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Aromatic Phosphoryl Thiocholines. II*. Syntheses and Physicochemical Properties

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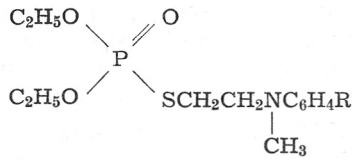
The synthesis of seven undescribed *O*-ethyl-*S*-[(2-*N*-methyl--*N*-arylamino)ethyl] methylphosphonothioates (compounds I—VII) and their methosulphates (compounds VIII—XIV) is presented together with their physicochemical characteristics.

From *N*,*N*-dimethylarylamines were prepared *N*-methyl-*N*--(2-hydroxyethyl)arylamines which with phosphorus oxychloride gave the corresponding *N*-methyl,*N*-(2-chloroethyl)arylamines. By reacting them with sodium *O*-ethyl methylphosphonothioate the substances I—VII were obtained. The substances VIII—XIV were obtained by quaternization of substance I—VII with dimethylsulphate.

As intermediate products the following new compounds were synthetized: *N*-methyl- *N*-(2-hydroxyethyl)*m*-methoxyphenylamine, *N*-methyl- *N*-(2-hydroxyethyl)*p*-methoxyphenylamine, *N*-methyl-*N*-(2-chloroethyl)*m*-methoxyphenylamine and *N*-methyl- *N*-(2--chloroethyl)*p*-methoxyphenylamine.

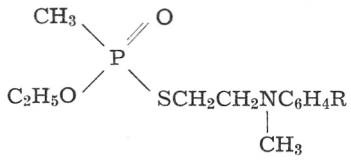
During the last years several representatives of a new group of biologically active aromatic phosphorylthioethylalkylaryl amines have been described. Kabachnik *et al.*[1] synthetized *O*,*O*-diethyl[*S*-(2-*N*-methyl-*N*-arylamino)ethyl] thiophosphorothioates:



with R = H, —CH_3, —OCH_3, —Cl in *p* and *m* position and their methosulphates. Studying the kinetics of their alkaline hydrolysis, the authors[1] found these compounds to be very stable, the tertiary compounds being more stable than the quaternary ones. Brestkin *et al.*[2] studied the kinetics of cholinesterase inhibition, and at the same time focussed their attention upon the influence of the aryl radical on the biological properties of these compounds.

For that reason it was of interest to synthetize the derivatives of the phosphonic acid corresponding to the general formula:

* Part I: ref. 3.



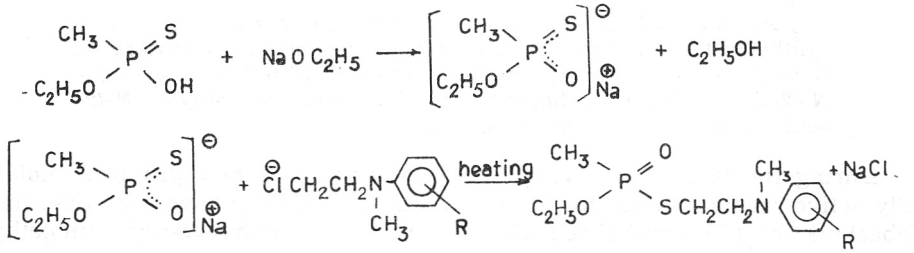
with R = H, $—CH_3$, $—OCH_3$, —Cl in *m* and *p* position and the methosulphate of their dimethylammonium analogues in order to learn how the quaternization of the nitrogen atom, aromatic nuclei and the position of different ring substituents influence their biological activity.[3]

The starting material *O*-ethyl methylthiophosphonic acid was synthetized by the method of Pelchovicz and coworkers.[4] The *N*-methyl *N*-(2-hydroxyethyl)-arylamines were prepared by the method of Naguski and Yosimoto[5] used for the synthesis of the unsubstituted *N*-methyl *N*-(2-hydroxyethyl)phenylamine:

$$(CH_3)_2NC_6H_4R + ClCH_2CH_2OH \xrightarrow{\text{heating}} HOCH_2CH_2NC_6H_4R + CH_3Cl$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

The corresponding N-methyl-N-(2-chloroethyl)arylamines were obtained by the reaction of $POCl_3$ with the above mentioned hydroxy compounds[6].

