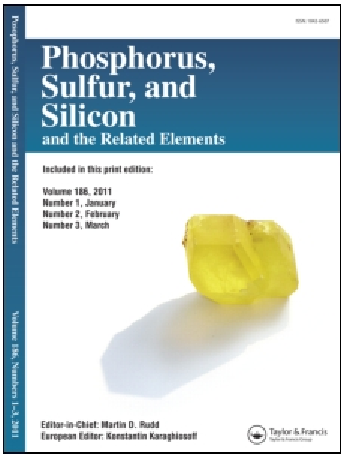

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B. I. Martynov[a]; G. P. Ponomarenko[a]; N. A. Pavlova[a]; E. N. Fetisova[a]
[a] State Research Institute of Organic Chemistry and Technology 23, Shosse Entuziastov, Moscow, Russia

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# ON THE SYNTHESIS OF DICHLOROFLUOROMETHYLPHOSPHONIC ACID DERIVATIVES

B. I. MARTYNOV, G. P. PONOMARENKO, N. A. PAVLOVA and
E. N. FETISOVA

*State Research Institute of Organic Chemistry and Technology 23, Shosse Entuziastov, Moscow, 111024 Russia*

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Preparation and reactivity of various derivatives of dichlorofluoromethylphosphonic acid are described. Some physico-chemical characteristics of these compounds are reported.

*Keywords:* Dichlorofluoromethylphosphonic acid; dichlorofluoromethyl phosphonates; dichlorofluoromethylphosnic dichloride and—bis(diethylamide)

In recent years, an increased focus upon the roles and significance of the biological activity of the phosphoryl group has resulted in heightened interest in phosphonates containing fluorine atoms in the $\alpha$-position as hydrolytically stable and biologically active phosphate analogues.[1,2] Several reports suggest that $\alpha$-fluoroalkylphosphonates are particularly effective phosphate mimics, as originally proposed by Blackburn[3–5].

Among the more interesting of these compounds which may become key compounds as very convenient materials for further conversions are dichlorofluoromethylphosphonic acid derivatives. Unfortunately, these substances are difficult to prepare, although some methods of their preparation have been published.[5] It has been reported that triethyl phosphite does react with fluorotrichloromethane in an autoclave during 8 h at 180°C resulting in a mixture of the target product with diethyl ethylphosphonate. This material was used without further purification for the following conversions. On the other hand it has been noted that the Arbusov reaction between fluorotrichloromethane and triisopropyl phosphite does not take place at all.[6] Another way for the preparation of these substances was the Michaelis-Becker reaction between fluorotrichloromethane and sodium diethyl phosphite.[5] According to these data only diethyl dichlorofluoromethylphosphonate and tetraethyl pyrophosphate have been observed as a result of this process. Unfortunately, we could not reproduce this procedure because of the reduction process and the concurrent formation of diethyl chlorofluoromethylphosphonate and dichlorofluoromethylphosphonate in a ratio of (1:1). At the same time, it has been noted that reaction between fluorotrichloromethane and sodium diisopropylphosphite takes place in a low yield.[6]

Thus, at present time there are no safe and convenient methods for the preparation of various derivatives of dichlorofluoromethylphosphonic acid.

## RESULTS AND DISCUSSION

We have considered a number of reactions for the preparation of dichlorofluoromethylphosphonic acid derivatives. The first step of our researches was an Arbusov reaction of 3-coordinated phosphorus derivatives with trichlorofluoromethane. It is well known that the electrophilic nature of fluorotrichloromethane is reduced as compared to carbon tetrachloride; therefore it requires more nucleophilic agents. From this viewpoint we examined the reactivity of bis(dialkylamino)alkoxyphosphines. The alkylation of these compounds allows to obtain the corresponding diamides of dichlorofluoromethylphosphonic acid at soft conditions:

$$(R_2N)_2POR' + CCl_3F \rightarrow (R_2N)_2P(O)CCl_2F + R'Cl$$
$$R,R' = CH_3,\ C_2H_5.$$

Persistent by-products (about 40–50%) in these reactions are the tetraalkyldiamides of phosphoric chloride. The proportion of the main reaction products and by-products depends on the size of substituents at nitrogen and oxygen atoms. In any case the replacement of methyl by ethyl groups leads to increasing by-products. However, the distillation of the reaction mixture affords the main products in a pure state.

