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Victoria Lachkova^a; Galin Petrov^a

^a Faculty of Chemistry, University of Sofia, Bulgaria

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INTERACTION BETWEEN PHENYLMETHANEPHOSPHONIC ACID DIETHYL ESTER AND ISOTHIOCYANATES

VICTORIA LACHKOVA and GALIN PETROV

Faculty of Chemistry, University of Sofia, Bulgaria

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Diethyl esters of 1-*N*-substituted thioamido-phenylmethanephosphonic acids are obtained from 0,0-diethyl phenylmethanephosphonate, sodium amide as a metallation agent and alkyl- or arylisothiocyanates. It is established that parallel reactions also occur, resulting in the formation of the respective 1,3-disubstituted thioureas and 0-ethylthiocarbamates. These represent the main reaction products in the cases when ethanephosphonic acid diethyl ester is used as a starting reagent.

Key words: 1-*N*-Substituted thioamido-phenylmethane phosphonic acids diethyl esters; synthesis; biological activity; phenylmethanephosphonates; isothiocyanates; carbamates; 1,3-diphenyl-2-thiourea.

INTRODUCTION

The reaction of $(RO)_2(O)P$ -activated CH-acidic compounds with iso- and isothiocyanates is little investigated in spite of the fact that in this way polyfunctional compounds with interesting properties could be obtained. The interaction of the diethyl esters of cyanomethane- and carbethoxymethanephosphonic acids and phenyliso-, phenylisothiocyanates and derivatives has been studied so far.^{1,2,3}

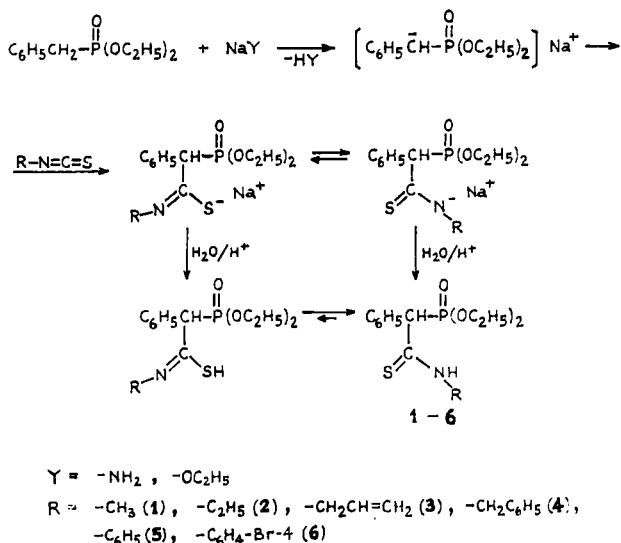
H. Zacharias and W. Mychajlowski⁴ have isolated oily products as a result of the reaction of the same phosphonates with phenyliso- and phenylisothiocyanates. Due to their inability to crystallize, these products were characterized solely by some spectral data.

We investigated the interaction between phenylmethanephosphonic acid diethyl ester and methyl-, ethyl-, allyl-, benzyl-, phenyl- and 4-bromophenylisothiocyanates as well as that of the dimethyl and diethyl esters of ethanephosphonic acid and phenylisothiocyanate in order to obtain *N*-substituted thioamide derivatives and to study the possibilities of the occurrence of parallel reactions. In this way *N*- and *S*-containing organophosphorus compounds with expected physiological activity can be obtained.

RESULTS AND DISCUSSIONS

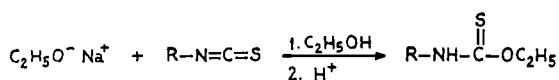
Thioamido-phenylmethanephosphonates should be obtained by nucleophilic addition of carbanions, stabilized by a phosphonic group and an aromatic ring, to

the isothiocyanate according to the following scheme (1):



SCHEME 1.

Addition products 4 (19%) and 5 (24%) as well as *N*-benzyl-, resp. *N*-phenylethylthiocarbamates (62% and 56% resp.) are isolated by metallation of phenylmethanephosphonic acid diethyl ester with sodium ethoxide in ethanol and subsequent reaction with benzyl- or phenylisothiocyanate. Under these conditions a parallel reaction of $\text{C}_2\text{H}_5\text{O}^-$ of the metallation agent with the isothiocyanate can take place, leading to the formation of thiocarbamates (scheme (2)):



SCHEME 2.

