SYNTHESIS AND PROPERTIES OF SOME PHOSPHORYLATED PHENOTHIAZINES

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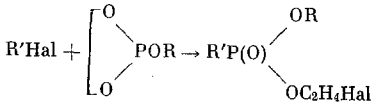
Earlier, in a search for new biologically active compounds, organophosphorus derivatives of phenothiazine differing in the nature of the phosphorylating residue and in the position of the substituents in the phenothiazine nucleus were obtained [1-7]. The results of a study of the larvicidal, anthelminthic, and antifungal activity of the compounds obtained showed that the most active were phosphonates substituted in position 10 of the phenothiazine. The preparation "Phosphen" – 10-(diethoxyphosphinylacetyl)phenothiazine possessed the highest larvicidal and anthelminthic activity [2, 8].

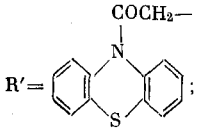
To obtain analogs of Phosphen with the general formula $\geq N-CO-CH(R)-P(O)(OC_2H_5)_2$, the alkylation of the K derivative of the diethyl phosphonate with methyl, ethyl, pentyl, hexyl, and benzyl iodides and bromides and with esters of bromine-substituted carboxylic acids has been performed. The substances obtained consisted of viscous liquids or vitreous masses incapable of being distilled in vacuum which were purified by reprecipitation from gasoline or cyclohexane. However, the compounds could not be obtained in the analytically pure state.

The IR spectra of the products of the reaction with esters of halogen-substituted acids had absorption bands at 1680 and 1720 cm^{-1} relating to a carbonyl group attached to the nitrogen atom of phenothiazine and to the carbonyl group of an ester, respectively.

The acid hydrolysis of the product of the methylation of 10-(diethoxyphosphinylacetyl)phenothiazine gave dihydroxyphosphinylpropionic acid, which was identified in the form of its aniline salt. Only the product of the addition of 10-chloroacetylphenothiazine – diethoxyphosphinylsuccindi(10-phenothiazinide) (I) – was obtained in the individual state.

Continuing work on the synthesis of new phenothiazine derivatives, we have obtained a number of analogs of Phosphen by replacing one of the ethoxy radicals by various halogenoalkoxy radicals. The synthesis of these compounds (Table 1) was performed by the reactions of halogenoacetylphenothiazines with alkyl alkylene phosphites:





; (III) R = C_2H_5, Hal = Cl; (IV) R = C_2H_5, Hal = I

(VI) R = $N(C_2H_5)_2$, Hal = Cl; (VII) R = $N(C_2H_5)_2$, Hal = I

The reactions take place when the participants are heated to 130-160° in the absence of a solvent. In a solvent (benzene) only iodoacetylphenothiazine reacted. In all the other cases in which a solvent was used the initial halogenoacetylphenothiazine was recovered unchanged.

The reactions with alkyl ethylene phosphites take place with the opening of the phosphite ring. The IR spectra of the products contain absorption bands of P=O groups (1250 cm^{-1}) and P–O–C groups (1050

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TABLE 1. [Alkoxy(halogenoalkoxy)phosphinylacetyl]phenothiazines

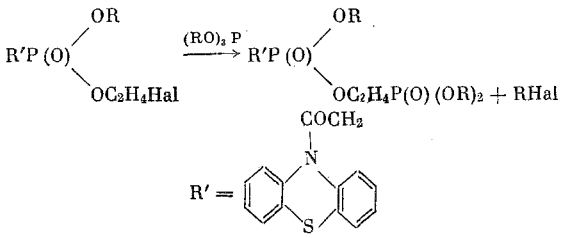
Phosphonates obtained	mp, °C	Found, %			Calculated, %			Yield, %
		P	N	Hal	P	N	Hal	
III	133—134	7,16	—	8,25	7,52	—	8,61	42
IV	131—132	5,75	—	*	6,15	—	*	63
V	128—129	5,94	—	7,51†	6,34	—	7,24†	34
VI	144—145	7,09	6,34	8,40	7,08	6,38	8,08	58
VII	—	6,10	5,34	‡	5,86	5,28	‡	45
VIII	145—147	7,14	6,50	none	7,43	6,69	—	38

*Found I 26.24, calculated 25.22%
†Found Br 16.90%, calculated 16.30%
‡Found I 24.65%, calculated 23.93%

cm^{-1}), which is in harmony with the proposed structure. The acid hydrolysis of 10-[(chloroethoxy)ethoxyphosphinylacetyl]phenothiazine gave phenothiazine and dihydroxyphosphinylacetic acid, which was identified in the form of the aniline salt.