Unfortunately, we could not convert the resultant phosphonic diamides into the other derivatives of dichlorofluoromethylphosphonic acid. That is why the chlorination procedure of chlorofluoromethylphosphonate has been elaborated. In accordance with the method reported for difluoromethylphosphonic dichloride generation[7] the corresponding chlorofluoromethylphosphonic dichloride has been produced:

$$(EtO)_2P(O)CHClF \xrightarrow[Pyridine]{SOCl_2} CHClFP(O)Cl_2$$

Chlorination of this phosphonic dichloride with chlorine under UV irradiation leads to traces of dichlorofluoromethylphosphonic dichloride only. More successful was the chlorination with phosphorus pentachloride. This method proceeds in two steps. The first is the formation of the intermediate complex, which transforms into dichlorofluoromethylphosphonic dichloride under sulphur dioxide action:

$$CHClFP(O)Cl_2 \xrightarrow{PCl_5} [CFCl_2\overset{+}{P}Cl_3 \cdot \overset{-}{P}Cl_6]$$
$$\xrightarrow{SO_2} CCl_2FP(O)Cl_2 + POCl_3$$

It is no wonder, that this reaction takes place with the corresponding phosphonic esters too. Thus, diethyl chlorofluoromethylphosphonate interacts with the phosphorus pentachloride and gives dichlorofluoromethylphosphonic dichloride according to the following scheme:

$$(EtO)_2P(O)CHClF \xrightarrow[-EtCl]{PCl_5} [CFCl_2\overset{+}{P}Cl_3 \cdot \overset{-}{P}Cl_6]$$
$$\xrightarrow{SO_2} CCl_2FP(O)Cl_2 + POCl_3$$

The interaction of this phosphonic dichloride with ethanol in the presence of triethylamine leads to the corresponding diethyl phosphonate:

$$CCl_2FP(O)Cl_2 + EtOH + 2\ Et_3N \rightarrow (EtO)_2P(O)CCl_2F + 2\ Et_3N \cdot HCl$$

It is important to keep the given conditions because otherwise replacement of the dichlorofluoromethyl group by an ethoxy group may take place yielding triethyl phosphate too.

## EXPERIMENTAL

$^1$H and $^{19}$F NMR spectra were measured with a Varian EM-390 spectrometer (90 MHz) utilising as external standards TMS and $CFCl_3$. $^{31}$P NMR spectra were obtained with a Varian HA-100D (40.5 MHz) spectrometer with external standard 85% $H_3PO_4$. IR spectra were recorded on UR-20 spectrometer in $CCl_4$ as solvent.

### *Synthesis of dichlorofluoromethylphosphonic bis(dimethylamide)*

An excess of fluorotrichloromethane (89 g, 0.65 mol) was added dropwise to bis(dimethylamino)methoxyphosphine (32.43 g, 0.22 mol) under nitrogen at 5°C in a three neck flask. Then the mixture was stirred for 3 h at refluxing (~30°C) and was allowed to stay overnight at room temperature. Removal of the fluorotrichloromethane in vacuo, followed by distillation of the residue afforded a crude product at b.p. 80–121°C/4 mm Hg. The resulting fraction was distilled again to give 15.72 g of the product, yield 31%, b.p. 110–112°C/4 mm Hg, $d_4^{20}$ = 1.3561 g/cm$^3$; $n_D^{20}$ = 1.4762.

NMR (without solvent) $^1$H: $\delta_H$ 2.6 ppm (12H, d, $^3J_{PH}$ 9 Hz, N$CH_3$); $^{31}$P: $\delta_P$ 19.32 ppm (d, $^2J_{PF}$ 67.2 Hz). $^{19}$F: $\delta_F$ 60.03 ppm (d, $^2J_{FP}$ 67.2 Hz).

IR $\nu_{max}$: 1235 (P=O); 1310 (P-$NCH_3$); 1000,990 (P-N) cm$^{-1}$.

Anal. found: C, 25.03; H, 5.04; N, 10.98; F, 7.89; P, 13.85; Cl, 30.12%. Calc. for $C_5H_{12}Cl_2FN_2OP$: C, 25.34; H,5. 10; N, 11.82; F, 8.01; P, 13.07; Cl 29.91%.

### *Synthesis of dichlorofluoromethylphosphonic bis(diethylamide)*

Using the procedure outlined above, this phosphonic diamide has been prepared with a yield of 30% utilising bis(diethylamino)ethoxyphosphine. The product had the following characteristicts: b.p. 128–130°C/3 mm Hg, $d_4^{20}$ = 1.1999 g/cm$^3$; $n_D^{23}$ = 1.4755.

NMR (without solvent) $^{31}$P: $\delta_P$ 20.5 ppm (d, $^2J_{PF}$ 64.5 Hz). $^{19}$F: $\delta_F$ 61.5 ppm (d, $^2J_{FP}$ 64.5 Hz).

Anal. found: C, 36.56; H, 6.58; N, 9.45; F 6.39; P 10.46; Cl 24.33%. Calc. for $C_9H_{20}Cl_2FN_2OP$: C, 36.88; H, 6.88; N, 9.56; F 6.48; P, 10.57; Cl, 24.19%.

### *Preparation of chlorofluoromethylphosphonic dichloride*

Thionyl chloride (60 g, 0.5 mol) was added dropwise to a solution of diethyl chlorofluoromethylphosphonate (11.77 g, 0.058 mol) in pyridine (60 ml). The mixture was stirred for 20 h at refluxing. The excess of thionyl chloride was removed and the product was distilled at reduced pressure. The second distillation gave 3.25 g of chlorofluoromethylphosphonic dichloride, yield 30%, b.p. 91–92.5°C/50 mm Hg, $d_4^{20}$ = 1.6908 g/cm$^3$; $n_D^{20}$ = 1.4656.

