SYMM-BIS(p-NITROPHENYLETHYL)ETHYLENE-1,2-DIPHOSPHONATE

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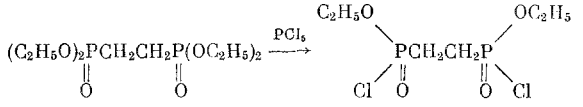
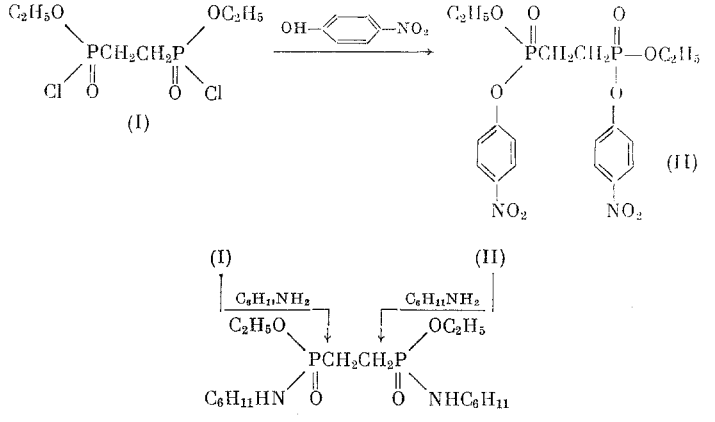
It is known that many monofunctional alkylating agents are mutagenic compounds, the activity of which is associated with their ability to react with the nucleophilic groups of nucleic acids. However, only bifunctional alkylating agents, such as bis-β-halodialkylamines, bis-expoxides, bis-ethylenimines, etc. have proved to be active antitumoral compounds. It is believed that the cause of the inhibition of cell division is the ability of these compounds to crosslin, the active groups of DNA and thereby prevent its separation during mitosis. A mutagenic effect of acylating organophosphorus compounds is also known [1]; however, thus far no antitumoral effect to them has been noted. Naturally, a possible antitumoral effect of bifunctional organophosphorus acylators was assumed.

We synthesized a bifunctional phosphorylating agent, symm-bis(p-nitrophenyl)ethylene-1,2-diphosphonate, as a potential antitumoral compound. The symm-dichloride of the diethyl ester of ethylene-1,2-diphosphonic acid was produced by the reaction of the tetraethyl ester of ethylene-1,2-diphosphonic acid with phosphorus pentachloride at 70°



The dichloride obtained represents a white crystalline substance with m. p. 51-52° and is hydroscopic. It is readily soluble in most organic solvents; it does not dissolve in petroleum ether. Attempts to redistill it under vacuum proved unsuccessful; it decomposes at 100° (0.007 mm). The dichloride of the diethyl ester of ethylene-1,2-diphosphonic acid reacts vigorously with cyclohexylamine, forming the symm-dicyclohexylamide of the diethyl ester of ethylene-1,2-diphosphonic acid, while with p-nitrophenol in the presence of triethylamine at a temperature of -10° it forms symm-bis(p-nitrophenylethyl)ethylene-2-diphosphonate in 72% yield



Symm-bis(p-nitrophenylethyl)ethylene-1,2-diphosphonate acylates cyclohexylamine at room temperature and forms the symm-dicyclohexylamide of the diethyl ester of ethylene-1,2-diphophonic acid, identical with a sample obtained from cyclohexylamine and the dichloride of the ethylene-1,2-diphosphonic acid triethyl ester.

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EXPERIMENTAL

Production of the Symm-dichloride of Ethylene-1,2-diphosphonic Acid Diethyl Ester. In a three-necked flask, equipped with a reflux condenser, mixer, and thermometer, were placed 15 g of the tetraethyl ester of ethylene-1,2-diphosphonic acid and 25 ml anhydrous CCl_4. Anhydrous PCl_4 (21.0 g) was added in small portions with mixing over a period of five hours at a temperature of 68-70°, after which the reaction mixture was mixed for another three hours at 75°. The solvent and phosphorus oxychloride were distilled off at 60° (120 mm). The oily residue was washed with petroleum ether and exposed at 80° (1 mm) for one hour.

