SYNTHESIS AND STUDY OF ANTIMICROBIAL PROPERTIES OF 1-(O,O′-DIETHYLDITHIOPHOSPHATO)-1-ALKOXYCARBONYL-2-PHENYLETHANES

B. D. Grishchuk,[1] L. I. Vlasik,[1] A. V. Blinder,[1] P. M. Gorbovoi,[1] and E. Ya. Kudrik[2]

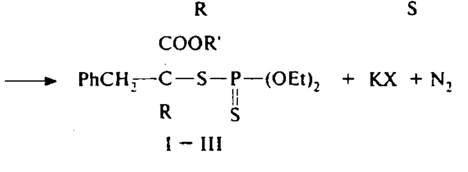
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 32, No. 1, pp. 34 – 35, January, 1998.

Original article submitted February 18, 1997.

As is known, O,O′-diethyldithiophosphoric acid derivatives are used as physiologically active compounds with a broad spectrum of biological activity [1, 2]. It would be also of interest to study in this respect a series of previously undescribed 1-(O,O′-diethyldithiophosphato)-1-alkoxycarbonyl-2-phenylethanes.

This work continues our earlier investigations [3 – 5] and is aimed at the development of a method for the synthesis of 1-(O,O′-diethyldithiophosphato)-1-alkoxycarbonyl-2-phenylethanes using the reaction of anionarylation [6] and the characterization of the reaction products with respect to their antimicrobial properties.

It was found that aromatic salts of diazonium may interact with esters of acrylic and methacrylic acids in a water – acetone (1 : 2) mixture in the presence of potassium O,O′-diethyldithiophosphate. The reaction is accompanied by the evolution of nitrogen and leads to the attachment of aryl and O,O′-diethyldithiophosphate groups at the site of the multiple bond rupture, resulting in the formation of 1-(O,O′-diethyldithiophosphato)-1-alkoxy-2-phenylethanes (I – III):



$$\mathrm{PhN_2X} + \mathrm{CH_2{=}\underset{\displaystyle R}{\underset{|}{C}}{-}COOR'} + \mathrm{K{-}S{-}\underset{\displaystyle S}{\underset{\|}{P}}(OEt)_2} \longrightarrow$$

$$\longrightarrow \mathrm{PhCH_2{-}\underset{\displaystyle R}{\overset{\displaystyle COOR'}{C}}{-}S{-}\underset{\displaystyle S}{\underset{\|}{P}}{-}(OEt)_2} + \mathrm{KX} + \mathrm{N_2}$$

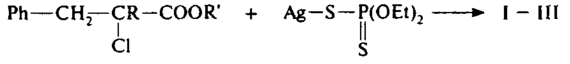
I – III

The reaction proceeds in the temperature interval from – 20 to – 10°C. The optimum reagent ratio diazonium salt – unsaturated compound – potassium O,O′-diethyldithiophosphate is 1 : 1.4 : 1.5. The yields of compounds I – III were 29 – 34%. It is important to note that diazonium salt must be the last reagent introduced into the reaction medium. Adding potassium O,O-diethyldithiophosphate in the last step to the mixture may result in the loss of control over the reaction and the outburst of the mixture from the reaction vessel.

In the case of using phenyldiazonium sulfates or nitrates, the yields of 1-(O,O′-diethyldithiophosphato)-1-alkoxycarbonyl-2-phenylethanes are lower by 18 – 23%. This fact can be explained by the fact that aqueous solutions of phenyldiazonium sulfates or nitrates have pH 3 – 4. Under these conditions, potassium O,O′-diethyldithiophosphate is transformed into the corresponding acid ester capable of partial oxidation to disulfide under the reaction conditions studied [7].

(O,O′-Diethyldithiophosphato)arylation of acrylates proceeds in virtually the same manner in the presence and in the absence of catalyst (copper or iron salt) and is accompanied by a side reaction leading to the formation of O,O′-diethyldithiophosphatobenzenes with a yield of 15 – 20%.

