

Phosphorylated isothiureas. III.

Preparation and properties of phosphorylated isothiureas

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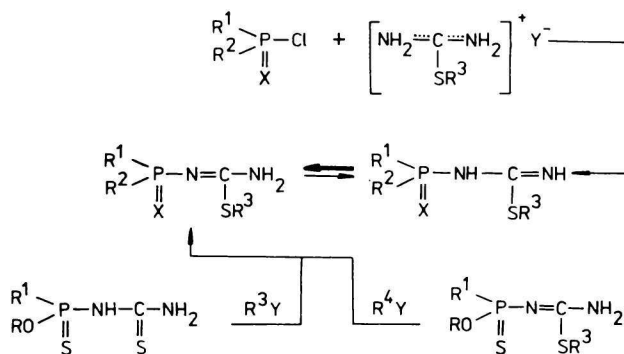
The synthesis of trisubstituted phosphorylated isothiureas by the reaction of *O*-alkyl *S*-alkyl phosphorochloridothioate, dipropyl phosphorochloridothioate, *O*-methyl *N,N*-dimethylamidophosphorochloridothioate, *O*-alkyl *N*-alkylamidophosphorochloridothioate, and *O*-alkyl alkylphosphonochloridothioate with thiouronium salts in the presence of different agents binding hydrogen halide or by treatment of *O,O*-dialkyl thionophosphoryl-*S*-alkylisothiurea, and *O,O*-dialkyl thionophosphorylisothiurea, respectively with alkyl iodides is described. The i.r., u.v., and ¹H-n.m.r. spectra as well as pesticidal activities of the synthesized compounds are discussed.

Описывается синтез трехзамещенных фосфорилированных изотиомочевин по реакции *O,S*-диалкилхлортиофосфата, дипропилхлортритиофосфата, *O,N,N*-триметиламидохлортиофосфата, *O,N*-диалкиламидохлортиофосфатов и *O,P*-диалкилхлортиофосфонатов с тиоуроновыми солями в присутствии различных реагентов, связывающих галогенводород, или при действии алкилиодидов на *O,O*-диалкилтиофосфорил-*S*-алкилизотиомочевины или *O,O*-диалкилтиофосфорилизотиомочевины. В работе приводятся и обсуждаются ИК, УФ и ¹Н-ЯМР спектры и пестицидное действие синтезированных соединений.

Synthesis, properties, and structures of *N*-(*O,O*-dialkyl thiophosphoryl)-*S*-alkyl(aralkyl)isothiureas and *N*-(*O,O*-dialkyl and diphenyl phosphoryl)-*S*-alkyl(aralkyl)isothiureas were described in our previous works [1, 2]. Cramer and Vollmar [3] described the preparation of some *N*-(*O,O*-diaryl phosphoryl)-*S*-methyl(ethyl)isothiureas by the reaction of *O,O*-diaryl chlorophosphates with methylthiuronium sulfate and ethylthiuronium bromide, respectively in the heterogeneous mixture of benzene—water in the presence of sodium hydroxide. Melnikov and coworkers [4] prepared *N*-(*O*-alkyl *N'*-alkylamidothiophospho-

ryl)-*S*-alkylisothioureases by the reaction of *O*-alkyl *N*-alkylamidochlorothiophosphates with alkylthiuronium salts in benzene in the presence of triethylamine under reflux, however, they reported different C=N bond position.

The aim of the present work was to find out suitable methods for the preparation of the studied compounds, to investigate their physicochemical properties, to enlighten their structures, mainly the position of the C=N bond, and to test these compounds for pesticidal activity. As seen from Scheme 1, various methods were chosen to synthesize the compounds presented in Table 1. Some compounds were prepared by two different methods.



