2-, 10-, AND 2,10-PHOSPHORYLATED PHENOTHIAZINES

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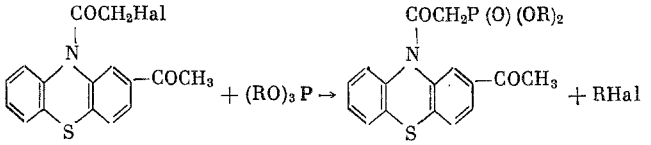
UDC 542.91+661.718.1

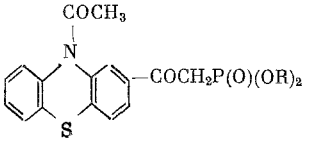
Phenothiazine has long found wide use in veterinary-helminthologic practice [1]. In 1961 the first organophosphorus derivatives of phenothiazine were obtained [2], and one of them – 10-(dialkoxyphosphinylacetyl)phenothiazine – also proved to be an active anthelminthic agent [3, 4].

In continuing these investigations, it was of interest to study the degree of biologic – in particular, anthelminthic – activity as a function of the presence of substituents in the phenothiazine ring and the position and number of dialkoxyphosphinyl groups. We have previously reported the preparation of organophosphorus derivatives of 2-chlorophenothiazine [5]. In the present paper we describe the phosphorylation of acetylphenothiazines with an acetyl group in positions 2 and 10 and also 2- and 2,10-phosphorylated phenothiazines having no other substituents. The synthesis of 2-acetyl-10-(dialkoxyphosphinylacetyl)phenothiazines (the compounds are given in Table 1) was carried out by the rearrangement reaction of trialkyl phosphites with 2-acetyl-10-(bromoacetyl)phenothiazine or the corresponding chloro compound



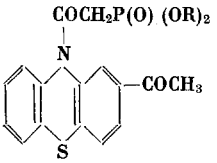
The reaction was carried out in the absence of a solvent. A mixture of the starting materials with a small excess of the trialkyl phosphite was heated at 150-160° for 2.5-3 h. The structure of the products obtained [the course of the reaction in the manner of an Arbuzov rearrangement is confirmed by the IR spectra (Fig. 1a)] is in agreement with the result obtained previously [2, 5, 6] and with literature data on the direction of the rearrangement reaction of trialkyl phosphites with amides of halogenocarboxylic acids [7]. Compounds 2 and 5 (see Table 1) are yellow substances crystallizing well from gasoline and cyclohexane. Compounds 1, 3, 4, and 6 could not be obtained in the crystalline state. They were purified by chromatography on Al_2O_3 and after the eluent (benzene) had been eliminated in vacuum, they consisted of viscous light yellow "oils" readily soluble in acetone, benzene, and ethanol, and insoluble in lower hydrocarbons and water. An attempt to crystallize compound 6 by freezing in liquid nitrogen with subsequent thermostatting at 60° for 2 weeks was also unsuccessful. The vacuum distillation (0.4 mm) of compound I proved unsuccessful – the distillate contained no nitrogen or sulfur.

The rearrangement of the trialkyl phosphites with 10-acetyl-2-(chloroacetyl)phenothiazine took place similarly. However, in this case none of the products could be isolated in the crystalline state. Attempts to recrystallize the reaction products led to the precipitation of oils which did not crystallize when they were allowed to stand for more than a year, or were frozen or thermostatted. Chromatographic purification on Al_2O_3 with subsequent elimination of the eluent (benzene) in vacuum gave light yellow very viscous liquids the elementary analyses of which were satisfactory for the expected rearrangement products. In order to establish the structure of the compounds obtained, their IR spectra were recorded. In the IR spectra of the 10-acetyl-2-(dialkoxyphosphinylacetyl)phenothiazines



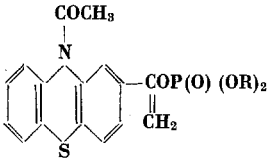
A. E. Arbuzov Institute of Organic and Physical Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 7, pp. 1583-1588, July, 1970. Original article submitted December 30, 1968.

