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Abstract

Full Text

Chemistry

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Chemical Structure and Antimicrobial Properties of Organophosphorus Compounds

(Presented by Academician A. E. Arbusov, 26 VI 1963)

It was shown earlier that esters of phosphorus acids possess fungicidal properties with respect to fungi—the causative agents of dermatomycoses in humans and warm-blooded animals. In a study of about 60 compounds, we were able to find that lengthening of the hydrocarbon radical located in the ester linkage at the phosphorus atom in esters of phosphoric, phosphinic, and pyrophosphoric acids leads to a decrease in toxicity

Table 1

Antimicrobial properties of imides of phosphorus acids

Compounds	Strain					Concentrations					Toxicity, LD_{50}
	Fungal cultures	of com-pounds	of com-pounds	of com-pounds	of staphylococ-cus	of com-pounds	of com-pounds	of com-pounds	of com-pounds	of com-pounds	
	%	%	%	%	%	%	%	%	%	%	
C_2H_5O	0.1	0.25	1		0.01	0.05	0.1	0.25	0.5		
C_2H_5O	+	+	+	29799	+	+	+	+	+		11
$P(=O)-N(C_4H_9)-P(=O)OC_2H_5$											
$P(=O)OC_2H_5$											

Compounds	Strain										
	Concentration of Fungal cultures	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Concentration of staphylococcus	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Toxicity, white mice, LD ₅₀
C_2H_5O	>	+	+	+							
C_2H_5O											
$P(=O)-N(C_4H_9)-P(=O)<OC_2H_5OC_2H_5C_2H_5O$											
C_2H_5O	>	+	+	+	30219	+	+	+	+	+	
C_2H_5O											
$P(=O)-N(C_4H_9)-P(=O)<OC_2H_5OC_2H_5C_4H_9OC_4H_9O$	>	-	-	-	29799	+	+	+	-	-	110
C_4H_9O											
C_4H_9O	>	-	-	-							
C_4H_9O											
$P(=O)-N(C_4H_9)-P(=O)<OC_4H_9OC_4H_9C_4H_9O$											
C_4H_9O											
C_4H_9O											

Compounds	Strain										
	Concentration of Fungal cultures	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Concentration of staphylococcus	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Concentration of com-pounds	Toxicity, white mice, LD ₅₀
C_4H_9O	>	-	-	-	30219	+	+	+	-	-	
C_4H_9O											
$P(=O)-N(C_4H_9)-P(=O)<OC_4H_9OC_4H_9$											
$iso-C_4H_9O$	>				29799	+	-	-	-	-	870
$iso-C_4H_9O$											
$P(=O)-N(C_2H_5)-P(=O)<OC_4H_9OC_4H_9$											
$iso-C_4H_9O$	>				30219	+	-	-	-	-	
$iso-C_4H_9O$											
$P(=O)-N(C_2H_5)-P(=O)<OC_4H_9OC_4H_9$											

Note. + microbial growth; - absence of growth; +- inhibition of growth.

a – *Trichophyton gypseum*, *b* – *Microsporium lanosum*, *c* – *M. ferrugineum*.

toward warm-blooded animals and to an enhancement of antifungal properties (1,2). Consequently, by changing the chemical structure of compounds in this direction, it is possible to approach the preparation of a drug. It seemed of interest to test the data obtained on other species of microbes with different types of organophosphorus compounds, in order to reveal the possibility of carrying out a purposeful synthesis.

For this purpose, another 74 compounds were investigated, synthesized at the A. E. Arbuzov Chemical Institute of the Academy of Sciences of the USSR and at the A. M. Butlerov Chemical Institute of Kazan University. The results of the studies are summarized in Tables 1-4, which present the most interesting compounds, making it possible to reveal the relationship between biological action and chemical structure.

The tables give the results of studies on white mice (with determination of LD_{50} according to Behrens), pathogenic fungi (*Trichophyton gypseum*, *Microsporium lanosum*, *Epidermophyton*) and golden staphylococcus (*Staphylococcus pyogenes aureus*).

