SYNTHESIS AND EXAMINATION OF THE COMPLEX-FORMING PROPERTIES OF SOME ORGANOPHOSPHORUS COMPOUNDS*

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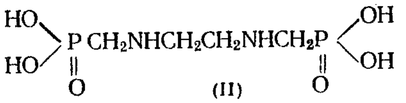
In a previous communication [1] we gave some data obtained in the examination of the complex-forming properties of (ethylenebisiminoalkylene) diphosphonic and some other aminoalkylphosphonic acids. The results showed that (ethylenebisiminoalkylene) diphosphonic acids form stable complex compounds with ytterbium and yttrium. It was of interest to continue work on the synthesis of aminoalkylphosphonic acids with the object of preparing new complex-formers, and also to compare the properties of these organophosphorus acids with the analogous amino carboxylic acids.

(Ethylenebisiminoalkylene) diphosphonic acids were synthesized by us earlier by the reaction of aldehydes or ketones with dialkyl phosphites and ethylenediamine. However, we did not then obtain the first member of this series: (ethylenebisiminomethylene) diphosphonic acid. We have now found that paraformaldehyde, like the aldehydes and ketones tried earlier, will react with ethylenediamine and diethyl phosphite, but the reaction proceeds much less readily:

$$NH_2CH_2CH_2NH_2 + 2CH_2O + 2HPO(OC_2H_5)_2 \rightarrow \underset{(I)}{[(C_2H_5O)_2OPCH_2NHCH_2]_2} + 2H_2O\,.$$

The resulting tetraethyl (ethylenebisiminomethylene) diphosphonate (I) was characterized as its picrate; the yield of the ester was about 10%. Hydrolysis of the ester with hydrochloric acid gave free (ethylenebisiminomethylene) diphosphonic acid (II):

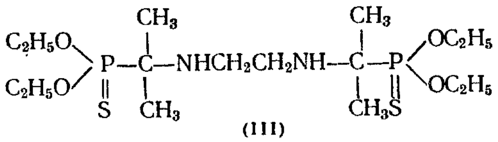


$$\begin{matrix}HO\\HO\end{matrix}\!\!>\underset{\underset{O}{\|}}{P}CH_2NHCH_2CH_2NHCH_2\underset{\underset{O}{\|}}{P}<\!\!\begin{matrix}OH\\OH\end{matrix}\,.$$

(II)

This reaction can be carried out not only with dialkyl phosphites, but also with O-diethyl phosphorothioite or diethyl phenylphosphonite.

O-Tetraethyl (ethylenebisiminoisopropylidene) diphosphonothioate (III)



$$\begin{matrix}C_2H_5O\\C_2H_5O\end{matrix}\!\!>\underset{\underset{S}{\|}}{P}-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-NHCH_2CH_2NH-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\underset{\underset{S}{\|}}{P}<\!\!\begin{matrix}OC_2H_5\\OC_2H_5\end{matrix}$$

(III)

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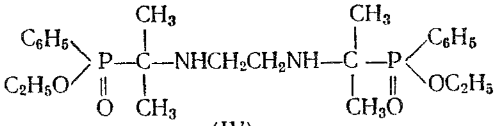
* Communication 2.

was obtained as the picrate in 26% yield. Attempts to obtain the corresponding acid were unsuccessful: on hydrolysis of the ester, sulfur was liberated.

In the reaction of ethylenediamine and acetone with diethyl phenylphosphonite we obtained diethyl(ethylenebisiminoisopropylidene)-bisphenylphosphinate (IV)



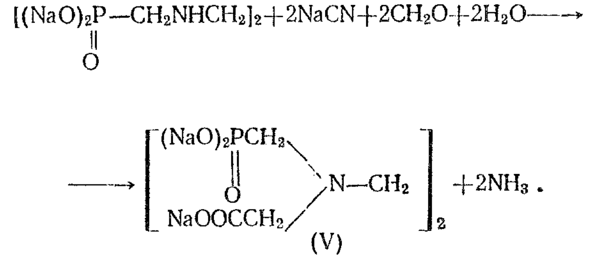
$$\begin{matrix}C_6H_5 \\ C_2H_5O\end{matrix}\!>\!\underset{\underset{O}{\parallel}}{P}-C(CH_3)_2-NHCH_2CH_2NH-C(CH_3)_2-\underset{\underset{O}{\parallel}}{P}\!<\!\begin{matrix}C_6H_5 \\ OC_2H_5\end{matrix}$$

(IV)

which was also isolated as the picrate; here also decomposition of the acid occurred when the ester was hydrolyzed.