TABLE 1



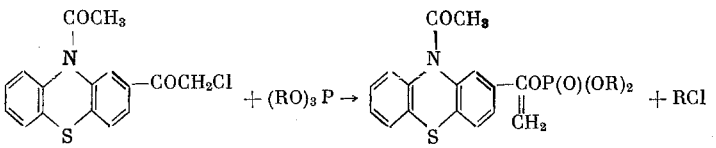
Compound No.	R	Mp, °C	Found, %				Calculated, %				Yield, %
			C	H	P	N	C	H	P	N	
1	CH_3	—	55,64	4,70	7,43	3,90	55,27	4,61	7,92	3,57	56
2	C_2H_5	160—161	—	—	7,28	3,21	—	—	7,38	3,34	76
3	i-C_3H_7	—	59,68	5,61	7,32	2,92	59,07	5,81	6,92	3,13	71
4	C_4H_9	—	61,19	6,40	6,14	2,78	60,65	6,33	6,53	2,97	80
5	i-C_4H_9	99—100	—	—	6,59	3,08	—	—	6,53	2,97	75
6	C_6H_{13}	—	63,73	7,36	6,17	2,40	63,29	7,15	5,85	2,64	77

TABLE 2

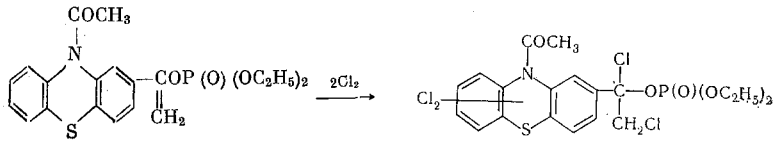


Compound No.	R	Found, %				Calculated, %				Yield, %
		C	H	P	N	C	H	P	N	
1	CH_3	—	—	7,65	3,37	—	—	7,92	3,58	26
2	C_2H_5	57,94	5,47	7,52	3,12	57,30	5,25	7,38	3,34	78
3	C_3H_7	59,70	5,86	7,25	2,78	59,07	5,81	6,92	3,13	29
4	i-C_3H_7	—	—	7,31	2,90	—	—	6,92	3,13	43
5	C_4H_9	61,12	6,55	6,67	2,91	60,64	6,33	6,53	2,97	57
6	i-C_4H_9	—	—	6,63	2,75	—	—	6,53	2,97	85

there was to be expected the appearance of a new absorption band in the 1700-1680 cm^{-1} region for a C=O group conjugated with an aromatic ring ([8], p. 188) of phenothiazine and the C=O group of cyclic amides ([8], p. 289). In the spectra of the compounds obtained, in addition to a strong absorption band at 1690-1680 cm^{-1}, there was another band of lower intensity with a maximum at 1635-1632 cm^{-1} (Fig. 1b). Obviously, if the first band is ascribed to the stretching vibrations of a carbonyl group in a cyclic amide, the second may be ascribed to the stretching vibrations of a $\rangle C=CH_2$ group conjugated with an aromatic ring of phenothiazine ([8], p. 54) on the assumption that as a result of the rearrangement the product of the Perkow reaction – a 10-acetyl-2-(dialkoxyphosphinyloxyvinyl)phenothiazine – is formed

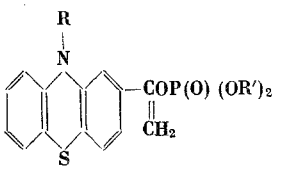


To confirm this hypothesis, 10-acetyl-2-(diethoxyphosphinyloxyvinyl)phenothiazine was chlorinated. The IR spectrum of the chlorination product did not contain the absorption band of a $\rangle C=CH_2$ group at 1632 cm^{-1} (Fig. 1c). The results of elementary analysis show that the chlorination of the phenothiazine nucleus takes place, besides the addition of chlorine to the double bond of the vinyl group



The position of the chlorine atoms in the phenothiazine nucleus was not established. The results of the acid hydrolysis of compounds 1, 2, and 4 (Table 2) also confirmed the structure of the vinyl compound