In studying the fungicidal action of the compounds, Sabouraud medium containing increasing doses of the compounds was inoculated with a fungal culture. The absence of fungal growth in the test tubes for 30 days, with luxuriant growth in the control, served as the criterion of the fungistatic action of the compounds. In studying the antibacterial action, a one-day culture of staphylococcus was incubated at 37° in physiological solution containing various concentrations of the compounds. Each 1 ml of sample contained 500 million microbial bodies. After 6 hours of incubation, inoculations were made

Table 2

Antimicrobial properties of mixed esters of phosphoric and phosphinic acids

Compounds	Concentration of com- pounds, fungal cul- %:						Concentration of com- pounds, Staphylococcus					Toxicity, mg/kg (white mice, LD_{50})
	0.005	0.01	0.05	0.1	0.25	1.0	0.01	0.05	0.1	0.5	1.0	
$(C_2H_5O)(C_2H_5)P(=O) - OCH = CCl_2$	+	+	+	+	+	+	29799	+	+	+	-	0.9
$(C_2H_5O)(C_2H_5)P(=O) - OCH = CCl_2$												0.9
$(C_2H_5O)(C_2H_5)P(=O) - OCH = CCl_2$												0.9
$(C_2H_5O)(C_2H_5)P(=O) - OCH = CCl_2$							30219	+	+	+	-	0.9
$(C_5H_{11}O)(C_2H_5)P(=O) - OCH = CCl_2$							29799	+	-	-	-	1
$(C_5H_{11}O)(C_2H_5)P(=O) - OCH = CCl_2$												1
$(C_5H_{11}O)(C_2H_5)P(=O) - OCH = CCl_2$												1
$(C_5H_{11}O)(C_2H_5)P(=O) - OCH = CCl_2$							30219	+	-	-	-	1

Compounds	Concentration of com-pounds, Fungal cul- %:						Concentration of com-pounds, Staphylococcus strains					Toxicity, mg/kg (white mice, LD ₅₀)	
	0.005	0.01	0.05	0.1	0.25	1.0	0.01	0.05	0.1	0.5	1.0		
(CH ₃) ₂ C(CN) - Θ - P(= O)(OC ₂ H ₅) ₂	+	+	+	+	+	+	29799	+	+	+	+	+	150
(CH ₃) ₂ C(CN) - Θ - P(= O)(OC ₂ H ₅) ₂	+	+	+	+	+	+	30219	+	+	+	+	+	150
(CH ₃) ₂ C(CN) - Θ - P(= O)(OC ₅ H ₁₁) ₂	+	+	+	+	+	+	29799	+	+	-	-	-	300
(CH ₃) ₂ C(CN) - Θ - P(= O)(OC ₅ H ₁₁) ₂	+	+	+	+	+	+	30219	+	+	-	-	-	300
(CH ₃ O) ₂ P(= O) + CH(CCl ₃) - O - C(= O) - CH ₃	+	+	+	+	+	+	29799	+	+	-	-	-	700
(CH ₃ O) ₂ P(= O) + CH(CCl ₃) - O - C(= O) - CH ₃	+	+	+	+	+	+	30219	+	+	-	-	-	700
(CH ₃ O) ₂ P(= O) + CH(CCl ₃) - O - C(= O) - CH ₃	+	+	+	+	+	+	29799	+	+	-	-	-	700
(CH ₃ O) ₂ P(= O) + CH(CCl ₃) - O - C(= O) - CH ₃	+	+	+	+	+	+	30219	+	+	-	-	-	700
(C ₄ H ₉ O) ₂ P(= O) + CH(CCl ₃) - O - C(= O) - CH ₃	+	+	+	+	+	+	29799	+	+	-	-	-	2300
(C ₄ H ₉ O) ₂ P(= O) + CH(CCl ₃) - O - C(= O) - CH ₃	+	+	+	+	+	+	30219	+	+	-	-	-	2300

Note. a - *Trichophyton gypseum*, b - *Microsporum lanosum*, c - *M. ferrugineum*, d - *Epidermophyton*, e - *Achorion Schönleini*, f - *Trichophyton faviforme*.

Table 3

Antimicrobial properties of quaternary phosphonium salts and arsine sulfides

Compounds	Concentration of com-pounds, Fungal cul- %:					Concentration of com-pounds, Staphylococcus strains					Toxicity, mg/kg (white mice, LD ₅₀)
	0.01	0.05	0.1	0.25	1	0.01	0.05	0.1	0.5	1.0	
[CH ₃ (C ₇ H ₇)(C ₂ H ₅)(C ₆ H ₅)P] Br	+	+	+	+	+	29799	+	+	+	+	16.8
[CH ₃ (C ₇ H ₇)(C ₂ H ₅)(C ₆ H ₅)P] Br	+	+	+	+	+	30219	+	+	+	+	16.8
[CH ₃ (C ₁₈ H ₃₇)(C ₂ H ₅)(C ₆ H ₅)P] Br	-	-	-	-	-	29799	-	-	-	-	9
[CH ₃ (C ₁₈ H ₃₇)(C ₂ H ₅)(C ₆ H ₅)P] Br	-	-	-	-	-	30219	-	-	-	-	9
CH ₃ (C ₂ H ₅)(C ₆ H ₅)As = S	-	-	-	-	-						90
CH ₃ (C ₂ H ₅)(C ₆ H ₅)As = S	+	+	+	+	+						90
C ₉ H ₁₉ (C ₂ H ₅)(C ₆ H ₅)As = S	-	-	-	-	-						100
C ₉ H ₁₉ (C ₂ H ₅)(C ₆ H ₅)As = S	-	-	-	-	-						100

