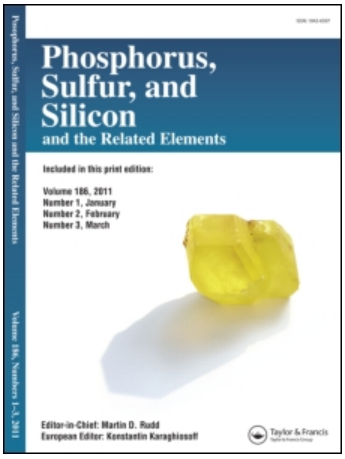

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PYROCATECHIN CYCLOPHOSPHONATES AS PHOSPHORYLATING AGENTS

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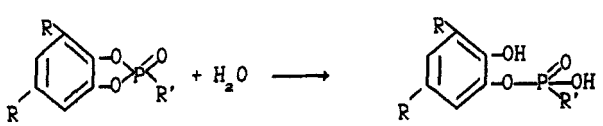
Cyclic ethers of pentavalent phosphorus acids are known to have a high electrophility. However, the process of the opening of cyclophosphorylated pyrocatechins has been studied only slightly. In the present work a detailed study has been carried out on the reactions of pyrocatechincyclophosphonates and the corresponding thiophosphonates with proton-containing nucleophiles: water, alcohols, glycols, amines. The results of these reactions are discussed here. A characteristic feature of the opening of medium catechin phosphonates is their easy cyclization caused by the location of the phenol hydroxyl and the phosphorus-containing function in the benzene ring plane. In the case of pyrocatechinphosphonates the opening of the ring is accompanied by desulphurization.

Key words: Pyrocatechine; cyclophosphonates; cyclization; hydrolisis; alcoholisis; ortho-oxyphenylmethylphosphonate.

DISCUSSION

One can find,[1] that cyclic ethers of pentavalent phosphorus acids vigorously interact with water and alcohol to produce the corresponding open derivatives which have synthetic importance. Thus, it has been proposed to obtain natural primary phosphates[2] and phosphorus podants[3] based on the above open ethers. The influence of acids and bases on the course of the reactions was not investigated. Secondary processes were not analized due to destruction of the side functions and desulphurization for thionic systems.[4] Taking into account the aforesaid we have carried out a study of the reactions between cyclic pyrocatechin ethers of phosphonic acids and proton-containing nucleophiles. The phosphonates were chosen so the side reactions masking the opening of the cycle were reduced to the minimum.

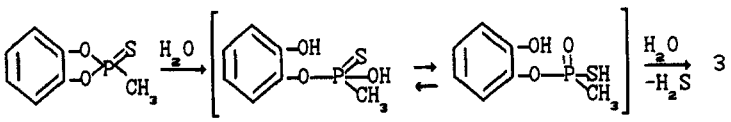
It was reported earlier that the simplest pyrocatechin-cyclophosphonates vigorously interact with water; the structure of the products, however, was not declared.[1] We have shown that the pyrocatechin ether of methilphosphonic acid **1**, its 3,5-ditertbutylated analogue **1-a**, and the pyrocatechin ether of triethylphosphonic acid **2**, when treated with an equimolar and excessive quantity of water are transformed in a good yield into acid phosphonates:



1. R = H, R' = CH_3
1-a. R = $C(CH_3)_3$, R' = CH_3
2. R = H, R' = CPh_3

3. R = H, R' = CH_3
3-a. R = $C(CH_3)_3$, R' = CH_3
4. R = H, R' = CPh_3

Acids and bases speed up the first stage of hydrolysis, but do not influence the breakage of the second ether bond at room temperature. Thus, the interaction of pyrocatechin cyclophosphonates with water can be regarded as an effective method of synthesizing acid pyrocatechinphosphonates. We have also investigated the hydrolysis of pyrocatechinthionmethylphosphonate **5**. This reaction goes much slower than the hydrolysis of phosphonate **1** and is speed up by acids and bases. In this case desulphurization is taken place together with the opening of the cycle and the acid methylphosphonate **3** is formed:

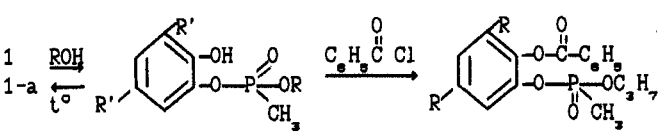


5 6

Desulphurization seems to be associated with fast isomerization of acid thionphosphonate into the thiol form, followed by the hydrolytic splitting of P—S bond with hydrogen sulphide release. To perform the reaction successfully it was best to use a small excess of water at room temperature. This method allowed to obtain a solution of acid thionphosphonate **6** itself. The ^{31}P NMR spectrum of the reaction showed a singlet in the region of 89.7 ppm. A partial desulphurization occurred with solvent removal in vacuo, and two signals in the ^{31}P NMR spectrum one now observes:

89.7 – 6 and 31.2 ppm – 3.