NMR (without solvent) $^1H$: $\delta_H$ 7.0 ppm (H, dd; $^2J_{PH}$ 25.5 Hz; $^2J_{FH}$ 48.0 Hz, P*CH*FCl); $^{31}P$: $\delta_P$ 29.8 ppm (d, $^2J_{PF}$ 111 Hz). $^{19}F$: $\delta_F$ 151.0 ppm (dd, $^2J_{FP}$ 111 Hz; $^2J_{FH}$ 48.0 Hz).

IR $\nu_{max}$: 1307, 1281 (P=O); 1066 (C-F); 590, 566, 507 (P-$Cl_2$) $cm^{-1}$.

Anal. found: C, 6.43; H, 0.55; F, 10.13; P, 16.58; Cl, 57.75%. Calc. for $C_1H_1Cl_3FOP$: C, 6.48; H, 0.54; F, 10.25; P, 16.71; Cl, 57.38%.

### *Preparation of dichlorofluoromethylphosphonic dichloride from chlorofluoromethylphosphonic dichloride*

The mixture of chlorofluoromethylphosphonic dichloride (39.18 g, 0.21 mol) and phosphorus pentachloride (132.11 g, 0.63 mol) was heated for 4 h at 100–110°C. Then the low boiling products were removed under reduced pressure at about 1–2 mm Hg. The residual solid state complex (91.4 g) was converted into a mixture of various acids chlorides by passing sulfur dioxide at 0°C through the mixture until the liquid state of the mixture was obtained. The volatile acids chlorides were removed at reduced pressure and distillation of the residue gave 26.5 g of dichlorofluoromethylphosphonic dichloride, yield 57%, b.p. 70–73°C/ 40 mm Hg, m.p. 63–65°C.

NMR ($CCl_4$) $^{31}P$: $\delta_P$ 24.3 ppm (d, $^2J_{PF}$ 112,8 Hz). $^{19}F$: $\delta_F$ 70.33 ppm (d, $^2J_{FP}$ 112,8 Hz).

IR $\nu_{max}$: 1304 (P=O); 1068 (C-F); 600, 564, 522, 511 (P-$Cl_2$) $cm^{-1}$.

Anal. found: C, 5.41; F, 8.56; P, 14.36; Cl, 64.93%. Calc. for $C_1Cl_4FOP$: C, 5.46; F, 8.64; P, 14.09; Cl, 64.52%.

### *Reaction of diethyl chlorofluoromethylphosphonate with phosphorus pentachloride*

The mixture of diethyl chlorofluoromethylphosphonate (36.68 g, 0.179 mol) and phosphorus pentachloride (186.98 g, 0.897 mol) was heated at 100–110°C about 4 h until fully dissolved. The low boiling products were removed under reduced pressure and the formed complex was treated with $SO_2$ as describe above. This manner allows to obtain 16.37 g of dichlorofluoromethylphosphonic dichloride with a yield of 42.8%.

### *Preparation of diethyl dichlorofluoromethylphosphonate*

Dichlorofluoromethylphosphonic dichloride (40.18 g, 0.183 mol) in diethyl ether (100 ml) was added dropwise to a solution of ethyl alcohol (16.80 g, 0.365 mol) and triethylamine (36.89 g, 0.365 mol) in diethyl ether (400 ml). The mixture was stirred for 3 h at room temperature. Removal of the solvent in vacuo, followed by distillation afforded the product with a yield of 63%, b.p. 89–92°C/ 6 mm Hg, $d_4^{20}$ = 1,3959 g/cm$^3$; $n_D^{20}$ = 1.4300.

NMR (without solvent) $^1$H: $\delta_H$ 1.47 ppm (6H, t, $^3J_{HH}$ 6.0 Hz, OCH$_2$*CH$_3$*), 4.37 ppm (4H, dq, $^3J_{HP}$ 7.2 Hz, $^3J_{HH}$ 6.0 Hz, PO*CH$_2$*CH$_3$); $^{31}$P: $\delta_P$ 1,4 ppm (d, $^2J_{PF}$ 84,66 Hz). $^{19}$F: $\delta_F$ 71,66 ppm (d, $^2J_{FP}$ 84,66 Hz). Lit.[5].

IR $\nu_{max}$: 1284 (P=O); 1089 (C-F); 1051, 1024, (P-OC) cm$^{-1}$.

Anal. found: C, 24.94; H, 4.17; F, 8.03; P, 12.82; Cl, 29.49%. Calc. for $C_5H_{10}Cl_2FO_3P$: C, 25.13; H, 4.22; F, 7.95; P, 12.96; Cl, 29.67%.

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