Note. a - *Trichophyton gypseum*, b - *Epidermophyton*.

onto Petri dishes with meat-peptone agar. The absence of growth served as the criterion of the antimicrobial action of the compounds.

As is evident from Tables 1, 2, and 4, lengthening of the hydrocarbon radical located at the phosphorus atom in esters of phosphoric and phosphinic acids,

Table 4

Antimicrobial properties of esters of organophosphorus acids of the general structure

$R_2 - P(=O)(OR)(OR)$, where $R = \text{Alk}$; $R_2 = \text{residue of a heterocyclic compound}$

Compounds	Concentrations of com- pounds, Fungal cul- tures, %				Staphylococcus strains	Concentrations of com- pounds, Staphylococcus				Toxicity, mg/kg; white mice, LD_{50}
	0.05	0.1	0.25	1.0		0.05	0.1	0.25	0.5	
Morpholine- $P(=O)(OC_2H_5)_2$	+	+	+	+	29799	+	+	+	+	450
Morpholine- $P(=O)(OC_2H_5)_2$	+	+	+	+	30219	+	+	+	+	450
Morpholine- $P(=O)(OC_4H_9)_2$ - iso	+	+	-	-	29799					450
Morpholine- $P(=O)(OC_4H_9)_2$ - iso	+	+	-	-	30219					450
Benzimidazole- $P(=O)(OC_2H_5)_2$	+	+	-	-	29799	+	-	-	-	750
Benzimidazole- $P(=O)(OC_2H_5)_2$	+	+	-	-	30219	+	-	-	-	750
Benzimidazole- $P(=O)(OC_4H_9)_2$ - iso	+	±	-	-	29799	-	-	-	-	900
Benzimidazole- $P(=O)(OC_4H_9)_2$ - iso	+	±	-	-	30219	-	-	-	-	900

Compounds	Concentrations of com- Fungal pounds, cul- %				Staphylococcus strains	Concentrations of com- pounds, %				Toxicity, mg/kg; white mice, LD_{50}
	0.05	0.1	0.25	1.0		0.05	0.1	0.25	0.5	
Quinoxaline deriva- tive, $C-CH_2-P(=O)(OC_2H_5)_2$, $C-CH_3$	+	+	+	+	29799	+	+	+	+	800
Quinoxaline deriva- tive, $C-CH_2-P(=O)(OC_2H_5)_2$, $C-CH_3$	+	+	+	+	30219	+	+	+	+	800
Quinoxaline deriva- tive, $C-CH_2-P(=O)(OC_3H_7)_2$ - iso, $C-CH_3$	+	-	-	-	29799					1000
Quinoxaline deriva- tive, $C-CH_2-P(=O)(OC_3H_7)_2$ - iso, $C-CH_3$	+	+	-	-	30219					1000

Note. a – *Trichophyton gypseum*, b – *Epidermophyton*.

in the imides of phosphorus acids leads to a change in physiological properties in the direction we need: the antimicrobial properties improve and, as a rule, toxicity toward warm-blooded animals decreases. From examination of Table 1 it is evident that the asymmetry of the compound decreases toxicity toward warm-blooded animals, while at the same time improving antimicrobial properties (Table 1). The antimicrobial properties of quaternary phosphonium salts and arsine sulfides are also enhanced when the hydrocarbon radical located at the phosphorus and arsenic atom is lengthened (Table 3).

Thus, by changing the structure of organophosphorus compounds in this direc-

tion, it is possible to obtain a compound with selective action against microorganisms.

Chemical Institute named after A. E. Arbuzov
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Kazan

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CITED LITERATURE

1. I. D. Neklesova, Z. Sh. Minyusheva, Proceedings of the Second Conference, 1959, Publishing House of the Academy of Sciences of the USSR, 1962, p. 524.
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