We then investigated the interaction of cyclophosphonates with alcohol and phenol. Phosphonates **1** and **1-a** were treated with propyl alcohol at room temperature. In several minutes quantitative formation of O-oxyphenyl-propyl-methylphosphonates **7** and **7-a** took place:



7. R' = H, R = C_3H_7

7-a. R' = $C(CH_3)_3$, R = C_3H_7

9. R' = H, R = Ph

10. R' = R = $C(CH_3)_3$

8. R' = H, R = C_3H_7

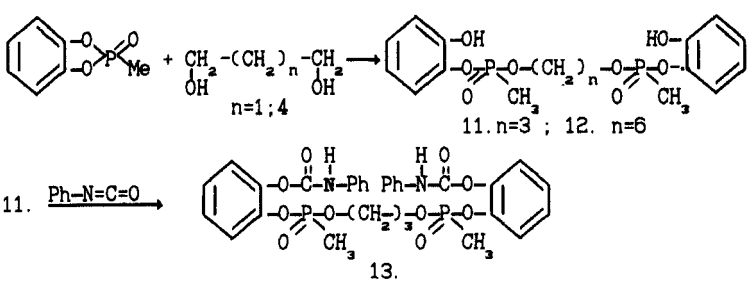
8-a. R' = $C(CH_3)_3$, R = C_3H_7

After distilling off the solvent in vacuo, from cyclophosphonate **1**, we obtained an individual product **7** which structure was proved by the ^{31}P and ^1H NMR data. When attempting to vacuum distill product **7**, we observed its partial recyclization to compound **1**, the data of the distilled liquid ^{31}P NMR indicating that. Taken into account with the aforesaid, we characterized the alcoholyis product as benzoyl derivative **8** which is to be a quite stable compound.

Phenolysis of cyclophosphonates **1** and **1-a** proceeds under more rigorous condition (80°C, 10 hours), with phenolysis of the substance **1-a** even under these conditions not resulting completion. The formed phenyl-*o*-oxyphenoxymethyl-

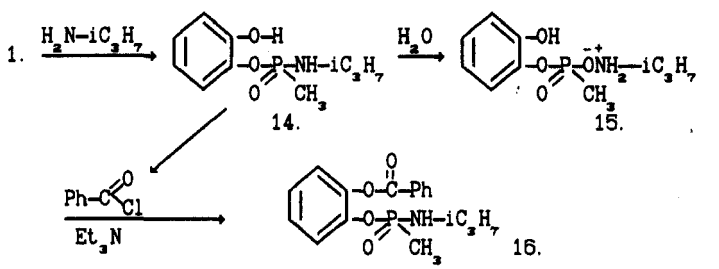
phosphonate **9** was isolated by crystallization from the reaction mixture with cooling. The open phenoxyphosphonate **9**, as its propyl analogue, has a tendency to cyclization. The process is already observed when the chloroform solution of the substance is stored at room temperature, confirmed by the NMR data. It can thus be concluded that the closeness of the vicinal hydroxyl and phosphoryloxyl groups of phosphonates **7** and **9** leads to their intramolecular interaction, ending under certain cyclization conditions. In the light of this conclusion we compared the alcoholysis rates of phosphonates **1** and **1-a**. Trimethylcarbinol reagent having the highest differentiating ability was chosen as the nucleophile. It was shown that phosphonate **1-a** having areal difficulties in its structure, does have a weak reactivity. Easy cyclization of monophosphorylated pyrocatechins is like a similar process with monophosphorylated pinacones.[5] However, in the given case the reason for cyclization is the interaction of four methyl groups in the molecule skeleton (Ingold-Thorpe effect), whereas in the presented case the location of phenol hydroxyl and phosphorus-containing function in the benzene ring plane seems to be the determining factor.

The interaction of cyclophosphonates with glycols: 1,3-propanediol and 1,6-hexane diol was investigated in the present work too. The reaction is fast and resultative at the 2:1 ratio of reagents:



Bis-phosphonate **11** could not be isolated by distillation and chromatographically because of cyclization. We therefore identified it as the phenylcarbamate. Bis-phosphonate **12** was a crystalline substance. Two products are simultaneously formed: mono- and bis-phosphonates when the reaction with glycols is conducted at the ratio of reagents 1:1, as indicated by studying the reaction mass ^{31}P NMR spectra.