Scheme 1

Experimental

O-Isopropyl *S*-ethyl phosphorochloridothioate and *O*-ethyl *S*-isopropyl phosphorochloridothioate were prepared by reaction of phosphorus trichloride with 2-propanol and ethanol, respectively, resulting in the appropriate diisopropyl chlorophosphite and diethyl chlorophosphite which were treated with ethylsulenyl chloride and isopropylsulenyl chloride, respectively [5–7]. Dipropyl phosphorochloridotriphosphite was prepared by the reaction of thiophosphoryl chloride with propanethiol in the presence of triethylamine in benzene [8]. *O*-Alkyl ethylphosphonochloridothioates were prepared by the reaction of ethyldichlorothiophosphonate with the appropriate alcohol in benzene in the presence of triethylamine [9]. *O*-Alkyl *N*-alkylamidophosphorochloridothioates were prepared from one equivalent of *O*-alkyl phosphorodichloridothioate with two equivalents of the appropriate amine in methylene chloride [10]. Thiuronium salts were prepared by the reaction of thiourea with the appropriate alkyl halides [11] or with dimethyl sulfate in ethanol [12]. *N*-(*O,O*-Diethyl thiophosphoryl)thiourea was prepared by the reaction of *O,O*-diethyl thiophosphoryl isothiocyanate [13, 14] with gaseous ammonia [15].

Data of elemental analysis, yields, reaction conditions, R_f , n_D^{20} , and m.p. values are presented in Table 1. The i.r. spectra of the studied compounds were measured on UR-20

and IR-71 Zeiss spectrophotometers in carbon tetrachloride (Table 2) and chloroform. The instruments were calibrated with polystyrene foil and the reading accuracy was $\pm 1 \text{ cm}^{-1}$. The u.v. spectra were taken with a Unicam SP 8000 spectrophotometer ($d = 1 \text{ cm}$, $c = 10^{-4}$ — 10^{-5} M) in methanol. The ^1H -n.m.r. spectra were measured on a Tesla BS 487 C apparatus (80 MHz) in CDCl_3 (99.5% D-isotope) at 25°C using TMS and HMDS as internal standards. The chemical shifts were calculated with regard to TMS.

The purity of compounds and the course of reactions were followed by t.l.c. (Silufol R UV 254 Kavalier with luminescent indicator and Silufol R Kavalier without indicator). The eluents are presented in Table 1. The compounds were detected with u.v. light (254 nm) and by spraying the plates with 0.5% DQC (2,6-dibromo-4-chloroimidoquinone) in petroleum ether and heating for 2—5 min at 120°C . The liquid compounds were purified by column chromatography on Silica gel L (100/160 mesh, Lachema, Brno). Mixtures of benzene and acetone or chloroform and acetone were used as eluting agents (the amounts of acetone increased from 0 to 30%).

The pesticidal activity was followed at the conditions reported in our previous work [1] using the methods published in [16, 17].

Substituted isothiureas (I—XV)

Method A

The reaction mixture of *N*-(*O,O*-diethyl thiophosphoryl)thiourea (0.05 mol) and alkyl iodide (0.5 mol) was heated to reflux under stirring and kept at this temperature until the starting compound disappeared from the solution. The reaction course was followed by t.l.c. At the end of the reaction alkyl iodide was distilled off under reduced pressure and the product was purified by column chromatography.

Method B

The reaction mixture of *N*-(*O,O*-dialkyl thiophosphoryl)-*S*-alkylisothiurea (0.02 mol) and alkyl iodide (0.2 mol) was worked up similarly as in the previous case.

Method C

Into the reaction mixture of *O*-isopropyl *S*-ethyl phosphorochloridothioate (0.05 mol), thiuronium salt (0.05 mol), potassium carbonate (0.05 mol), and acetonitrile (100 ml), water (50 ml) was added under stirring. Stirring was continued at laboratory temperature and the reaction was followed by t.l.c. The product was extracted with chloroform ($2 \times 50 \text{ ml}$) and dried and the solvent was distilled off under reduced pressure.

Method D

The reaction mixture of the appropriate *O*-alkyl alkylphosphonochloridothioate, *O*-alkyl *N*-alkylamidophosphorochloridothioate, dipropyl phosphorochloridothioate, and