TABLE 3



Compound No.	R	R′	Mp, °C	Found, %				Calculated, %				Yield, %
				C	H	P	N	C	H	P	N	
1	H	CH_3	101—102	—	—	8,90	4,08	—	—	8,86	4,01	27
2	H	C_2H_5	96—97	—	—	8,10	3,70	—	—	8,24	3,72	39
3	H	C_3H_7	—	59,69	6,00	7,91	3,09	59,27	5,93	7,65	3,46	45
4	H	i-C_4H_9	—	61,64	6,90	7,37	2,97	60,97	6,46	7,15	3,24	61
5	$COCH_2P(O)(OC_2H_5)_2$	C_2H_5	—	51,74	5,62	11,35	—	51,91	5,58	11,15	—	86
6	$COCH_2P(O)(OC_4H_9)_2$	C_4H_9	—	57,07	7,12	8,82	—	57,59	7,05	9,28	—	78

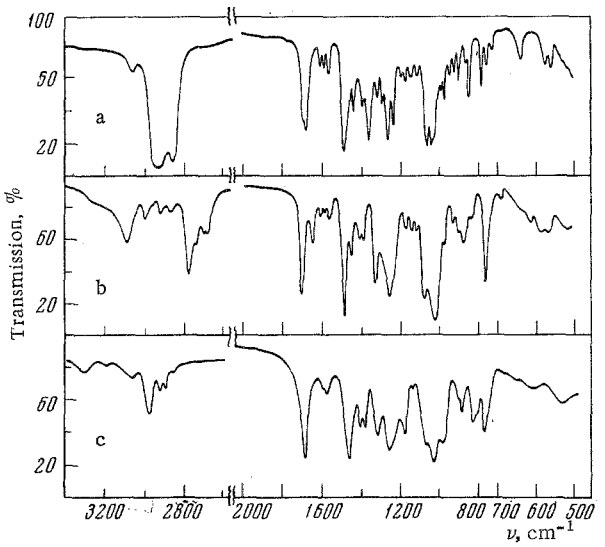
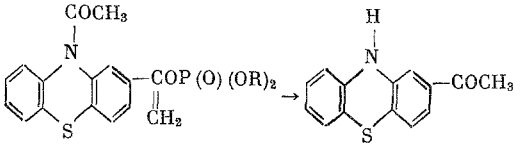


Fig. 1. IR spectra of phosphorylated phenothiazines: a) 2-acetyl-10-(diisobutoxyphosphinylacetyl)phenothiazine; b) 10-acetyl-2-(dipropoxyphosphinyloxyvinyl)phenothiazine; c) product of the chlorination of the vinyl phosphate derivative.



The hydrolysis reaction was carried out by heating the substance under investigation under reflux in a mixture of hydrochloric and acetic acids. Under these conditions an acetyl group at position 10 is split off [9]. The 2-acetylphenothiazine obtained was identified by analysis, and by literature [10] and spectral data. A mixed sample gave no depression of the melting point.

In order to determine the degree of biologic activity as a function of the position and number of the dialkoxyphosphinyl groups, we obtained the products of the rearrangement of trialkyl phosphites with 2-(chloroacetyl)phenothiazine and 2,10-bis(chloroacetyl)phenothiazine. It was found that in these cases, also, the formation of vinyl derivatives takes place at position 2 of the phenothiazine. The structure of the compounds was shown by hydrolysis and was confirmed by IR spectroscopy (Fig. 2) with $\nu_{C=C}$ 1632 and 1635 cm^{-1} and $\nu_{C=O}$ 1680 cm^{-1}. The compounds obtained are given in Table 3.

Preliminary results of tests of physiologic activity [on the larvae of midges (Chironomidae)] showed that the phenothiazine derivatives phosphorylated in position 10 had comparable larvicidal activities regardless of the presence of other, including phosphorus-containing, substituents. The larvicidal activity of the phenothiazines phosphorylated only in position 2 was insignificant.