The next objective of the work was to investigate the aminolysis of pyrocatechin cyclophosphonates. Compound **1** is shown to react poorly with organic amines although isopropylamine and piperidine are phosphorylated at 20°C with the formation of the corresponding amides, observed in solution by means of the ^{31}P NMR method.



Attempts at isolating the obtained amidophosphonates were unsuccessful because cyclization to primary compounds takes place even at slight heating. So, we characterized the reaction products as benzoyl derivatives **16** and **17**, which are stable substances. We isolated salt **15** in quantitative yield when water added to the phosphonate **1** and amine mixture. It is very interesting that amidophosphonate **14** has an exceptionally labile P—N bond hydrolized after a short-duration contact with water. This property is probably due to activation of the phosphamide group by the ortho-positioned phenol hydroxyl. This assumption is confirmed by the fact that benzoylated derivative **16** has a considerably higher hydrolytic stability.

EXPERIMENTAL

^{31}P NMR spectra were obtained at a frequency of 32.2 Hz on WP-80 Sy Bruker instrument, chemical shifts were measured relative to 85% phosphoric acid (external standard) at 30°C. NMR spectra were taken on H-360 Bruker instrument with a working frequency of protons 360 MHz. Proton chemical shifts were measured relative to HMDS as the internal standard.

Thin layer chromatography was performed on Silufol UV-254 plates with the use of the benzene/dioxane system, 3:1.

Chromatograms were developed with iodine vapour. All the syntheses were performed with carefully purified and dried reagents in an atmosphere of dry inert gas.

Pyrocatechintritylphosphonate **2**. Acetic acid (0.6 g, 0.01 mmol) was added to pyrocatechintritylphosphite (4 g, 0.01 mmol in 30 cm^3 of ether). The reaction mass was stirred for 10 h at 20°. The precipitated product was filtered off, crystallized from ether and dried. Yield 3.1 g (79%), m.p. 129–130°C, Rf 0.9. ^{31}P NMR spectrum: δ 45 ppm (1,4-dioxane). Found %: C 75.6; H 5.0; P 12.0 $C_{25}H_{19}O_3P$. Calculated %: C 75.4; H 4.8; P 12.1.

O-Oxyphenylmethylphosphonate **3**. Water (0.15 ml, 0.008 mmol in 1 cm^3 1,4-dioxane) was added to phosphonate **1** (1.3 g, 0.008 mmol in 10 cm^3 1,4-dioxane). The reaction mass was kept intact for 15 min at 20°C, the solvent was distilled off in vacuo. Yield 1.3 g (93%, oil), Rf 0.1. ^{31}P NMR spectrum: δ 30 ppm (benzene). Found %: C 45.0; H 4.5; P 16.6 $C_7H_9O_4P$. Calculated %: C 44.7; H 4.8; P 16.5.

2-Oxy-3,5-ditertbutyl-phenylmethylphosphonate **3-a**. Water (0.064 ml, 0.004 mmol in 1 cm^3 1,4-dioxane) was added to 3,5-ditertbutylpyrocatechinmethylphosphonate **1-a** (1.0 g, 0.004 mmol in 10 cm^3 1,4-dioxane). The reaction mass was stirred for 30 min at 20°C, the solvent was distilled off in vacuo, the substance was crystallized from benzene. Yield 0.9 g (90%), m.p. 119–120°C, Rf 0.5. ^{31}P NMR spectrum: δ 31.4 ppm. Found %: C 60.03; H 8.50; P 10.12 $C_{15}H_{25}O_4P$. Calculated %: C 60.00; H 8.33; P 10.33.

O-Oxyphenylpropylmethylphosphonate **7**. Propanol (0.5 g, 0.008 mmol in 1 cm^3 benzene) was added to phosphonate **1** (1.5 g, 0.008 mmol in 15 cm^3 benzene). The reaction mass was stirred for 20 min at 20°C, the solvent was distilled off in vacuo. Yield 1.9 g (98%). ^1H NMR spectrum ($CDCl_3$, δ ppm) 0.9 (CH_3); 1.6 (—CH_2—); 1.7 (CH_3—P); 4.1 (—O—CH_2—). J_{H-P} 7.3 Hz; 6.8–7.0 (4 Ar); 7.8 (OH). ^{31}P NMR spectrum: δ 31.6 ppm (benzene). Found %: C 52.4; H 6.4; P 13.7 $C_{10}H_{15}O_4P$. Calculated %: C 52.2; H 6.5; P 13.5.