It was of interest to determine the effect of the introduction of carboxylgroups into the molecule of an (ethylenebisiminoalkylene) diphosphonic acid on its complex-forming properties. Starting with aminoalkylphosphonic and (ethylenebisiminoalkylene) diphosphonic acids, we tried to synthesize the corresponding [(carboxymethyl)amino]alkylphosphonic and { ethylenebis [carboxymethylimino) methylene] } diphosphonic acids. Comparison of different methods of preparing these substances showed that the most convenient was carboxymethylation with formaldehyde and sodium cyanide in an alkaline medium. This variant of the long-known Strecker's reaction [2] was studied in detail comparatively recently by Bersworth [3], and it was found to be suitable in our case.

In the carboxymethylation of (ethylenebisiminomethylene) diphosphonic acid, the best results were obtained at 20-32° for a reaction time of 35-40 hours.



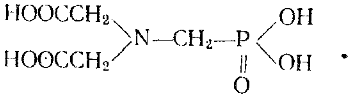
$$[(NaO)_2\underset{\underset{O}{\parallel}}{P}-CH_2NHCH_2]_2+2NaCN+2CH_2O+2H_2O\longrightarrow$$

$$\longrightarrow\left[\begin{matrix}(NaO)_2\underset{\underset{O}{\parallel}}{P}CH_2 \\ NaOOCCH_2\end{matrix}\!>\!N-CH_2\right]_2+2NH_3.$$

(V)

The acid (V) was isolated via the lead salt, which was then decomposed with hydrogen sulfide. An attempt to carboxymethylate (ethylenebisiminoisopropylidene) diphosphonic acid by this method was unsuccessful. It is probable that some steric hindrance was operative in this case.

As well as { ethylenebis [(carboxymethylimino) methylene] } diphosphonic acid (V), we synthesized some (biscarboxymethylamino) alkylphosphonic acids. Although the first three members of this group were described by Swarzenbach [4], it was interesting to compare their complex-forming properties with those of other aminoalkylphosphonic acids. In the synthesis of (biscarboxymethylamino) methylphosphonic acid (VI) we applied the above-mentioned carboxymethylation reaction to aminomethylphosphonic acid

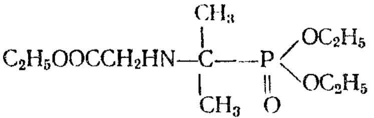


$$\begin{matrix}HOOCCH_2 \\ HOOCCH_2\end{matrix}\!>\!N-CH_2-\underset{\underset{O}{\parallel}}{P}\!<\!\begin{matrix}OH \\ OH\end{matrix}\ .$$

(VI)

The yield of acid was about 60%.

By the reaction of diethyl 1-amino-1-methylethylphosphonate with ethyl chloroacetate we obtained triethyl 1-(carboxymethylamino)-1-methylethylphosphonate (VII).



$$C_2H_5OOCCH_2HN-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\underset{\underset{O}{\parallel}}{P}\!<\!\begin{matrix}OC_2H_5 \\ OC_2H_5\end{matrix}$$

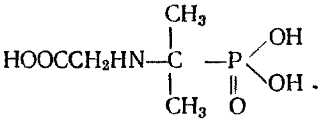
(VII)

in about 60% yield. The reaction was carried out by leaving the mixture of reactants at room temperature for many days. Rise in temperature led to a sharp reduction in yield. The same ester was prepared also by the general method for the synthesis of aminoalkylphosphonic esters [5] with glycine ethyl ester as the amine component:

$$HPO(OC_2H_5)_2 + NH_2CH_2COOC_2H_5 + CH_3COCH_3 \longrightarrow$$

$$\longrightarrow H_5C_2OOCCH_2NHC(CH_3)_2PO(OC_2H_5)_2 + H_2O .$$

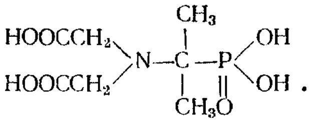
In this case the yield of ester was 25%. Under the action of hydrochloric acid the ester (VII) was hydrolyzed with formation of 1-(carboxymethylamino)-1-methylethylphosphonic acid (VIII):



$$HOOCCH_2HN{-}C(CH_3)_2{-}P(=O)(OH)_2 .$$

(VIII)

1-Biscarboxymethylamino-1-methylethylphosphonic acid (IX) was prepared by the method used by Swarzenbach in the synthesis of 2-biscarboxymethylaminoethylphosphonic acid.



$$(HOOCCH_2)_2N{-}C(CH_3)_2{-}P(=O)(OH)_2 .$$

(IX)

The complex-forming powers of the compounds synthesized were tested by the previously described chromatographic method [6]. Both the amino phosphonic and also the corresponding amino polycarboxylic acids were tested chromatographically in order to obtain a comparative characterization of their complex-forming powers. The yttrium isotope Y^{91} was used in experiments with a column of KU-2 cationite. In the testing of amino phosphonic acids and the corresponding amino carboxylic acids, solutions of identical concentration, pH (6.7), and ionic strength were used. The results are presented in the table.