It can be concluded that sodium ethoxide in ethanol is unsuitable as a metallation agent for the preparation of the desired thioamide derivatives 1-6.

The interaction according to scheme (1) proceeds better upon metallation of phenylmethanephosphonic acid diethyl ester with sodium amide in liquid ammonia followed by replacement of the latter by anhydrous diethyl ether and subsequent reaction with the corresponding isothiocyanate at room temperature. The increase in the temperature up to the boiling point of diethyl ether for 4 hours does not lead to higher yields of 1-6.

The physical constants, elemental analyses and yields of the obtained diethyl esters of 1-*N*-substituted thioamido-phenylmethane-phosphonic acids 1-6 are presented in Table I, while IR-spectral data are given in Table II. The following signals are observed in the ^1H -NMR spectra (CDCl_3) of the compounds obtained: δ 1-1.5 (t, 3H, CH_3 , J_{HH} 8 Hz), 3.4-4.5 (m, 2H, CH_2 , J_{HH} 6-10 Hz), 4.5-5 (d, 1H, CH, J_{PH} 20 Hz), 7-10 (m, 5H, C_6H_5), 11.1-11.5 (br. 1H, NH).

Physical constants and yields of the

$$\text{C}_6\text{H}_5-\text{CH}-\overset{\overset{\text{O}}{\parallel}}{\text{P}}(\text{OC}_2\text{H}_5)_2$$

$$\text{S}=\text{C}-\text{NH}-\text{R}$$

No.	R =	M.p. °C	Formula (M. W.)	Analysis		$\frac{\text{found}}{\text{calc.}}$ %		Yield %
				C	H	P	N	
1	—CH ₃	132–133	C ₁₃ H ₂₀ NO ₃ PS (301.35)	51.60 51.82	6.21 6.69	9.85 10.28	4.70 4.65	38.7
2	—C ₂ H ₅	139.5–140	C ₁₄ H ₂₂ NO ₃ PS (315.38)	53.54 53.32	6.83 7.03	9.40 9.82	4.55 4.44	41.2
3	—CH ₂ —CH=CH ₂	107–108	C ₁₅ H ₂₂ NO ₃ PS (327.39)	55.28 55.03	6.45 6.77	9.88 9.46	4.23 4.27	42.5
4	—CH ₂ C ₆ H ₅	138–139	C ₁₉ H ₂₄ NO ₃ PS (377.43)	60.10 60.46	6.21 6.41	7.94 8.21	3.82 3.71	39.8
5	—C ₆ H ₅	125–126	C ₁₈ H ₂₂ NO ₃ PS (363.42)	59.55 59.49	5.92 6.10	8.24 8.52	3.79 3.85	48.6
6	—C ₆ H ₄ —Br—4	145–146	C ₁₈ H ₂₁ BrNO ₃ PS (442.33)	49.23 48.88	4.94 4.79	7.32 7.00	3.17 3.17	51.2

For instance, 1,3-diphenylthiourea can be obtained from phenylisothiocyanate as reported by Bamberger⁵ in 1881. The reaction could proceed according to the

IR-spectral data (cm^{-1}) of the compounds of general formula

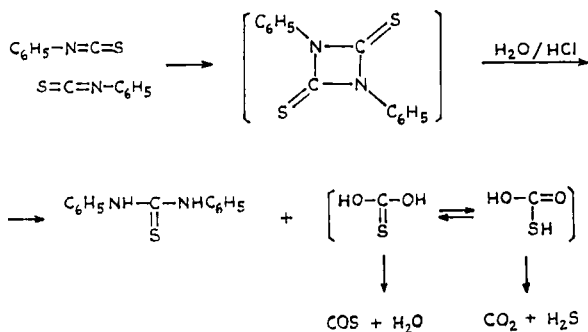
$$\text{C}_6\text{H}_5-\text{CH}-\overset{\overset{\text{O}}{\parallel}}{\text{P}}(\text{OC}_2\text{H}_5)_2$$