Table 1. Characterization of the synthesized compounds

Compound	R ¹	R ²	R ³	X	Formula	M	Calculated/found			Yield, % Method of preparation	Reaction time, h T, °C	n_D^{20} M. p., °C Solvent	T.l.c. R _f
							% N	% P	% S				
I	C ₂ H ₅ O	C ₂ H ₅ S	C ₂ H ₅	O	C ₇ H ₁₇ N ₂ O ₂ PS ₂	256.34	10.94	12.09	25.05	28.9 A	13	1.5383	0.40 ^a
							10.71	12.43	25.40		72		0.01 ^b 0.52 ^c
II	C ₂ H ₅ O	C ₂ H ₅ S	PhCH ₂	O	C ₁₂ H ₁₉ N ₂ O ₂ PS ₂	318.41	8.80	9.73	20.01	45.5 B	22	1.5840	0.41 ^a
							9.10	9.53	20.51		72		0.01 ^b 0.54 ^c
III	C ₂ H ₅ O	iC ₃ H ₇ S	iC ₃ H ₇	O	C ₉ H ₂₁ N ₂ O ₂ PS ₂	284.39	9.85	10.89	22.55	27.1 A	7.5	1.5249	0.13 ^a
							9.63	10.70	22.91		100		0.03 ^b 0.53 ^c
IV	iC ₃ H ₇ O	C ₂ H ₅ S	CH ₃	O	C ₇ H ₁₇ N ₂ O ₂ PS ₂	256.34	10.39	12.07	25.05	60.6 C	11	67.5—69 Heptane	0.14 ^a
							11.06	11.93	25.4		18		0 ^b 0.52 ^c
V	iC ₃ H ₇ O	C ₂ H ₅ S	PhCH ₂	O	C ₁₃ H ₂₁ N ₂ O ₂ PS ₂	332.43	8.43	9.32	19.3	70.6 C	10	1.5736	0.20 ^a
							8.63	9.16	19.45		18		0 ^b 0.32 ^c
VI	C ₂ H ₅ O	C ₄ H ₉ S	PhCH ₂	O	C ₁₄ H ₂₃ N ₂ O ₂ PS ₂	346.46	8.08	8.94	18.5	30 B	12	1.5610	0.38 ^a
							8.30	8.75	18.8		100		0.07 ^b 0.31 ^c
VII	iC ₃ H ₇ O	iC ₃ H ₇ S	C ₂ H ₅ SCH ₂ CH ₂	O	C ₁₁ H ₂₅ N ₂ O ₂ PS ₃	344.57	8.13	8.99	27.92	34.1 B	12	1.5632	0.32 ^a
							8.44	8.61	28.37		100		0.02 ^b 0.31 ^c
VIII	C ₃ H ₇ S	C ₃ H ₇ S	PhCH ₂	S	C ₁₄ H ₂₃ N ₂ PS ₄	378.57	7.40	8.18	33.9	83.2 D	16	1.6320	0.34 ^b
							7.29	7.88	34.6		81		0.40 ^d 0.12 ^e
IX	CH ₃ O	(CH ₃) ₂ N	PhCH ₂	S	C ₁₁ H ₁₁ N ₃ OPS ₂	303.40	13.85	10.21	21.1	49.5 D	10	1.6139	0.12 ^b
							13.41	9.93	21.48		81		0.18 ^d 0.12 ^e

Table 1 (Continued)

Compound	R ¹	R ²	R ³	X	Formula	M	Calculated/found			Yield, % Method of preparation	Reaction time, h T, °C	n _D ²⁰ M.p., °C Solvent	T.l.c. R _f
							% N	% P	% S				
X	C ₂ H ₅ O	iC ₃ H ₇ NH	PhCH ₂	S	C ₁₃ H ₂₂ N ₃ OPS ₂	331.42	12.68	9.35	19.35	77.9 D	16	1.5700	0.15 ^b
							12.42	9.84	18.9		81		0.24 ^d
													0.25 ^e
XI	iC ₃ H ₇ O	iC ₃ H ₇ NH	PhCH ₂	S	C ₁₄ H ₂₄ N ₃ OPS ₂	345.45	12.18	8.97	18.57	67.9 D	18	1.5696	0.13 ^b
							12.25	8.64	18.1		81		0.19 ^d
													0.15 ^e
XII	CH ₃ O	C ₂ H ₅	PhCH ₂	S	C ₁₁ H ₁₇ N ₂ OPS ₂	288.38	9.72	10.73	22.24	78.8 D	7	1.6154	0.13 ^b
							10.08	10.92	22.7		81		0.27 ^d
													0.14 ^e
XIII	C ₂ H ₅ O	C ₂ H ₅	PhCH ₂	S	C ₁₂ H ₁₉ N ₂ OPS ₂	302.41	9.25	10.23	21.2	64.4 D	6.5	1.5869	0.25 ^b
							8.96	9.93	20.6		90		0.36 ^d
													0.36 ^e
XIV	iC ₃ H ₇ O	C ₂ H ₅	PhCH ₂	S	C ₁₃ H ₂₁ N ₂ OPS ₂	316.43	8.95	9.78	20.24	71.5 D	16	1.5740	0.27 ^b
							9.09	10.1	20.6		81		0.37 ^d
													0.40 ^e
XV	iC ₄ H ₉ O	C ₂ H ₅	PhCH ₂	S	C ₁₄ H ₂₃ N ₂ OPS ₂	330.45	8.48	9.38	19.4	81.5 D	14	1.5763	0.27 ^b
							8.09	9.81	19.9		81		0.38 ^d
													0.42 ^e