The activity of a complex-former was characterized by the value of V_{max}, the total volume of filtrate leaving the cationite column containing the sorbed ions of the element from the start of the washing to the attainment of a maximum concentration of the element in the eluate. Other things being equal, the value of V_{max} depends on the stability of the complex compound; and the lower it is, the higher the stability.

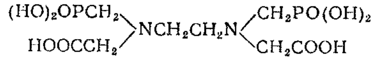
From a comparison of values of concentration and of V_{max} (see Table) it follows that the complex-forming powers of the compounds tested increase from the first to the third compound and from the fourth to the fifth.

Comparison of values of V_{max} for members of horizontal lines shows that, as complex-formers, all the amino phosphonic acids are stronger than the corresponding amino carboxylic acids. The difference in values of V_{max} is least for the last compound.

EXPERIMENTAL

Picrate of Tetraethyl (Ethylenebisiminomethylene) diphosphonate (I). Gradual addition was made of 1.5 g (0.05 mole) of paraformaldehyde to a stirred mixture of 6.9 g (0.05 mole) of diethyl phosphite and 1.5 g (0.025 mole) of ethylenediamine. Reaction occurred with dissolution of the paraform and rise of temperature to 70°. The reaction mixture was then heated for one hour at 85°. The resulting sirup was extracted with ten times its volume of dry ether. The ether extract was dried with sodium sulfate, and an ether solution of picric acid was then added. We obtained 1.9 g (10%) of (I); decomp. temp. 191-192° (from ethanol). Found: C 34.6; 34.5; H 4.4; 4.3; P 7.4; 7.6; N 13.6; 13.6%. $C_{24}H_{36}P_2N_8O_{20}$. Calculated: C 35.2; H 4.4; P 7.6; N 13.7%.

V_{max} (ml) on the Curve for the Elution of Y^{3+} from a Column of KU-2 Cationite

Aminoalkylphosphonic acids				Amino carboxylic acids			
formula	ionic strength	concentration (moles/liter)	V^*_{max}	formula	ionic strength	concentration (moles/liter)	V^*_{max}
$NH_2CH_2PO(OH)_2$	1,2	0,53	0,25	NH_2CH_2COOH	1,2	0,53	2,7
$HOOCCH_2NHC(CH_3)_2PO(OH)_2$	0,16	0,0387	3,1	$HOOCH_2CNHCH_2COOH$	0,16	0,0387	9,0
$(HOOCCH_2)_2NCH_2PO(OH)_2$	0,03	0,01	2,1	$(HOOCCH_2)_2NCH_2COOH$	0,03	0,01	4,8
$(HOOCCH_2)_2NC(CH_3)_2PO(OH)_2$	0,03	0,01	2,2				
$(HO)_2OPCH_2NHCH_2CH_2NHCH_2PO(OH)_2$	0,31	0,014	2,1	$HOOCCH_2NHCH_2CH_2NHCH_2COOH$	0,31	0,014	9,0
 $\frac{(HO)_2OPCH_2}{HOOCCH_2}>NCH_2CH_2N<\frac{CH_2PO(OH)_2}{CH_2COOH}$	0,024	0,003	3,7	$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$	0,024	0,003	4,2

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*The value of V_{max} is the mean of the values from several parallel experiments; departures from this value amount to ± 0.1 ml.

<u>(Ethylenebisiminomethylene) diphosphonic Acid (II).</u> The first part of the experiment was as before. Ether was removed from the ether extract, and to the residue (1.95 g of a sirup) we added 10 ml of concentrated hydrochloric acid. The solution was refluxed for seven hours. Hydrochloric acid was vacuum-distilled off until the residue was of constant weight. Water was added to the residue, when a precipitate formed, which was filtered off and crystallized from dilute hydrochloric acid. We obtained 0.7 g (10%); decomp. temp. 276-277°. Found: C 17.0; 16.8; H 6.3; 6.1; P 21.8; 21.7; N 9.5; 9.6; H_2O 12.6%. $C_4H_{18}P_2N_2O_8$. Calculated: C 16.9; H 6.4; P 21.8; N 9.9; H_2O 12.7%. The substance (II) is sparingly soluble in water, but readily soluble in acids and alkalis; it is insoluble in organic solvents; it crystallizes with two molecules of water.