O-benzyloxyphenylpropylmethylphosphonate **8**. Benzoylchloride (1.4 g, 0.01 mmol in 15 cm^3 benzene) was added to a mixture of phosphonate **7** (2.3 g, 0.01 mmol) and triethylamine (1 g, 0.01 mmol) in 40 cm^3 benzene. The reaction mass was kept for 2 h at 20°C, triethylamine hydrochloride was filtered off, the solvent was distilled off in vacuo, the residue was purified on a column with silica gel. Yield 2.4 g (72%), m.p. 117–118°C, b.p. $150/10^{-4}$ mm merc. Rf 0.6. ^1H NMR spectrum ($CDCl_3$, δ ppm) 0.8 (CH_3); 1.5 (CH_3—P). J_{P-C-H} 17.6 Hz; 1.6 (—CH_2—); 3.9 (—O—CH_2—). J_{H-P} 9.3 Hz; 7.2–8.2 (9 Ar). ^{31}P NMR spectrum: δ 28 ppm (chloroform). Found %: C 61.3; H 5.5; P 9.2 $C_{17}H_{19}O_5P$. Calculated %: C 61.1; H 5.7; P 9.3.

2-Benzyloxy-3,5-ditertbutyl-phenyl-propylmethylphosphonate **8-a**. Propanol (0.3 g, 0.005 mmol) was added to 3,5-ditertbutylpyrocatechincyclomethylphosphonate **1-a** (1.4 g, 0.005 mmol in 15 cm^3 benzene). After 10 min benzoylchloride (0.7 g; 0.005 mmol) and triethylamine (0.5 g; 0.005 mmol in 10 cm^3 benzene) were added to the reaction mass. 2 h later triethylamine hydrochloride was filtered off, the solvent was distilled off in vacuo, the substance was isolated by chromatography (column with silica gel, B:D = 3:1). Yield 1.2 g (54%) n_D^{20} = 1.5207; Rf 0.7. (B:D = 3:1). ^1H NMR spectrum ($CDCl_3$,

δ ppm): 0.73 (CH_3) (s); 1.29; 1.43 $C(CH_3)_3$ (s); 1.35 (—CH_2) (m); 1.55 (CH_3—P) (d). $J_{P—C—H}$ 17.6 Hz; 3.78; 3.92 (—O—CH_2) (m); 7.02–8.23 (Ar). ^{31}P NMR spectrum: δ 24.8 ppm (chloroform). Found %: C 67.4; H 7.8; P 6.9 $C_{25}H_{35}O_5P$. Calculated %: C 67.3; H 7.9; P 6.9.

Phenyl-o-oxyphenoxymethylphosphonate **9**. Phenol (0.8 g, 0.009 mmol in 2 cm^3 benzene) was added to phosphonate **1** (1.5 g, 0.009 mmol in 15 cm^3 of benzene). The reaction mass was kept intact for 10 h at 30°C, the mixture was cooled to 5°C, the precipitated product was filtered off the crystallized from benzene. Yield 1.8 g (81%), m.p. 110–111°C, Rf 0.7. ^1H NMR spectrum ($CDCl_3$, δ ppm) 1.6 (CH_3—P). $J_{P—C—H}$ 17.6 Hz; 6.8–7.3 (9 Ar). ^{31}P NMR spectrum: δ 33 ppm (chloroform). Found %: C 58.9; H 5.1; P 11.9 $C_{13}H_{13}O_4P$. Calculated %: C 59.1; H 4.9; P 11.7.

2-Oxy-3,5-ditertbutyl-phenyl-tertbutyl-methyl-phosphonate **10**. Tertbutanol (0.74 g; 0.01 mmol) was added to 3,5-ditertbutylpyrocatechincyclomethylphosphonate **1-a** (2.8 g, 0.01 mmol in 20 cm^3 benzene). The reaction mass was stirred for 100 h at 20°C. The solvent was distilled off in vacuo, the substance was crystallized from benzene. Yield 2.1 g (62%), m.p. 137–138°C, Rf 0.8 (B:D = 3:1). ^1H NMR spectrum ($CDCl_3$, δ ppm): 1.27; 1.45 $C(CH_3)_3$ (s); 1.42 (—OC—$(CH_3)_3$) (s); 1.61 (P—Me) (d). J = 17.6 Hz; 6.90–7.10 (Ar) (s). ^{31}P NMR spectrum: δ 29.2 ppm. Found %: C 64.1; H 9.5; P 8.6 $C_{19}H_{33}O_4P$. Calculated %: C 64.0; H 9.3; P 8.7.