The syntheses of *O*-ethyl *S*-[(2-*N*-methyl-*N*-arylamino)ethyl]methylphosphonothioates were performed by reacting sodium *O*-ethyl methylphosphonothioate and corresponding *N*-methyl-(2-chloroethyl) arylamines:



Under the conditions mentioned the reaction is a bimolecular nucleophilic substitution (S_N2) in which the nucleophile is the sulphur atom of the sodium *O*-ethyl methylphosphonothioate[7]. In the syntheses of *O*-ethyl *S*-[(2-*N*-methyl--*N*-arylamino)ethyl]methylphosphonothioates the *S*-alkylated products were always obtained because the reaction was performed with a weak electrophile in a protonated solvent which does favor *S*-alkylation. *O*-Ethyl *S*-[(2-*N*,*N*--dimethylarylammonium)ethyl]methyl phosphonothioate methosulphates were prepared by methylating the corresponding tertiary compounds with the equimolecular quantity of dimethylsulphate using the method of Volkova *et al.*[8]

In relation to the analogous thiocholine compounds with alkyl groups on the nitrogen atom[9], the syntheses of the described tertiary compounds and the methylation process are of longer duration. Probably this can be attributed to the presence of the aromatic radical on the nitrogen atom, which slows down the described reactions by enhancing the thermochemical stability. Resonance effects from the aromatic ring are likely to cause the diminished reactivity of the described aromatic compounds in relation to the corresponding aliphatic ones.

EXPERIMENTAL

O-Ethyl methylthiophosphonic acid was obtained in 70% yield from methylthiophosphonic dichloride, ethanol and potassium hydroxyde[4] as yellowish oil b. p. 80 °C (0.3 mmHg), $n_D^{25} = 1.4910$ [lit.[4] 87—93 (0.55 mmHg); $n_D^{28} = 1.4927$].

N-*Methyl*,N-*(2-hydroxyethyl)-arylamines*[5]

The mixture of *N,N*-dimethylalkylarylamine (2 mol) and ethylenechlorhydrine (2 mol) was refluxed for 5—15 h under constant stirring at 190—200 °C until no more methyl chloride was formed. The reaction time was dependent on the ring substituent. The described products were isolated from the reaction mixture by fractionated vacuum distiliation. In this manner *N*-methyl,*N*-(2-hydroxyethyl)-phenylamine and the corresponding *m*-methyl, *p*-methyl, *m*-chloro, and *p*-chloro phenylamines were prepared.

N-*Methyl*,N-*(2-hydroxyethyl)*-m-*methoxyphenylamine.* — The mixture of *N,N*--dimethyl-*m*-methoxyphenylamine (2 mol) and ethylenechlorhydrine (2 mol) was refluxed for 15 h at 200 °C. After vacuum distillation the yellowish oil with a b. p. 100—106 °C (0.08 mmHg), $n_D^{20} = 1.5620$, was obtained in 70% yield.

Anal. $C_{10}H_{15}NO_2$ (181.24) calc'd.: C 66.28; H 8.34; N 7.70%
found: C 66.48; H 8.24; N 7.36%

N-*Methyl*,N-*(2-hydroxyethyl)* p-*methoxyphenylamine.* — *N,N*-Dimethyl-*p*-methoxyphenylamine (2 mol) was added to ethylenechlorhydrine (2 mol) and the mixture was refluxed for 12 h at 195 °C. After vacuum distillation the yellowish oil with a b. p. 160—161° (0.1 mmHg), $n_D^{20} = 1.5560$, was obtained in 70% yield.

Anal. $C_{10}H_{15}NO_2$ (181.24) calc'd.: C 66.28; H 8.34; N 7.70%
found: C 66.50; H 8.20; N 7.30%

N-*Methyl*,N-*(2-chloroethyl)-arylamines*[6]

Corresponding *N*-methyl-*N*-(2-hydroxyethyl)-arylamine (1.3 mol) was dissolved in 200 ml of dried benzene in a 500 ml flask and, phosphorus oxychloride (0.65 mol) added drop by drop at 15 °C. The reaction mixture was then heated for 1 h in a water bath at 80 °C, cooled to room temperature and poured into cooled water (500 ml). Under continuous cooling a 10% sodium hydroxide solution was then added (to pH = 7.5). The separated oil layer was extracted twice with benzene (100 ml) and the extract kept overnight on anhydrous sodium sulphate. After filtration the benzene was evaporated and the remainder distilled in vacuum. In this manner *N*-methyl,*N*-(2-chloroethyl)-phenyl amine and the corresponding *m*-methyl, — *m*--chloro, *p*-methyl and *p*-chlorophenyl amines were prepared.

N-*Methyl*,N-*(2-chloroethyl)* m-*methoxyphenylamine.* — After vacuum distillation a clear oil, b. p. 110—12 °C (0.13 mmHg), $n_D^{20} = 1.5590$ in 48% yield was obtained.

Anal. $C_{10}H_{14}ClNO$ (199.69) calc'd.: C 60.04; H 7.01; N 7.02%
found: C 60.24; H 6.83; N 6.95%

N-*Methyl*,N-*(2-chloroethyl)* p-*methoxyphenylamine.* — A clear oil, b. p. 122—5 °C (1.5 mmHg), $n_D^{20} = 1.5540$ in 62% yield was obtained.