<u>Picrate of O-Tetraethyl (Ethylenebisiminoisopropylidene) diphosphonothioate (III).</u> Acetone (5.8 g, 0.1 mole) was added dropwise to a mixture of 15.4 g (0.1 mole) of diethyl phosphorothioite and 3 g (0.05 mole) of ethylenediamine. The temperature rose to 80°. The reaction mixture was then heated at 85° for 15 minutes, after which it was extracted with ether. The ether extract was dried with sodium sulfate. From the ether solution we prepared the picrate (12 g, yield 26°), decomp. temp. 130°. Found: C 37.4; 37.4; H 5.0; 5.0; P 6.7; 6.7; N 12.7; 12.8; S 6.6; 6.7%. $C_{22}H_{44}P_2N_8S_2O_{18}$. Calculated: C 37.1; H 5.0; P 6.8; N 12.3; S 7.1%.

<u>Picrate of Diethyl (Ethylenebisiminoisopropylidene) bisphenylphosphinate (IV).</u> This was prepared similarly to (III) from 8.75 g (0.05 mole) of diethyl phenylphosphinite, 1.5 g (0.025 mole) of ethylenediamine, and 2.9 g (0.05 mole) of acetone. We obtained 7.5 g (32%) of the picrate, decomp. temp. 152°. Found: C 45.9; 46.0; H 4.6; 4.8; P 6.4; 6.4; N 11.6; 11.7. $C_{36}H_{44}P_2N_8O_{18}$. Calculated: C 46.0; H 4.7; P 6.6; N 11.9%.

When an attempt was made to obtain (ethylenebisiminoisopropylidene)-bisphenylphosphinic acid by hydrolysis of the ester with hydrochloric acid, we isolated a substance of m.p. 80° (from dioxane). Analysis indicated that the substance was phenylphosphonous acid. Found: C 50.6; 50.8; H 4.8; 4.9; P 21.5; 21.6%. $C_6H_7PO_2$. Calculated: C 50.7; H 5.0; P 21.8%.

<u>{Ethylenebis [(carboxymethylimino) methylene]} diphosphonic Acid (V).</u> A mixture of 7.1 g (0.016 mole) of tetrasodium (ethylenebisiminomethylene) diphosphonate and a solution of 2.3 g (0.048 mole) of sodium cyanide in 20 ml of water was prepared in a four-necked flask. With stirring we added 4.3 g (0.048 mole) of a 36% solution of formaldehyde diluted with water to 25 ml; the formaldehyde was added dropwise over 40 hours with gradual raising of the reaction temperature from 20° to

32°. After the addition of each 5 ml of formaldehyde, 5 ml of liquid was vacuum-distilled from the reaction mixture. After the addition of all the formaldehyde the reaction mixture was neutralized with hydrochloric acid, and was then treated with basic lead acetate until completely precipitated. The precipitate of the lead salt was washed with hot water until chloride ions had been removed, and it was then treated with hydrogen sulfide. Lead sulfide was filtered off, and the filtrate was evaporated to dryness on a water bath. Crystallization from water gave 3.6 g (62%) of substance, decomp. temp. 215°. Found: C 26.3; 26.4; H 5.1; 5.2; P 17.4; 16.8; N 7.8; 7.7%. $C_8H_{16}P_2N_2O_{18}$. Calculated: C 26.4 H 5.0; P 17.0; N 7.7%. The substance (V) is readily soluble in water.

(Biscarboxymethylamino) methylphosphonic Acid (VI). This was prepared from 3.2 g (0.02 mole) of disodium aminomethylphosphonate, 3.2 g (0.06 mole) of sodium cyanide, 0.5 g of sodium hydroxide in 15 ml of water, and 6 g (0.06 mole) of 36% formaldehyde solution, as in the synthesis of the substance (V). After neutralization of the reaction mixture and addition of alcohol there was a precipitate. Crystallization from aqueous alcohol gave (VI) (3.2 g, yield 61%), decomp. temp. 208°. Found: C 26.3; 26.0; H 4.5; 4.5; P 13.5; 13.5; N 6.4; 6.4%. $C_5H_{10}PNO_7$. Calculated: C 26.4; H 4.4; P 13.6; N 6.2%. The substance is readily soluble in hot water.