The symm-dichloride of ethylene-1,2-diphosphonic acid diethyl ester crystallized upon standing. Yield 13.36 g (94.5%); m.p. 51-52° (in a sealed capillary). Found %: C 25.73; H 5.14; P 22.52; Cl 23.33. $C_6H_{14}P_2Cl_2O_4$. Calculated %: C 25.4; H 4.95; P 21.9; Cl 24.80.

Symm-dicyclohexylamide of Ethylene-1,2-diphosphonic Acid Diethyl Ester. To 2.0 g of the dichloride of ethylene-1,2-diphosphonic acid diethyl ester in a dry ether solution was added an equal solution of 2.8 g of cyclohexylamine. After an hour the precipitate formed was filtered off, washed with ether, dried, and treated with water. The undissolved diamide was filtered off and crystallized from aqueous alcohol (1 : 1). Yield 0.69 g (82.1%); m.p. 211-214°. Found %: C 52.86; H 9.45; N 6.96; P 15.12. $C_{18}H_{38}P_2O_4N_2$. Calculated %: C 52.94; H 9.31; N 6.86; P 15.14.

Production of Symm-bis(p-nitrophenylethyl)ethylene-1,2-diphosphonate. In a three-necked flask, equipped with calcium chloride tube, dropping funnel, thermometer, and mixer, was placed 8.81 g of the dichloride of ethylene-1,2-diphosphonic acid diethyl ester in 200 ml of abs. ether, which was cooled to -45°, and then 8.7 g of p-nitrophenol in 50 ml abs. ether was added. Over a period of 35 min, 10.9 g of dry triethylamine was added with mixing; the temperature was maintained at ~-10°. After addition of the entire amount of triethylamine, the mixing was continued for another two hours; during this period the temperature rose to room temperature. On the following day the precipitate formed was filtered off. The precipitate was treated with benzene at 40°. The undissolved triethylamine hydrochloride was removed. Evaporation of the benzene mother liquor under vacuum yielded 11 g (72.5%) symm-bis(p-nitrophenylethyl)ethylene-1,2-diphosphonate with m.p. 96-104°. The diphosphonate is readily soluble in acetone, benzene, and ethyl acetate, poorly soluble in alcohol and water. It was crystallized from abs. alcohol: m.p. 103-106°. Found %: C 44.37; H 4.66; N 5.54; P 12.58. $C_{18}H_{22}P_2O_{10}N_2$. Calculated %: C 44.26; H 4.50; N 5.74; P 12.69%.

Reaction of Symm-bis(p-nitrophenylethyl)ethylene-1,2-diphosphonate with Cyclohexylamine. A 0.5 g portion of symm-bis)p-nitrophenylethyl)ethylene-1,2-diphosphonate was carefully triturated with cyclohexylamine. The reaction mass was left for 12 h at room temperature. After dilution with abs. ether, the precipitate was filtered off (0.75 g), dissolved in ethanol, and diluted with an equal amount of water; a crystalline precipitate was formed. Yield. 0.3 g (70%) of the symm-dicyclohexylamide of 1,2-diphosphonic acid diethyl ester with m.p. 211°. A mixed sample with a specimen obtained from the dichloride of ethylene-1,2-diphosphonic acid diethyl ester gave no depression of the melting point.

CONCLUSIONS

Symm-bis(p-nitrophenylethyl)ethylene-1,2-diphosphonate, which is a bifunctional phosphorylating agent, was produced.

LITERATURE CITED

1. M. A. Rapoport and R. G. Kostyanovskii, Dokl. AN SSSR, 131, 1 (1960).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