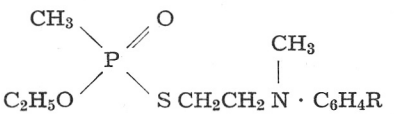
Anal. $C_{10}H_{14}ClNO$ (199.69) calc'd.: C 60.04; H 7.01; N 7.02%
found: C 59.80; H 7.01; N 7.00%

O-*Ethyl* S-*[(2-*N-*methyl*,N-*arylamino)ethyl]methyl phosphonothioates (I—VII)*

In a 250 ml flask fitted with a mechanical stirrer, condenser, dropping funnel and thermometer *O*-ethyl methylthiophosphonic acid (0.2 mol) was placed, and under constant stirring a 5% solution of sodium in anhydrous ethanol was added drop by drop until a phenolphtalein colour change. Corresponding *N*-methyl-*N*-(2--chloroethyl) arylamine (0.2 mol) was added drop by drop at 40—50 °C under

TABLE I

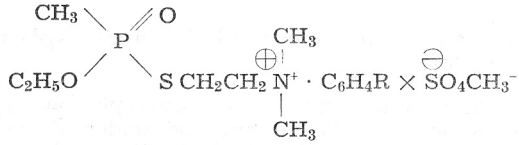
O-*Ethyl* *S*-[2-N-*methyl*,N-*arylamino*)*ethyl*] *methylphosphonotioates*



No.	R	b. p./°C (*p*/mmHg)	n_D^{25}	d_4^{25}	MR_D		YIELD %	Calc'd				Found			
					calc.	found		C	H	N	P	C	H	N	P
I	H	162 (8×10^{-2})	1.5590	1.1430	76.94	77.35	48	52.23	7.40	5.13	11.25	52.43	7.60	5.40	10.95
II	*m*-CH_3	150 (10^{-3})	1.5550	1.1136	82.55	82.56	50	54.33	7.71	4.87	10.78	54.55	7.93	4.62	10.68
III	*p*-CH_3	148 (10^{-3})	1.5535	1.1241	82.55	81.95	57					54.07	7.88	4.37	10.38
IV	*m*-OCH_3	165—8 (10^{-3})	1.5603	1.1576	84.11	84.75	36	51.47	7.31	4.60	10.21	51.22	7.22	4.25	9.92
V	*p*-OCH_3	170—5 (10^{-3})	1.5570	1.1556	84.11	84.50	35					51.35	7.41	4.34	10.05
VI	*m*-Cl	160—5 (10^{-3})	1.5707	1.2176	82.64	82.94	21	46.83	6.22	4.55	10.06	46.70	6.21	4.42	9.98
VII	*p*-Cl	160—3 (10^{-3})	1.5695	1.2256	82.64	82.29	35					46.65	6.09	4.58	9.82

TABLE II

O-*Ethyl* S-[2-N,N-*dimethylarylammonium)ethyl]methylphosphonothioate methosulphate*



No.	R	YIELD %	Calc'd.				Found			
			C	H	N	P	C	H	N	P
VIII			42.10	6.56	3.81	7.76	42.33	6.67	3.87	7.58
IX	*m*-CH_3	85	43.50	6.83	3.38	7.49	43.05	7.07	3.29	7.19
X	*p*-CH_3	78					43.70	6.99	3.05	7.46
XI	*m*-OCH_3	70	41.70	6.57	3.25	9.25	41.35	6.68	3.00	9.07
XII	*p*-OCH_3	73					41.50	6.87	3.05	9.21
XIII	*m*-Cl	47	38.74	5.81	3.22	7.13	38.38	5.53	3.15	6.90
XIV	*p*-Cl*	69					38.44	5.66	3.32	7.26

* m. p. 114 °C.

continuous stirring, and heated and stirred at 70—80 °C for additional 8—14 h. The sodium chloride which separates during the reaction was filtered off and ethanol evaporated from the filtrate. The residual oil was washed with water and separated. The water layer was added to the rest of the crude product. The mixture was dried overnight on anhydrous sodium sulphate. After filtration, benzene was evaporated *in vacuo* and the oily residue was redistilled in high vacuum. The data for compounds I—VII are summarized in Table I.

Infrared spectra of compounds I—VII show characteristic absorption maxima which correspond to the vibrations between phosphorus and neighboring atoms: 1220—1245 (P=O); 775—780 of low intensity (P—O); 1030—1040 (P—O—CH_2); 735—745 (P—C); 530—540 (P—S); 1300—1305 (P—CH_3); ~ 1160 and 960 of low intensity (P—OCH_2); 900 and 880—885 cm^{-1} (P—CH_3 »rocking«). As well as these absorption bands in the spectra, there exist other vibration bands characterizing the type and position of substituents in the benzene ring. The unsubstituted derivative absorbs at 690 and 755 cm^{-1}, the *m*-substituted at 750—775 cm^{-1} and the *p*-substituted at 810—820 cm^{-1}.