When the reaction was performed with 1,3-butylene ethyl phosphite, a product was obtained in which the phosphite ring had been retained (see Table 1, VIII). The performance of reactions with the retention or opening of a phosphite ring according to its size has been observed previously [9, 10]. The compounds obtained consisted of crystalline substances or viscous liquids the crystallization of which could not be brought about by freezing in liquid nitrogen, by thermostating at 60-80°, or by emulsion crystallization [11]. Attempts at distillation in high vacuum invariably led to decomposition. The substances were purified by chromatography on Al_2O_3 and by reprecipitation from solvents.

Until now, only a few phosphorylated phenothiazines containing two phosphorus atoms were known [4]. In our work we have also attempted to obtain "diphosphorylated" phenothiazines by using the halogenoalkyl phosphonates for rearranging trialkyl phosphites:

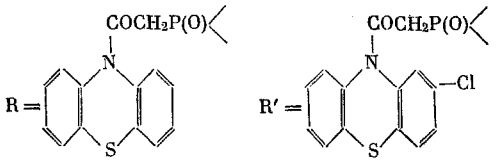


However, it was impossible to perform the reaction in the desired direction. When the starting materials were briefly heated in a solvent or in the absence of a solvent, no rearrangement took place. The substance isolated proved to be the initial phosphonate. When the reaction was carried out under severe conditions (180-200°, 16 h, triethyl phosphite), the compound isolated proved to be 10-ethylphenothiazine. Apparently under these conditions the C—N bond undergoes thermal cleavage. In addition to this process, the rearrangement of the triethyl phosphite takes place and the ethyl chloride formed alkylates the phenothiazine. During the present investigation, we have also obtained 10-(dimethoxyphosphinylacetyl)phenothiazone, the first member of the 10-(dialkoxyphosphinylacetyl)phenothiazine series, the synthesis of which had not previously been possible [1].

The larvicidal, anthelminthic, antifungal, and bacteriostatic properties of the compounds synthesized have been studied (Table 2). The 10-[alkoxy(halogenoalkoxy)phosphonylacetyl]phenothiazines possess various biocidal activities, but the anthelminthic properties are the most pronounced. The greatest helminthocidal activity is possessed by 10-[(bromoethoxy)ethoxyphosphonylacetyl]-2-chlorophenothiazine. A comparison of the preparations (see Table 2, preparations 1 and 4) shows that the introduction of a chlorine atom into the ethyl radical somewhat increases the anthelminthic effect, but a still greater effect is obtained by the replacement of the second ethoxy radical by a diethylamino group (preparations 1 and 3).

The preparations tested showed a very weak antifungal action. Their bacteriostatic action was stronger. The most active preparations in 1% concentration completely prevented the growth of Proteus, and in 0.1% solution they retarded its growth.

TABLE 2. Biological Properties of the 10-[Alkoxy-(halogenoalkoxy)phosphonylacetyl]phenothiazines



Number of preparation	Formula	Percentage helminthocidal action on Ascaridia galli. 24 h' exposure		Static action* on			
				Mucor rac.		Proteus vulg.	
		1%	0,1%	1%	0,1%	1%	0,1%
1	R, OC_2H_5, OC_2H_4Cl	20	0	+	+	−	+
2	R', OC_2H_5, OC_2H_4Br	80	50	+	+	−	±
3	R, $N(C_2H_5)_2$, OC_2H_4Cl	40	20	+	+	+	+
4	R, OC_2H_5, OC_2H_5 (Phosphen)	10	0	+	+	−	±

* −)no growth; + retardation of growth; ± normal growth.