Triethyl 1- (Carboxymethylamino)-1-methylethylphosphonate (VII). 1) By reaction of diethyl 1-amino-1-methylethylphosphonate with ethyl chloroacetate: A mixture of 39 g (0.2 mole) of diethyl 1-amino-1-methylethylphosphonate and 12.2 g (0.1 mole) of ethyl chloroacetate was allowed to stand at room temperature. After several days crystals (diethyl 1-amino-1-methylethylphosphonate hydrochloride) began to separate from the solution. After 40-45 days an excess of ether was added to the mixture, the crystals were separated, and the filtrate was washed with a little water and dried with sodium sulfate. Ether was removed, and vacuum distillation of the residue gave 16.8 g (60%) of (VII); b.p. 77-81° ($3 \cdot 10^{-4}$ mm); n^{20}_D 1.4444; d_4^{20} 1.0810, found MR 69.05; calculated MR 69.10. Found: H 8.7; 8.8; C 47.0; 46.4; P 11.0; 11.2; N 4.9; 5.2%. $C_{11}H_{24}PNO_5$. Calculated: H 8.6; C 46.9; P 11.0; N 5.0%.

2) By reaction of glycine ethyl ester with diethyl phosphite and acetone: Anhydrous glycine ethyl ester prepared by Gavrilov and Akimova's method [8] polymerizes after 2-3 hours. We found that, after three distillations in a stream of nitrogen, glycine ethyl ester [b.p. 42° (6 mm); 52° (10 mm); n^{20}_D 1.4241; d_4^{20} 1.002; found MR 25.74; calculated MR 25.75] does not change in the course of 2-3 days at 0-4° and may be used in the reaction described below.

A mixture of 13.8 g (0.1 mole) of diethyl phosphite, 10.3 g (0.1 mole) of glycine ethyl ester, and 8.7 g (0.15 mole) of acetone was stirred in an atmosphere of nitrogen and gradually heated to 90°. This temperature was maintained for three hours. The reaction mixture was extracted with ten times its volume of ether. The ether solution was added to the sirupy residue and dried with sodium sulfate. Ether was removed, and vacuum distillation of the residue gave 7 g (25%) of substance; b.p. 79-83° ($2 \cdot 10^{-4}$ mm); n^{20}_D 1.4440; d_4^{20} 1.0810; found MR 69.05; calculated MR 69.10.

1-(Carboxymethylamino)-1-methylethylphosphonic Acid (VIII). A mixture of 7 g of triethyl 1-(carboxymethylamino)-1-methylethylphosphonate (VII) and 40 ml of concentrated hydrochloric acid was refluxed for seven hours. The hydrochloric acid was removed, and the residual sirup was decolorized with charcoal and treated with absolute ethanol. The precipitate was recrystallized from water. We obtained 0.8 g (15%) of acid, decomp. temp. 197-198°. Found: C 30.4; 30.3; H 6.1; 6.1; P 15.4; 15.6; N 7.1; 7.3%. $C_5H_{12}NPO_5$. Calculated: C 30.5; H 6.1; P 15.7; N 7.1%.

1-Biscarboxymethylamino-1-methylethylphosphonic Acid (IX). Sodium chloroacetate (23.5 g, 0.2 mole) was added to a solution of 15.7 g (0.1 mole) of 1-amino-1-methylethylphosphonic acid in 25 ml of 8 N NaOH (0.2 mole). The mixture was heated in a boiling water bath, and addition was made of 25 ml of 8 N NaOH (0.2 mole) at such a rate that the pH of the medium was kept at 10-11. The amount of chloride ion was determined on separate test samples. Reaction was complete when the amount of chloride ion reached the calculated value. The reaction mixture was then neutralized, and the acid was isolated as the lead salt, as in the synthesis of (V). After the removal of lead sulfide, the filtrate was concentrated until the residue attained constant weight. The resulting sirup was mixed with absolute alcohol, and gradually a precipitate (5.4 g, yield 20%) separated from the solution. After two recrystallizations from water it had decomp. temp. 150-151°. Found: C 32.7; 32.7; H 5.9; 5.9; P 11.6; 11.7; N 5.4; 5.4%. $C_7H_{14}NPO_7$. Calculated: C 32.9; H 5.5; P 12.1; N 5.5%.

Iminodiacetic acid was synthesized by Chase and Downes's method [7]; decomp. temp. 235°. (Ethylenediimino) diacetic acid was kindly presented by V.G. Yashunskii, to whom the authors express their thanks.

SUMMARY

1. Some (carboxymethylamino) alkylphosphonic acids were synthesized, and it was shown by the chromatographic method that they have complex-forming properties.

2. The complex-forming power of amino phosphonic acids is greater than that of the corresponding amino carboxylic acids.

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