Hexamethylene-bis-(2-oxy-phenyl-methylphosphonate) **12**. 1,6-hexanediol (0.35 g, 0.003 mmol) was added to pyrocate-chincyclomethylphosphonate **1** (1 g, 0.006 mmol in 10 cm^3 1,4-dioxane). The reaction mass was stirred for 30 min, the solvent was distilled off in vacuo, the substance was crystallized from benzene. Yield 1 g (74%), m.p. 121–123°C, Rf 0.1 (B:D = 3:1). Found %: C 52.44; H 6.28; P 13.70. Calculated %: C 52.40; H 6.11; P 13.54.

Trimethylene-bis-(2-phenyl-carbamyl-phenyl-methyl-phosphonate) **13**. 1,3-propanediol (0.7 g, 0.01 mmol) was added to pyrocatechincyclomethylphosphonate **1** (3 g, 0.02 mmol in 30 cm^3 1,4-dioxane). The reaction mass was stirred for 30 min at 20°C, then phenylisocyanate (2.1 g; 0.02 mmol) and pyridine (1.5 ml in 10 cm^3 1,4-dioxane) were added. The reaction was conducted for 10 hours at 20°C. The solvent was distilled off in vacuo, the substance was isolated by chromatography (column with silica gel, B:D = 3:1). Yield 3.1 g (54%). Rf (B:D = 3.1) = 0.4. ^1H NMR spectrum ($CDCl_3$, δ ppm): 1.65 (d) (CH_3—P). $J_{P—C—H}$ 17.09 Hz; 1.92 (m) (—CH_2—); 4.20 (m) (—O—CH_2—) 6.73–7.48 (m) (Ar); 8.28 (s) (OH). ^{31}P NMR spectrum: δ 28.2 ppm (chloroform). Found %: C 56.8; H 9.95; P 9.50; N 4.40. Calculated %: C 56.88; H 4.89; P 9.48; N 4.28.

2-Oxybenzoyl-isopropylamide-phenylmethylphosphonate **16**. Isopropylamine (1 cm^3, exceed) was added to pyrocatechincyclomethylphosphonate **1** (1 g, 0.006 mmol). 30 min later benzoylchloride (1.7 ml) and triethylamine (2.1 ml in 5 cm^3 benzene were added to the reaction mass. After 1.5 h triethylamine hydrochloride was filtered off, the solvent was distilled off in vacuo, the substance was isolated by chromatography (column with silica gel B:D = 3:1). Yield 1.1 g (56%), m.p. 118–119°C, Rf 0.2 (B:D = 3:1). ^1H NMR spectrum ($CDCl_3$, δ ppm) 0.95; 0.98 (CH_3) (s); 1.43/47 (CH_3—P). J 16.6 Hz; 2.68 (NH) (m); 3.37 (i—CH—) (m); 7.19–8.20 (Ar). ^{31}P NMR spectrum: δ 31.52. Found %: C 61.3; H 6.0; P 9.3; N 4.5 $C_{17}H_{20}O_4PN$. Calculated %: C 61.0; H 6.1; P 9.1; N 4.8.

2-Oxybenzoyl-piperidide-phenylmethylphosphonate **17**. Piperidine (3 ml) was added to pyrocatechin-cyclomethylphosphonate **1** (1.5 g, 0.009 mmol). The reaction mass was stirred at 20°C, 1 h later benzoylchloride (4.5 ml) and triethylamine (4.3 ml in 10 cm^3 benzene) were added to the reaction mass. After 2 h triethylamine hydrochloride was filtered off, the solvent was distilled off in vacuo, the substance was isolated by chromatography (column with silica gel B:D = 3:1). Yield 1.1 g (50%), n_D^{20} = 1.5557, Rf 0.5 (B:D = 3:1). ^1H NMR spectrum ($CDCl_3$, δ, ppm) 1.27 (—CH_2) (s); 1.32 (—CH_2—) (m); 1.43–1.44 (CH_3—P) (d). J 16.11 Hz; 3.00 (—N—CH_3—) (m); $J_{P—H}$ 7.32 Hz; 7.20–8.20 (Ar). ^{31}P NMR spectrum; δ 30.3 ppm. Found %: C 63.51; H 6.13; P 8.64; N 3.90 $C_{19}H_{22}O_4PN$. Calculated %: C 63.49; H 6.15; P 8.51; N 4.11.

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