To purify the arecoline base, to the combined benzene extracts was added 25 ml of water and with mixing and maintaining a temperature of 20-22°C the mixture was acidified with 35 ml of dilute hydrochloric acid (1:1) to an acidic reaction to Congo, after which the contents of the flask were stirred for 2 h. The acidic aqueous layer was separated and the benzene layer was washed twice with small portions of water, which were combined with the main aqueous solution. Then with stirring and a temperature of 20-22° the aqueous arecoline hydrochloride solution under a fresh portion of 50 ml of benzene was made basic with solid potassium carbonate to phenolphthalein. The benzene extracts were evaporated at reduced pressure on a water bath. The residue was fractionated in vacuum, collecting the fraction with bp 80-82° (5 mm). The yield of IV was 42.2% calculated on III.

Arecoline Hydrobromide (V). An aqueous solution of arecoline base was acidified with 40% hydrobromic acid to pH 4.5-5.0 (pH meter reading) and at a temperature of 25-30°. The solution was evaporated to dryness on a water bath at 50°. The residue was recrystallized from absolute alcohol, mp 169-173°. Yield of V was 67.8% calculated on IV.

Found, %: N 5.59. $C_8H_{23}NO_2\cdot HBr$. Calculated, %: N 5.93.

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HYDROLYSIS OF DIARYL N,N-BIS[2-(METHYLSULFONYLOXY)ETHYL]AMINOPHOSPHATES IN ACIDIC AND ALKALINE SOLUTION

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Since the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates whose synthesis we reported in [1] possess marked antiblastic properties, we decided to study their hydrolysis in acidic and alkaline solution. Our intentions were twofold: to confirm the chemical structure of these compounds and to ascertain the behavior of new and promising antiblastic preparations in acidic and alkaline solution.

According to published data, esters of methanesulfonic acid in aqueous solution and acidic and alkaline solution are easily hydrolyzed with loss of the methanesulfonate anion. Hydrolysis or reaction with nucleophilic reagents of esters of methanesulfonic acid that contain a heteroatom with a lone pair in a certain orientation to the reaction center initially gives a cyclic cation with loss of the methanesulfonate anion [2, 3].

On the other hand, hydrolysis of phosphorylated chloroethylamines such as diaryl N,N-bis(2-chloroethyl)aminophosphates in acidic or alkaline solution forms the diaryl phosphates and bis(2-chloroethyl)amine, i.e., they are cleaved at the P—N bond [4].

However attempted hydrolysis of the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates in 1 N aqueous solution with hydrochloric acid contrary to all expectations resulted in cleavage of the P—OAr bond, forming the phenols and N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid.

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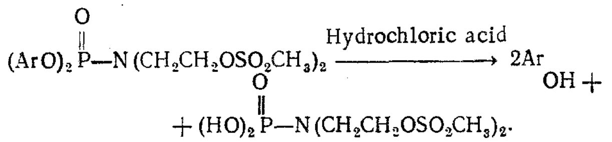
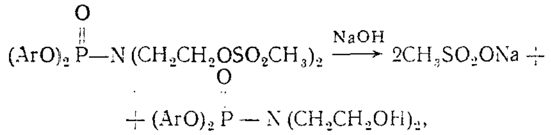


$$(ArO)_2\overset{O}{\overset{\|}{P}}-N(CH_2CH_2OSO_2CH_3)_2 \xrightarrow{\text{Hydrochloric acid}} 2ArOH + (HO)_2\overset{O}{\overset{\|}{P}}-N(CH_2CH_2OSO_2CH_3)_2.$$

Similarly the P—OAr bond was cleaved in hydrolysis of these compounds in aqueous solution with sodium hydroxide, forming the phenolates and disodium-N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphate. However because of difficulty in isolating the reaction products in the pure state we converted them to the acid forms by neutralizing the reaction mixture with hydrochloric acid solution and separating the phenols and N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid.

Alkaline hydrolysis of diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates in nonaqueous solution follows a completely different path. On heating these substances in 1 N methanolic sodium hydroxide, cleavage of the C—O bond took place, forming sodium methanesulfonate and diaryl N,N-bis(2-hydroxyethyl)aminophosphates



$$(ArO)_2\overset{O}{\overset{\|}{P}}-N(CH_2CH_2OSO_2CH_3)_2 \xrightarrow{NaOH} 2CH_3SO_2ONa + (ArO)_2\overset{O}{\overset{\|}{P}}-N(CH_2CH_2OH)_2,$$

i.e., in this case the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates behave as typical alkylating compounds.

We confirmed the structures of the substances obtained from hydrolysis of the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates from their IR spectra.

Thus, the spectrum of N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid contains characteristic absorption bands with maxima near 3400, 1320 and 1060, 1200, 780, and 550 cm^{-1}, which can be assigned, respectively, to ν (OH), ν_{as} and ν_s (SO_2), ν (P=O), ν (P—N), and ν (C—S) [5, 6]. This spectrum lacks the absorption bands of ν (C=C) and ν (C—H) of aromatic rings that are characteristic for diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates.

The spectra of the diaryl N,N-bis(2-hydroxyethyl)aminophosphates lack the absorption bands of ν (SO_2), which are characteristic for the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates and contain absorption bands in the 3240 and 3250 cm^{-1} regions, which are due to ν (OH) of these substances. Moreover the spectra of the diaryl N,N-bis(2-hydroxyethyl)aminophosphates contain a series of characteristic absorption bands near 1180, 1240, 750, 1710, and 3000 cm^{-1}, which can be assigned, respectively, to ν (P=O), ν (P—OAr), ν (P—N), ν (C=C), and ν (C—H) of the aromatic rings.