Mobile phase: *a*) CHCl₃: C₂H₅OH (95:5); *b*) benzene; *c*) petroleum ether: acetone (7:3); *d*) petroleum ether: acetone (9:1); *e*) chloroform (dried).

Compounds *I*, *II* prepared in C₂H₅I; *III*, *VII* in iC₃H₇I; *IV*, *V* in CH₃CN:H₂O (2:1); *VI* in C₄H₉I; *VIII*—*XII*, *XIV*, *XV* in CH₃CN; *XIII* in CH₃COOC₄H₉.

O-methyl *N,N*-dimethylamidophosphorochloridothioate, respectively (0.1 mol), *S*-benzylthiuronium chloride (0.1 mol), triethylamine (0.2 mol), and acetonitrile (100 ml) was heated to reflux and kept at this temperature until the starting compound disappeared from the solution. The formed triethyl ammonium chloride was filtered off and the filtrate was evaporated under reduced pressure. The obtained products were purified by column chromatography.

Results and discussion

The compounds presented in Table 1 were prepared by some of the methods mentioned above. The lowest yields were obtained by the method *A* where *N*-(*O,O*-diethyl thiophosphoryl)thiourea was treated with alkyl iodides — the most suitable reagents among alkyl halides. It was always necessary to purify the reaction products because they contained a great amount of polymeric compounds of R_f equal to zero in the systems investigated. Somewhat better results were obtained by the method *B* where *N*-(*O,O*-dialkyl thiophosphoryl)-*S*-alkylisothiurea was treated with alkyl iodide, however, the reaction products had to be purified as well. Both reactions belong to the so-called special cases of the Pishchimuka reaction. The kinetics of this reaction at the preparation of *O,S*-dialkyl *N*-alkylamidophosphorothioates and *O,O,S*-trialkyl phosphorothioates was studied by many authors [18–20]. The course of the above-mentioned reactions was easily followed by t.l.c. The isomeric *N*-(*O,S*-dialkyl thiophosphoryl)isothiureas are more polar, therefore their R_f values are lower and also give different colours at detections: with DQC gave yellow spots contrary to the starting *N*-(*O,O*-dialkyl thiophosphoryl)isothiureas which gave brown spots. This difference is due to sulfur bound differently to phosphorus. The thione form ($P=S$) gives brown colour while with the thiol form ($P-S$) yellow colour is obtained [21].

The compounds from the group of *N*-(*O,S*-dialkyl thiophosphoryl)-*S*-alkylisothiureas were prepared in the most pure state and in the highest yields by the method *C*, i.e. by the reaction of *O,S*-dialkyl phosphorochloridothioates with thiuronium salts. The disadvantage of this method is the complicated and difficult synthesis of *O,S*-dialkyl phosphorochloridothioates on a preparative scale.

The most suitable way to prepare *N*-(*O*-methyl *N',N'*-dimethylamidothiophosphoryl), *N*-(*O*-alkyl *N'*-alkylamidothiophosphoryl)-*S*-benzylisothiureas and *N*-(*O*-alkyl *P*-alkylthiophosphonyl)-*S*-benzylisothiureas was found to be the method *D*, i.e. the reaction of amidophosphorochloridothioate or phosphonochloridothioate with *S*-benzylthiuronium chloride in the presence of triethylamine in organic solvent. When these compounds were prepared after the method *C*, it was necessary to prolong the reaction time and increase the temperature because of the lower reactivity of the initial aminophosphorochloridothioates and phos-