1-(O,O′-Diethyldithiophosphato)-1-alkoxycarbonyl-2-phenylethanes (I – III) are high-boiling oils; the proposed structures were confirmed by the method of counter synthesis using a reaction between the corresponding 1-chloro-1-alkoxy-2-phenylethanes and silver O,O′-diethyldithiophosphate:



$$\mathrm{Ph{-}CH_2{-}\underset{\displaystyle Cl}{\underset{|}{C}}R{-}COOR'} + \mathrm{Ag{-}S{-}\underset{\displaystyle S}{\underset{\|}{P}}(OEt)_2} \longrightarrow \text{I – III}$$

The IR spectra of compounds I – III contain the absorption bands in the regions of 1715 – 1735 cm^{-1} characteristic of the carbonyl group. Their ^1H NMR spectra display signals due to protons of the phenyl rings, ester fragments, and methylene and methyl groups, and methine hydrogen. The ^1H NMR and IR spectra of compounds I – III obtained by the direct and counter reactions were identical.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – III were recorded on an IKS-29 spectrophotometer using samples prepared as thin films. The ^1H NMR spectra were recorded on a Tesla BS-487

---

[1] Research Institute of Medico-Ecological Problems, Ministry of Health of the Ukraine, Chernovtsy, Ukraine.

[2] Ternopol Pedagogical Institute, Ternopol, Ukraine.

0091-150X/98/3201-0033$20.00

TABLE 1. Physicochemical Characteristics 1-(O,O′-Diethyldithiophosphato)-1-alkoxy-2-phenylethanes

Compound	R	R′	Yield, %	B.p., °C (1 Torr)	n_D^{20}	d_4^{20}	Empirical formula	^{1}H NMR spectrum (δ_{max}, ppm)
I	H	Et	32	135 – 137	1.5474	1.2130	$C_{15}H_{23}O_4PS_2$	7.36 – 7.42 (m, 5H, C_6H_5), 4.44 – 4.55 (m, 6H, $3OCH_2$), 3.82 – 3.94 (m, 1H, CH), 3.12 – 3.18 (m, 2H, CH_2Ph), 1.21 – 1.27 (m, 9H, $3CH_3$)
II	H	Bu	39	146 – 148	1.5570	1.2087	$C_{17}H_{27}O_4PS_2$	7.39 – 7.48 (m, 5H, C_6H_5), 4.39 – 4.52 (m, 6H, $3OCH_2$), 3.79 – 3.92 (m, 1H, CH), 3.14 – 3.22 (m, 2H, CH_2Ph), 0.94 – 1.26 (m, 7H, C_3H_7, 6H, $2CH_3$)
III	Me	Et	29	140 – 142	1.5462	1.2034	$C_{16}H_{25}O_4PS_2$	7.32 – 7.40 (m, 5H, C_6H_5), 4.41 – 4.53 (m, 6H, $3OCH_2$), 3.13 – 3.19 (m, 2H, CH_2Ph), 1.21 – 1.69 (m, 12H, $4CH_3$)

(80 MHz) spectrometer using CCl_4 as the solvent and HMDS as the internal standard. The purity of the synthesized substances was checked by TLC on Silufol UV-254 plates eluted with a benzene – chloroform (1 : 2) mixture. The results of elemental analyses agree with the values calculated according to the empirical formulas. The physicochemical values, yields, and parameters of the ^{1}H NMR spectra of the synthesized compounds are presented in Table 1.

1-(O,O′-Diethyldithiophosphato)-1-butoxy-2-phenylethane (I).

(a) To 0.14 mole of an acrylic acid ester and 0.15 mole of potassium O,O′-diethyldithiophosphate in 150 ml of a water – acetone mixture (1 : 2) was gradually added during 60 min with stirring 0.1 mole of phenyldiazonium tetrafluoroborate at a temperature between – 20 and – 10°C. The reaction mixture was kept within this temperature interval until the nitrogen evolution ceased (~ 1.5 h). Then the reaction mixture was extracted with 200 ml of ethyl ether. The extract was washed with water and dried over magnesium sulfate. Then ethyl ether was evaporated and the residue distilled in vacuum to obtain 7.8 g (18%) of O,O′-diethyldithiophosphatobenzene and 11.6 g (32%) of compound I. Compounds II and III were obtained by similar procedures.