EXPERIMENTAL METHOD

Potassium Derivative of 10-(Diethoxyphosphinylacetyl)phenothiazine. A suspension of 19 g of 10-(diethoxyphosphinylacetyl) phenothiazine in 200 ml of benzene was treated with 2 g of K, and the mixture was stirred at 70° for 2 h. The precipitate was dried in a vacuum desiccator giving 19 g of product with mp 130-132°. Found: P 7.79; C 51.52; H 4.53%. $C_{18}H_{19}KO_4NPS$. Calculated: P 7.95; C 51.97; H 4.58%.

Diethoxyphosphinylsuccindi(10-phenothiazinide) (I). A suspension of 7.4 g of 10-(diethoxyphosphinylacetyl)phenothiazine and 2 g of K in 50 ml of benzene was stirred at 40-70° for 3 h, and then 5.5 g of 10-(chloroacetyl)phenothiazine was added and the mixture was stirred at 60-70° for 2 h and left at 20° for 15 h. The precipitate was dried in a vacuum desiccator, giving 14.4 g of a substance with mp 190°. To eliminate the excess of K and the KCl, the substance was added in small portions with vigorous stirring to 200 ml of water, and the mixture was stirred for 5-10 min. The residue was filtered off and washed with water until the reaction for Cl^- was negative, giving 11.1 g of (I) with mp 203°. Found: C 62.12; H 5.02; P 4.99; N 4.99%. $C_{32}H_{29}O_5N_2PS_2$. Calculated: C 62.35; H 4.70; P 5.02; N 4.54%.

10-[2-(Diethoxyphosphinyl)propionyl]phenothiazine (II). With stirring, 1 g of K was added to a solution of 9.5 g of 10-(diethoxyphosphinylacetyl)phenothiazine in 75 ml of xylene at 50-60°, and after 3 h 4.2 g of CH_3I was added. The mixture was heated at 60-80° for 3 h. The precipitate of KI was filtered off and washed on the filter with acetone and ethanol; yield 4 g. The filtrate was evaporated in vacuum and the residue was heated at 130° for 2 h. The melt obtained was purified on a column of Al_2O_3 with benzene elution. This gave 6.8 g of (II) in the form of a cherry-red melt, R_f 0.68 (benzene–ether, 1:1). Found: C 60.18; H 5.70; P 6.77%. $C_{19}H_{22}O_4NPS$. Calculated: C 58.35; H 5.62; P 7.91%.

The product of the addition of ethyl bromoacetate to 10-(diethoxyphosphinylacetyl)phenothiazine was obtained similarly. The product was purified by chromatography on Al_2O_3 in the petroleum ether–benzene (75:25) system.

Hydrolysis of 10-(Diethoxyphosphinylacetyl)phenothiazone. A mixture of 4 g of 10-(diethoxyphosphinylacetyl)phenothiazine and 20% HCl was boiled for a day. The precipitate was filtered off and washed with water, giving 2 g (91%) of phenothiazine, mp 178-180°. The filtrate, after repeated evaporation, yielded 1.7 g of dihydroxyphosphinylacetic acid with mp 128-130°. According to [12], mp 142-143°. Aniline was added to a solution of the acid in ethanol, giving the aniline salt with mp 170°. Found: P 12.55; N 6.74%. $C_8H_{12}O_5NP$. Calculated: P 12.52; N 6.27%.

Hydrolysis of 10-[2-(Diethoxyphosphinyl)propionyl]phenothiazine (II). Under similar conditions, 3.4 g of (II) gave 1.8 g of phenothiazine with mp 180° and 1.7 g of dihydroxyphosphonylpropionic acid. Aniline salt 183°. Found: P 12.85; N 5.85%. $C_9H_{14}O_5NP$. Calculated: P 12.52; N 5.64%.

10-[(Chloroethoxy)ethoxyphosphinylacetyl]phenothiazine (III) and Its Reaction with Triethyl Phosphite. A mixture of 6.7 g of ethyl ethylene phosphite and 13.5 g of 10-(chloroacetyl)phenothiazine was heated at 150-170° for 15 h. After the completion of the heating process, the weight of the reaction mixture had not changed. On recrystallization from benzene, 8.4 g of (III) was recovered.