EXPERIMENTAL

2-Acetyl-10-(diethoxyphosphinylacetyl)phenothiazine. A flask for vacuum distillation was charged with 3.6 g of 2-acetyl-10-bromoacetylphenothiazine together with a few drops of triethyl phosphite and then the mixture was heated until it fused. Over 15 min, triethyl phosphite to a total amount of 2.1 g was added to the melt obtained through a dropping funnel drawn out into a capillary in a vacuum of 100 mm Hg. After all the phosphite had been added, the vacuum was switched off and the temperature was raised to 160-165° and kept there for another hour. The mass was poured rapidly into a dish, where it crystallized in the course of a day. Recrystallization from gasoline (bp 100-130°) gave 3.2 g (76%) of yellow crystals, mp 160-161°.

The other compounds given in Tables 1-3 were obtained similarly.

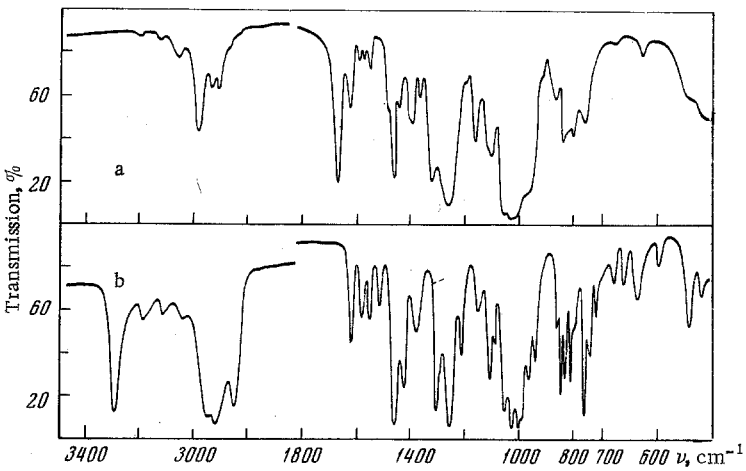


Fig. 2. IR spectra: a) 10-(dibutoxyphosphinylacetyl)-2-(dibutoxyphosphinyloxyvinyl)phenothiazine; b) 2-(diethoxyphosphinyloxyvinyl)phenothiazine.

Hydrolysis of 10-Acetyl-2-(diethoxyphosphinyloxyvinyl)phenothiazine. A solution of 2.8 g of the substance in a mixture of 20 ml of glacial CH_3COOH and 5 ml of 20% HCl was boiled under reflux for 15 min. After cooling, 1.3 g (81%) of 2-acetylphenothiazine was obtained in the form of lustrous yellow crystals with mp 186°. According to the literature [10], mp 191°. A mixture of the product with authentic 2-acetylphenothiazine gave no depression of the melting point. Found: C 68.87; H 4.67%. $C_{14}H_{11}NOS$. Calculated: C 69.79; H 4.55%.

Similarly, 1.2 g of 10-acetyl-2-(diisopropoxyphosphinyloxyvinyl)phenothiazine and of 10-acetyl-2-(dimethoxyphosphinyloxyvinyl)phenothiazine gave, respectively, 78 and 73% of 2-acetylphenothiazine with mp 186-187°.

A sample of the vinyl phosphate derivative was dissolved in CCl_4. A current of gaseous chlorine was passed into the solution with ice-water cooling and with stirring until the solution, from which a precipitate had deposited at the beginning of the passage of chlorine, had become clear again. After the solvent had been driven off in vacuum, the product obtained consisted of a cherry-red liquid.

CONCLUSIONS

1. Previously-undescribed 2-acetyl-10-(dialkoxyphosphinylacetyl)phenothiazines, 10-acetyl-2-(dialkoxyphosphinyloxyvinyl)phenothiazines, 2-(dialkoxyphosphinyloxyvinyl)phenothiazines, and 10-(dialkoxyphosphinylacetyl)-2-(dialkoxyphosphinyloxyvinyl)phenothiazines have been synthesized.

2. The reaction of 2-chloroacetyl-10-R-phenothiazines with trialkyl phosphites takes place in the manner of a Perkow rearrangement.

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