.87, P 12.89%, N 5.83%, found: P 12.30%, N 6.04%. ^{1}H-NMR 6.69 (d, 2H, PH, J_{PH} = 521.6 Hz); 7.20–6.60 (m, 14H, ArH), 3.57 (d,d 2H, PCH, J_{PH} = 15.6 Hz, J_{HH} = 4.5 Hz), 3.48 (d, 2H, NCH_ACH_BAr, J = 12.9 Hz), 3.29 (d, 2H, NCH_ACH_BAr, J = 12.8 Hz); $^{31}P\{^1H\}$ NMR 27.29; IR (KBr) 3450 (broad), 2308, 1606, 1460, 1198, 1052, 776 cm^{-1}.

1,3-Phenylene-bis-aminomethanephosphonous acid

This compound was obtained from 4.6 g bisamide (method C) and 2 g anhydrous H_3PO_2, yield 1.05 g (28.5%) as white powder. m.p. 265–267°C, microanalysis calculated for: $C_8H_{14}N_2O_4P_2 \cdot 2HCl$, Mol. Weight 337.08, P 18.38%, N 8.31%, found: P 18.63%, N 8.15%. ^{1}H-NMR 6.70 (d, 2H, PH, J_{PH} = 515.7 Hz), 7.31–7.29 (m, 4H, ArH), 3.79 (d, PCH, J_{HP} = 13.2 Hz); $^{31}P\{^1H\}$ NMR 29.80; IR (KBr) 2340, 2136, 1550, 1536, 1184, 1052, 898 cm^{-1}.

1,4-Phenylene-bis-aminomethanephosphonous acid

This compound was obtained from 6.12 g bisamide (method C) and 2.64 g anhydrous H_3PO_2, yield 2.1 g (43.48%) of white powder. m.p. 280–283°C, microanalysis calculated for: $C_8H_{14}N_2O_4P_2 \cdot 2HCl$, Mol. Weight 337.08, P 18.38%, N 8.31%, found: P 18.71%, N 8.60%. ^{1}H-NMR 6.78 (d, 2H, PH, J_{PH} = 515.3 Hz), 7.33 (s, 4H, ArH), 3.88 (d, 2H, PCH, J = 12.7 Hz); ^{31}P{^{1}H} NMR 29.25; IR (KBr) 2900 (broad), 2320, 1612, 1534, 1174, 1050, 848 cm^{-1}.

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