The NMR spectra of the compounds I—VII are characterized by the fact that the common part of the molecule gave similar spectra (shape and position of the signals). So the P—CH_3 in all the spectra in the region $\tau = 8.30$—8.42 gave a doublet (because of coupling with phosphorus, $J_{HP} = 16$ Hz), the CH_3 from the ethoxy group gave a triplet $\tau = 8.60$—8.78), the CH_2 group from the ethoxy group gave a multiplet because of coupling with the CH_3 group and phosphorus ($\tau = 5.6$—6.3), with a center at $\tau = 6.0$. The S—CH_2 gave an unresolved multiplet ($\tau = 6.6$—7.5) with a center at $\tau = 7.2$, the N—CH_2 gave also a multiplet ($\tau = 6.2$—6.7) with a center at $\tau = 6.6$. The position of the N—CH_3 singlet depends on the kind of benzene ring substituent. The protons of the benzene ring gave characteristic resonance signals, the shape of the signal depends on the substituent position. The multiplet of *p*-substituted

compounds is a symmetrical AA'BB' quartet and the *m*-substituted compounds gave an unsymmetrical signal.

The compounds I—VII are colorless or yellowish liquids with a high boiling point. They are soluble in most organic solvents and practically insoluble in water.

O-Ethyl S-[(2-N,N-dimethylarylammonium)ethyl]methyl-phosphonothioate methosulphates (VIII—XIV)

O-Ethyl *S*-[(2-*N*-methyl-*N*-arylamino)ethyl]methyl phosphonothioate (0.2 mol) was dissolved in anhydrous benzene (25—30 ml) and under stirring, freshly distilled dimethyl sulphate (0.02 mol) was added. The reaction ended and the two layers separated during this operation. The solvent was decanted and the operation repeated pressure (18 mm Hg) and the residue was dissolved in abs. ethanol (10—15 ml) or abs. chloroform. To the solution, dried ether (100—150 ml) was added and a dense oil separated during this operation. The solvent was decented and the operation repeated three times. The solvent was then evaporated in vacuo. The last residues of the solvents disappeared by heating the oily or crystalline substance for 3 h in vacuo (0.05—1 mmHg) at 50—60 °C. The data for compounds VIII—XIV are given in Table II.

The IR spectra of the compounds VIII—XIV have three very intensive and large vibration bands: 1230 (P=O), 1030 (P—O—CH_2), and 750—770 (P—C) cm^{-1} which prove that these links become more strongly polarized because of the quaternization. The other bands are of diminished intensity.

The NMR spectra of the compounds VIII—XIV differ from those of the compounds I—VII insofar that the singlet corresponding to the NCH_3 group is shifted to a lower magnetic field corresponding by its intensity to $N^+(CH_3)_3$. At a somewhat higher magnetic field of this singlet there appeared a singlet which is characteristic for the CH_3 group from $CH_3SO_4^-$.

The compounds VIII—XIV are very dense oils excluding the compound XIV which is crystalline. Because of their high polarity all of them dissolve well in water and are insoluble in nonpolar organic solvents.

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IZVOD

Aromatski fosforiltioholini. II. Sinteza i fizikalno-kemijske osobine

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Opisana je sinteza sedam dosad neopisanih *O*-etil-*S*-(2-metil-*N*-arilamino)etil metiltiofosfonata (spojevi I—VII) i njihovih metosulfata(spojevi VIII—XIV) i prikazane njihove fizikalno-kemijske karakteristike.

Iz *N*,*N*-dimetilarilamina pripremljeni su *N*-metil- *N*-(2-hidroksietil)arilamini koji sa $POCl_3$ daju odgovarajuće *N*-metil- *N*-(2-kloretil)arilamine koji reakcijom sa natrijumovom soli *O*-etilmetiltiofosfonske kiseline daju supstance I—VII. Njihovom kvaternizacijom dimetilsulfatom dobijaju se spojevi VIII—XIV.

U toku ovih sinteza pripravljeni su još i ovi dosada neopisani spojevi: *N*-metil-*N*-(2-hidroksietil) *m*-metoksifenilamin, *N*-metil- *N*-(2-hidroksietil)*p*-metoksifenilamin, *N*-metil- *N*-(2-kloretil)*m*-metoksifenilamin i *N*-metil-*N*-(2-kloretil)*p*-metoksifenilamin.

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