Table 2

Infrared spectral data of the studied compounds (in CCl_4)

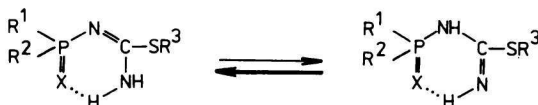
Compound	ν, cm^{-1}						
	$\nu(\text{P}=\text{O})$	$\delta(\text{NH}_2)$	$\nu(\text{C}=\text{N})$	$\nu(=\text{NH})$	$\nu_s(\text{NH}_2)$	$\nu(\text{NH})$	$\nu_{as}(\text{NH}_2)$
<i>I</i>	1206	1557	1621	3204	3276	3357	3475
<i>II</i>	1197	1551	1616	3205	3273	3355	3470
<i>III</i>	1198	1550	1615	3204	3271	3355	3476
<i>IV</i>	1191	1550	1617	3204	3270	3352	3471
<i>V</i>	1195	1549	1614	3204	3269	3360	3471
<i>VII</i>	1194	1551	1615	3204	3270	3358	3471
<i>VIII</i>	—	1560	1625	3195	3255	3340	3464
<i>IX</i>	—	1558	1629	3202	3267	3371	3471
<i>X^a</i>	—	1563	1631	3200	3274	3370	3474
<i>XI^a</i>	—	1558	1627	3199	3267	3380	3471
<i>XII</i>	—	1553	1627	3200	3264	3346	3471
<i>XIII</i>	—	1547	1622	3196	3266	3363	3464

a) $\nu(\text{NH})$ in RNH groups $\sim 3410 \text{ cm}^{-1}$.

phosphorochloridothioates, respectively. This led to decomposition of the products which were obtained in low yields and impure.

In the i.r. spectra of the investigated compounds (Table 2) four bands belonging to vibrations of N—H bonds were observed. The attribution of these bands was proved by the spectra of the compounds *I* and *VIII* measured in CDCl_3 as well as by the spectra of the model compounds used in our previous works [1, 2].

The bands at ~ 3200 and $\sim 3360 \text{ cm}^{-1}$ belong to $\nu(=\text{NH})$ and $\nu(\text{NH})$, while the bands at ~ 3270 and $\sim 3470 \text{ cm}^{-1}$ belong to $\nu_s(\text{NH}_2)$ and $\nu_{as}(\text{NH}_2)$ of the amido groups. The intensity of these bands is much higher than that of the previous bands. This fact indicates that the compounds investigated are mainly in the amido form



The presence of the NH_2 groups in the investigated compounds was indicated by the bands at $\sim 1550 \text{ cm}^{-1}$ (deformation vibrations of —NH_2 groups). In the case of the compounds with an aromatic ring these bands were overlapped by the bands of $\nu(\text{C}=\text{C})$. The spectra of all compounds revealed relatively strong bands at $\sim 1620 \text{ cm}^{-1}$ belonging to $\nu(\text{C}=\text{N})$. In the spectra of the compounds *I—VII* the bands of $\nu(\text{P}=\text{O})$ were observed at $\sim 1200 \text{ cm}^{-1}$.

The ^1H -n.m.r. spectra of the compounds studied showed broad double-proton signals which could be attributed to protons of the $-\text{NH}_2$ groups similarly as with the compounds reported in the previous works [1, 2].

In the u.v. spectra very strong absorption bands were observed in the region of 220–240 nm ($\log \varepsilon = \sim 4.0$) similarly as with the compounds reported in the previous works.

In tests for insecticidal activity on *Musca domestica* L. the compound XIII was found to be the most active, the compound XI showed the highest systemic insecticidal activity on *Macrosiphoniella sanborni* THEOB., and the best contact insecticidal activity on *Aphis fabae* SCOP was obtained with the compounds VIII and XIII. In tests for acaricidal activity on *Tetranychus urticae* KOCH the compound XIII was most active; the highest ovicidal activity on the eggs of *Tetranychus urticae* KOCH was found with the compounds IX, XII, and XIII. However, none of the synthesized compounds showed so high insecticidal activity as the used standards Malathion, Fenitrothion, and Karbofenthion. The studied group of compounds did not exhibit herbicidal and fungicidal activities.

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