A mixture of 8.2 g of (III) and 3.5 g of triethyl phosphite was heated under reflux for 4 h, the temperature being raised gradually to 200°. After cooling, the melt was diluted with a mixture of petroleum ether and benzene, yielding 5.2 g of the initial phosphonate with mp 131°.

A mixture of 5.2 g of (III) and 3 g of triethyl phosphite was heated at 180-200° for 16 h. After cooling, the mixture crystallized. Recrystallization from ethanol yielded 1 g of 10-ethylphenothiazine with mp 102-103°. A mixture with an authentic sample [13] gave no depression of the melting point. Found: C 73.60; H 5.95%. $C_{14}H_{13}NS$. Calculated: C 74.00; H 5.72%.

10-[Ethoxy(iodoethoxy)phosphinylacetyl]phenothiazine (IV) and Its Reaction with Triethyl Phosphite. A mixture of 2.7 g of ethyl ethylene phosphite and 7.3 of 10-(iodoacetyl)phenothiazine in 10 ml of benzene was heated at 120° for 3 h. After two days, the crystals that had separated out were filtered off and washed with hot benzene. The yield of (IV) was 6.3 g, and this was recrystallized from benzene. The (IV) obtained was heated with triethyl phosphite in benzene for 4 h. After the end of the heating, the initial (IV) was recovered.

When 2.8 g of (IV) was heated with 2 g of triethyl phosphite at 180-200° for 4 h, 0.6 g of 10-ethylphenothiazine with mp 100-102° was obtained.

10-[(Bromoethoxy)ethoxyphosphinylacetyl]-2-chlorophenothiazine (V). A mixture of 3 g of ethyl ethylene phosphite and 7 g of 10-(bromoacetyl)-2-chlorophenothiazine was heated at 150° for 4 h. The melt was cooled and was treated with a mixture of benzene and petroleum ether (25:75). The precipitate was washed with ether and recrystallized from benzene, giving 3.3 g of (V).

10-[(Chloroethoxy)diethylaminophosphinylacetyl]phenothiazine (VI). A mixture of 3.5 g of ethylene N,N-diethylphosphoramidite and 5.5 g of 10-(chloroacetyl)phenothiazine was heated at 160° for 2.5 h. A benzene solution of the melt was passed through a column of Al_2O_3 (35-40 g). The eluate yielded 5.2 g of (VI) in the form of a colorless crystalline precipitate.

10-[(Diethylamino)(iodoethoxy)phosphinylacetyl]phenothiazine (VII). A mixture of 2.8 g of ethylene N,N-diethylphosphoramidite and 6.3 g of 10-(iodoacetyl)phenothiazine in 10 ml of benzene was boiled for 3 h, left for 5 days, and poured into 100 ml of petroleum ether. The resulting oil was reprecipitated from hot cyclohexane, dissolved in ether, and heated with carbon. This gave 4.1 g of (VII) in the form of a cherry-red melt, n_D^{50} 1.604.

10-Ethyl-3-[4-methyl-2-oxo-1,3,2-dioxaphosphorin-2-yl)acetamido]phenothiazine (VIII). A mixture of 3 g of 1,3-butylene ethyl phosphite and 3.6 g of 3-(chloroacetamido)-10-ethylphenothiazine was heated at 140-150° for 3 h. Recrystallization from benzene yielded 1.8 g of (VIII).

10-(Dimethoxyphosphinylacetyl)phenothiazine. A mixture of 5 g of 10-(chloroacetyl)phenothiazine and 3 g of trimethyl phosphite was heated at 120-130° for 1 h. Recrystallization from benzene yielded 1.2 g of a product with mp 134-135°. Found: P 8.88; N 4.57%. $C_{16}H_{16}NPSO_4$. Calculated: P 8.86; N 4.04%.

CONCLUSIONS

1. New phosphorylated phenothiazines containing halogen in the ester group at the phosphorus atom have been synthesized.

2. The anthelminthic activity of the [alkoxy(halogenoalkoxy)phosphinylacetyl]phenothiazines is higher than that of the dialkoxyphosphinyl analogs.

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