EXPERIMENTAL

The IR absorption spectrum of N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid was recorded in potassium bromide tablets, and those of the diaryl N,N-bis(2-hydroxyethyl)aminophosphates were recorded as liquid films with a Perkin-Elmer 325 spectrometer in the 400-4000 cm^{-1} region.

Acid Hydrolysis of Diphenyl-N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphate. After 0.05 mole of diphenyl-N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphate in 150 ml of 1 N hydrochloric acid had been heated and stirred for 2 h, the reaction mixture was cooled to room temperature and 100 ml of benzene were added. The mixture was stirred for 5-10 min and the layers were separated. The benzene solution was dried with anhydrous calcium chloride and filtered; the benzene was removed by vacuum distillation. The residue yielded a pink crystalline product — phenol (yield 98%), which distilled at 88-90°C 24-25 mm (mp 41-43°C). Found, %: C 76.41; H 6.38. C_6H_6O. Calculated, %: C 76.55; H 6.42.

After removal of the water from the aqueous solution by vacuum distillation, the residue was dissolved in 200 ml of methanol and dried with anhydrous calcium oxide. After filtration, the methanol was removed by vacuum distillation, and the crystalline residue was recrystallized from methanol—acetone. We obtained N,N-bis[2-methylsulfonyloxy)ethyl]aminophosphoric acid as a colorless crystalline powder in 94% yield, mp 61-63°C, Found, %: N 3.48, 3.57; P 8.01, 8.04; S 16.79, 16.84. $C_6H_{14}NO_9PS_2$. Calculated, %: N 3.69; P 8.16; S 16.90.

Similarly in acid hydrolysis of di-p-cresyl and bis(o-chlorophenyl)-N,N-bis[2-methylsulfonyloxy)ethyl]aminophosphates we obtained p-cresol in almost theoretical yield (94.6%, bp 91-93°C/14 mm. (Found, %: C 77.64; H 7.38. C_7H_8O. Calculated, %: C 77.74; H 7.46), o-chlorophenol (96%, bp 88-90°C/18 mm). Found, %: Cl 27.38, 27.45. C_6H_5ClO. Calculated, %: Cl 27.58, and N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid.

Alkaline Hydrolysis of Diphenyl-N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphate in Aqueous Solution. After 0.05 mole of diphenyl N,N-bis[2-methylsulfonyloxy)ethyl]aminophosphate in 120 ml of 1 N sodium hydroxide had been heated and stirred for 3 h, the reaction mixture was cooled to room temperature and neutralized to pH 7.0 with hydrochloric acid solution; 100 ml of benzene were added. The mixture was stirred for 5-10 min, whereupon the benzene layer was separated from the aqueous layer. Subsequently phenol (97.3%) was isolated from the benzene solution and N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid (94.6%) was isolated from the aqueous solution by the method used in the acid hydrolysis.

Alkaline hydrolysis of di-p-cresyl and bis(p-fluorophenyl)-N,N-bis[2-(methylsulfonyloxyethyl]aminophosphates under the same conditions yielded p-cresol (93.3%), p-fluorophenol (95.2%, bp 81-85°C/18 mm. Found, %: C 63.98; H 4.42. C_6H_5FO. Calculated, %: C 64.27; H 4.48, and N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphoric acid in 96.8% and 97.5% yield, respectively.

Alkaline Hydrolysis of Diphenyl-N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphate in Nonaqueous Solution. After addition of a solution of 4 g of sodium hydroxide in 50 ml of methanol to a solution of 0.02 mole of diphenyl-N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphate in 75 ml of anhydrous methanol, the reaction mixture was heated under reflux with constant stirring for 2 h. Then after cooling to room temperature, the precipitate was filtered off, washed with methanol, and dried. We obtained sodium methanesulfonate as a colorless crystalline powder, yield 91%. Found, %: Na 19.38; S 26.93, 27.06. CH_3O_3SNa. Calculated, %: Na 19.47; S 27.15.

After removal of the solvent from the methanol solution by vacuum distillation, the residue was dissolved in 50 ml of water and hydrochloric acid solution was added to pH 7.0; 70 ml of chloroform were then added to extract the oily substance accompanying the precipitate. The chloroform solution was separated, dried with anhydrous calcium chloride, and for further purification passed through an aluminum oxide column. The chloroform was then removed by vacuum distillation, and the residue was twice purified by dissolving in 30 ml of anhydrous acetone, followed by filtration and removal of the solvent by vacuum distillation. We obtained diphenyl-N,N-bis(2-hydroxyethyl)aminophosphate as a yellow viscous liquid, yield 92%, n_D^{20} 1.5478. Found, %: N 3.83, 3.99; P 9.00, 9.02. $C_{16}H_{20}NO_5P$. Calculated, %: N 4.15; P 9.18.

By the same method alkaline hydrolysis of di-p-cresyl-N,N-bis[2-(methylsulfonyloxy)-ethyl]aminophosphate in anhydrous methanol gave sodium methanesulfonate (92%) and di-p-cresyl-N,N-bis(2-hydroxyethyl)aminophosphate, yield 90.2%, n_D^{20} 1.5274. Found, %: N 3.72, 3.90; P 8.17, 8.28. $C_{18}H_{24}NO_5P$. Calculated, %: N 3.83; P. 8.48.

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