$$\quad \quad \quad |$$

$$\quad \quad \quad \text{S}=\text{C}-\text{NH}-\text{R}$$

No.	<i>R</i> =	ν_{POC}	$\nu_{\text{C}=\text{S}}$	$\nu_{\text{P}=\text{O}}$	$\nu_{\text{N}-\text{C}=\text{S}}$	$\nu_{\text{C}_6\text{H}_5}$	$\nu_{\text{N}-\text{H}}$
1	—CH ₃	1030 1050	1210	1230 1250	1565	1500 1600	3215
2	—C ₂ H ₅	1035 1060	1220	1240 1250	1560	1500 1600	3230
3	—CH ₂ —CH=CH ₂	1030 1060	1215	1230 1250	1565	1500 1600	3215
4	—CH ₂ C ₆ H ₅	1015 1040	1210	1230 1255	1550	1500 1600	3220
5	—C ₆ H ₅	1030 1050	1220	1235 1270	1570	1500 1600	3220 3240
6	—C ₆ H ₄ —Br-4	1020 1050	1210	1230 1240	1560	1500 1600	3240

following scheme (3):



SCHEME 3.

It is interesting to note that *N*-phenylethylthiocarbamate is also obtained even when instead of sodium ethoxide, sodium amide in liquid ammonia is used as metallation agent. This fact as well as the interaction of the carbanion and phenylisothiocyanate in anhydrous diethyl ether indicate that a parallel reaction occurs. The possibility of decomposition of the products 1-6 to thiocarbamates can be excluded since under similar reaction conditions these compounds remain unchanged even by refluxing for 3 hours in ethanol.

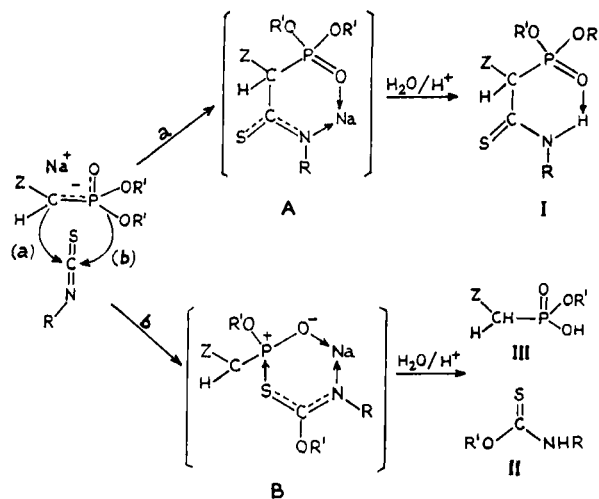
In order to obtain additional data on the parallel reaction leading to the formation of thiocarbamates and to establish the influence of an alkyl group, instead of a phenyl one, in the starting phosphonate, experiments were carried out with ethanephosphonic acid dimethyl, resp. diethyl ester and phenylisothiocyanate under the same reaction conditions. The basic reaction product is *N*-phenylmethyl-, resp. *N*-phenylethylthiocarbamate (yields of 58%-61%). In both cases 1,3-diphenylthiourea is also formed.

In the reaction of phenylmethanephosphonic acid dimethyl ester with phenylisothiocyanate, the presence of *N*-phenylmethylthiocarbamate was proved by TLC.

The results of the interaction of 0,0-dialkoxy-ethanephosphonic or phenylmethanephosphonic acid carbanions and isothiocyanates suggest the possible occurrence of two parallel reactions since in the treatment of the reaction mixtures use is not made of alcohol; the latter and unreacted isothiocyanate would afford the corresponding thiocarbamate.

Most probably these parallel reactions follow the scheme (4):

The existence of intermediates (A) and (B) is established by their IR spectral data in the solid state. A band at 1590 cm^{-1} characteristic of $\text{C}\equiv\text{N}$ in the $\text{N}\equiv\text{C}\equiv\text{S}$ group is observed in the IR spectrum of the intermediate complex (A). The frequency of this band is considerably higher than that of the $\text{N}-\text{C}=\text{S}$ group. A complex band of stretching vibrations of $\text{P}-\text{O}-\text{C}$ is detected within the range $1000\text{--}1100\text{ cm}^{-1}$, at 1130 cm^{-1} a band for $\text{C}=\text{S}$ is observed, and at $1220\text{--}1230\text{ cm}^{-1}$ there is a band for $\text{P}=\text{O}$. The IR spectrum of the intermediate complex (B) reveals an intense band at 1580 cm^{-1} for $\text{C}\equiv\text{N}$ of the $\text{S}\equiv\text{C}\equiv\text{N}$ group, with higher frequency than that of $\text{N}-\text{C}=\text{S}$ in thiocarbamate II. A complex band with four maxima is observed in the range from 1000 to 1200 cm^{-1}



SCHEME 4.

for $C\equiv S$, $P\equiv O$, $C\equiv P$ and $P-O-C$, the latter being at higher frequency as compared to that of the analogous band in the starting phosphonate.