Reactions with phenyldiazonium sulfate and nitrate were performed by a similar procedure. The process under catalyzed conditions was studied by adding 0.014 mole of copper acetate to the reaction mixture.

(b) A mixture of 0.05 mole of 1-chloro-1-ethoxy-2-carbonyl-2-phenylethane and 0.075 mole of silver O,O′-diethyldithiophosphate in 50 ml of acetonitrile was heated for 12 h on a boiling water bath. Then the reaction mixture was treated with 120 ml of water and extracted with ethyl ether. The extract was dried over magnesium sulfate. The solvent was evaporated and the residue was distilled in vacuum to obtain 3.5 g of compound I.

The analogous procedure was used to obtain compounds II and III by interaction of the corresponding 1-chloro-1-alkoxycarbonyl-2-phenylethanes and silver O,O′-diethyldithiophosphate.

EXPERIMENTAL BIOLOGICAL PART

The antibacterial activity of the synthesized compounds was studied by the method of double serial dilutions in liquid nutrient media (a beef-infusion broth for bacteria, a modified Sabouraud liquid medium for fungi) using 96-cavity immunological plates and a Takachi microtitrator.

The initial stock solutions were prepared by dissolving 10 mg of each compound in 0.25 ml of DMF, followed by adding 9.75 ml of distilled water. The tests were performed on Gram-positive (*S. aureus* F-49), Gram-negative (*P. mirabilis*, *S. typhimurium*, *P. aeruginosa* 40), and spore-forming (*B. subtilis* 39) bacteria and yeast fungi species (*S. cerevisiae* and *C. albicans* 669/1080).

As is seen from the experimental data presented in Table 2, almost all of the synthesized compounds were inactive with respect to the test objects studied, except for the yeast fungus *S. cerevisiae* and *P. aeruginosa* 40 bacteria (the latter being sensitive only to compound I).

A comparison of the results obtained in this work with the previous data [3, 4] indicates that a factor responsible for the antimicrobial properties of the compounds studied is apparently a functional group in the carbon chain. Therefore, the replacement of the thiocyanate group [3] by an O-alkylthiocarbonate [4] or O,O′-diethyldithiophosphate groups leads to the loss of the antimicrobial activity.

ACKNOWLEDGMENTS

This work was partly supported by the Soros International Science Foundation for Education in Natural Sciences in the Ukraine, grant No. PSU 053075.

TABLE 2. Antimicrobial Properties of Compounds I – III

Compound	MIC, μg / ml						
	P. mirabilis	*S. typhymurium*	*S. aureus* F-49	*P. aeruginosa* 40	*B. subtilis* 39	*C. albicans* 669/1080	*S. cerevisiae*
I	NA	NA	NA	500	NA	NA	500
II	NA	NA	NA	NA	NA	NA	500
III	NA	NA	NA	NA	NA	NA	500

Note. NA — nonactive.

REFERENCES

1. N. N. Mel'nikov, Pesticides [in Russian], *Khimiya*, Moscow (1985), pp. 445 – 451.
2. A. N. Pudovik, I. V. Gur'yanova, É. A. Ishmaev, in: *Reactions and Methods for the Investigation of Organic Compounds*, Issue 19 [in Russian], *Khimiya*, Moscow (1968), pp. 71 – 79.
3. 3. B. D. Grishchuk, N. G. Prodanchuk, P. M. Gorbovoi, et al., *Khim.-Farm. Zh.*, **24**(2), 139 – 140 (1990).
4. B. D. Grishchuk, L. I. Vlasik, A. V. Blinder, et al., *Khim.-Farm. Zh.*, **30**(11), 46 – 48 (1996).
5. B. D. Grishchuk, L. I. Vlasik, A. V. Blinder, et al., *Abstracts of Papers. The 17th Ukrainian Conf. on Organic Chemistry* [in Ukrainian], Kharkov (1995).
6. B. D. Grishchuk, P. M. Gorbovoi, N. I. Ganushchak, et al., *Usp. Khim.*, **53**(10), 266 – 279 (1994).
7. N. N. Mel'nikov, A. F. Grapov, and K. D. Shvetsova-Shilovskaya, *Zh. Obshch. Khim.*, **27**(71), 1905 – 1907 (1957).