It turns out that the substituent Z in the carbanion of the starting phosphonic acid diester influences substantially the occurrence of the two reactions. In the case of $Z = C_6H_5$, the regioselective reaction in the direction (a) is observed, i.e. nucleophilic attack of the carbanion-like center of the phosphonate reagent to the isothiocyanate, with I as the main reaction product. When $Z = CH_3$, the reaction takes the direction (b) with probable nucleophilic attack of an alkoxide ion at the isothiocyanate and thiocarbamate II is the main product in this case. The probability of such an alkoxide migration is determined by the increased electron density in the phosphonic moiety of the starting phosphonyl reagent due to the +I effect of its CH_3 group.

The product III cannot be isolated since it probably reacts with the isothiocyanate leading to unstable thiocarbamoylphosphonates and pyrophosphonates, as established by F. Lipmann⁶ in the reaction of phosphates with isocyanates.

Physiological activity tests reveal that compounds 1–6 act as growth regulators and herbicides.⁷

EXPERIMENTAL

Melting points are determined on a Boetius hotstage microscope and are uncorrected. The IR spectra are recorded on a Specord 71 IR and 75 IR spectrophotometers. 1H -NMR spectra are measured in $CDCl_3$ with a Tesla-BF 467 C spectrometer at a working frequency of 80 MHz.

The qualitative TLC studies are carried out on Kieselgel 60 F_{254} plates (Merck).

Interaction between phenylmethanephosphonic acid esters and isothiocyanates. General procedure for the synthesis of compounds 1–6. The phenylmethanephosphonic acid dialkyl ester (0.03 mol) is metallated with sodium amide obtained from 0.76 g sodium (0.03 g atom and an excess of 10%) in liquid ammonia (300 cm^3) for 1 hour with subsequent gradual replacement of the ammonia by dry diethyl ether. The reaction mixture is then heated to the boiling point of diethyl ether so as NH_3 to be

completely removed. Alkyl- or arylisothiocyanate (0.03 mol) dissolved in dry diethyl ether (10–15 cm³) is dropped to the reaction mixture. The latter is stirred for two hours at room temperature and allowed to stay overnight. Water (about 20 cm³) is added to the reaction mixture, followed by the addition of HCl (1:1) until a slightly acidic medium is achieved. The ether layer is separated and the aqueous one is extracted several times with ether. The combined ether extracts are dried over anhydrous sodium sulphate and the ether is distilled off under vacuum, leaving a viscous liquid residue which is dissolved in ethanol or methanol. After cooling of this solution a crude product precipitates which is recrystallized in the same solvent yielding the respective diethyl esters of the 1-*N*-substituted thioamido-1-phenylmethanephosphonic acids (1–6) Table I) as well as the respective 1,3-disubstituted thioureas.

Unreacted isothiocyanate, phenylmethanephosphonic acid diethyl ester as well as some 1,3-disubstituted thiourea are isolated from the mother liquor by distillation under vacuum.

Example: Interaction between phenylmethanephosphonic acid diethyl ester and phenylisothiocyanate. Phenylmethanephosphonic acid diethyl ester (6.85 g, 0.03 mol), sodium amide from 0.76 g sodium (0.03 g atom and an excess of 10%), phenylisothiocyanate (4.06 g, 0.03 mol) are reacted according to the procedure described above to yield product 5 (5.3 g, 48.6%). The crude product is recrystallized three times in methanol order to achieve a constant melting point of 125–126°C. IR (nujol): 1030–1050 cm⁻¹ (P—O—C); 1220 cm⁻¹ (C=S); 1235, 1270 cm⁻¹ (C=S, P=O) 1570 cm⁻¹ (N—C=S); 1500, 1600 cm⁻¹ (C₆H₅); 3220, 3240 cm⁻¹ (N—H). Analysis % found: C 59.55; H 5.92; P 8.24; N 3.79. Calc. for C₁₈H₂₂NO₃PS (363.42) C 59.49; H 6.10; P 8.52; N 3.85. ¹H-NMR: δ 0.97 (t, 3H, CH₃, J = 7 Hz), 1.26 (t, 3H, CH₃, J = 7 Hz), 3.14–4.37 (m, 4H, 2xCH₂), 4.73 (d, 1H, CH, J = 20 Hz), 6.89–7.86 (m, 10H, 2xCH₆H₅), 11.1 (br, 1H, NH).

1,3-Diphenylthiourea (0.4 g, 5.8%) m.p. 155°C (lit.⁸ 154–155°C) by concentration of the mother liquor and filtration of the crystals obtained is also isolated. IR (nujol): 1220 cm⁻¹ (C=S); 1500, 1600 cm⁻¹ (C₆H₅) 1550 cm⁻¹ (N—C=S); 3220 cm⁻¹ (N—H).

By distillation under vacuum of the mother liquor, the following compounds are isolated: (a) unreacted C₆H₅NCS (0.8 g, 19.7%), b.p. 65–67°C at 2 mm Hg, n_D²⁰ 1.6440 (lit.⁹ b.p. 95°C at 12 mm Hg, n_D²⁵ 1.6492); (b) 0,0-diethyl phenylmethanephosphonate (2.1 g, 30.7%) b.p. 115–120°C at 0.2 mm Hg, n_D²⁰ 1.4995 (lit.¹⁰ b.p. 155°C at 14 mm Hg), IR (capillary layer): 1045 cm⁻¹ (P—O—C); 1250 cm⁻¹ (P=O); 1500, 1600 cm⁻¹ (C₆H₅); (c) 1,3-diphenylthiourea is isolated in a purer state than that described in the literature.⁸ It crystallizes in the receiver with a m.p. of 163–163.5°C. The IR spectrum is exactly the same as that of the substance isolated by recrystallization.

Traces of *N*-phenylethylthiocarbamate are detected in the crude product by TLC on Kieselgel 60 F₂₅₄ and *n*-hexane/ethylacetate (4:1) as eluent.

Interaction between ethanephosphonic acid dimethyl ester and phenylisothiocyanate. Ethanephosphonic acid dimethylester (5.52 g, 0.04 mol), sodium amide from 1.0 g sodium (0.04 g atom and an excess of 10%), and phenylisothiocyanate (5.41 g, 0.04 mol) are reacted according to the above general procedure to yield *N*-phenylmethylthiocarbamate (4.0 g, 60.2%) m.p. 90–92°C. After recrystallization in diluted ethanol m.p. 92–93°C (lit.¹¹ m.p. 93–94°C). IR (nujol): 1210 cm⁻¹ (C=S); 1500, 1600 cm⁻¹ (C₆H₅); 1540 cm⁻¹ (N—C=S), 3200 cm⁻¹ (N—H). ¹H-NMR: δ 4.10 (s, 3H, CH₃O), 7.31 (m, 5H, C₆H₅), 8.92 (br. 1H, NH).

By distillation under vacuum of the mother liquor 1,3-diphenyl thiourea (0.8 g, 8.8%) b.p. 130–132°C at 0.4 mm Hg, m.p. 163–163.5°C is isolated as well as a fraction representing a mixture of phenylisothiocyanate and dimethyl ester of ethanephosphonic acid which are difficult to separate, due to their close boiling points.

Under the same conditions the interaction of diethyl ester of ethanephosphonic acid, sodium amide and phenylisothiocyanate result in: *N*-phenyl-ethylthiocarbamate (3.8 g, 52.4%) m.p. 67–68°C from dil. methanol (lit.¹² m.p. 68–69°C). IR (nujol): 1220 cm⁻¹ (C=S); 1500, 1600 cm⁻¹ (C₆H₅), 1550 cm⁻¹ (N—C=S), 3220 cm⁻¹ (N—H). ¹H-NMR δ 1.44 (t, 3H, CH₃CH₂O), 4.65 (m, 2H, CH₂CH₂O), 7.37 (m, 5H, C₆H₅), and 9.25 (br., 1H, NH); 1,3-diphenylthiourea (0.6 g 6.6%), b.p. 130–133°C at 0.4 mm Hg, m.p. 163°C, and a mixture of phenylisothiocyanate and diethyl ester of ethanephosphonic acid.

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