PHOSPHORYLATED 3-THIOINDOLES

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Phosphorylated mercaptoindoles are not described in the literature, although their biological activity is no doubt of interest. It has already been found [3] that certain derivatives of P^{3+} acids are used as N- and C³-phosphorylating agents.

In the present work we showed that in the reaction of 3-mercaptoindole (I) [1] with chlorides of P^{3+} acids, mixtures of S- and N-phosphorylation products (II-IV and IX-XI) are formed in a ratio depending on the reaction temperature.



II, IX : $R=R^1=NEt_2$; III, VI. X: $R=R^4=OEt$; IV, XI. R-OEt, $R^1=NEt_2$; V : $R=R^1=OMe$; VII: $R=R^1=CH_2CI$; VIII: R=-CH=CHOEt, $R^1=indoly1-3-thio$; II-IV, IX-XI: Z = (none), P^{3+} ; V, VI, Z=S; VII, VIII: Z=0.

According to the data of ^{31}P NMR spectrum, at -15°C in the reaction products there are 85% of II-IV and 15% of IX-XI, at 5°C 60 and 40%, respectively, and at the temperature of boiling ether, 50 and 50%. Hence, the mercapto group is more reactive in the reaction with chlorides of P³⁺ acids.

Chlorides of P^{5+} acids selectively phosphorylate I in boiling benzene at the SH group. Thiophosphoryl chlorides are thus less active [2] in these reactions. It requires 4.5-5 h to complete their reaction with I, while with phosphoryl and phosphonyl chlorides the reaction is completed after 3-3.5 h.

 β -Ethoxyvinylphosphonyl dichloride reacts with I in benzene already at room temperature in the presence of a two- to threefold excess of Et₃N. By frequently removing the Et₃N·HCl precipitate that separates out, the reaction can be completed in 16-18 h. Increase in temperature to 50-60°C shortens the duration of the reaction to 4-5 h.

Com-	Yield.	bp, °C,		Found, %				Empirical	Calculated, %			
pound	%	mm Hg (mp, °C)	831P	с	н	N	Р	formula	с	н	N	р
Ш	50,0	Light- yellow	136	59,30	8,01	12,80	9,34	$C_{16}H_{26}N_3PS$	59,41	8,10	12,99	9, 38
111	61,8	$\frac{124,6}{0,09}$	126	53,38	5,84	5,53	11,08	C ₁₂ H ₁₆ NO ₂ PS	5 3 ,5 2	5, 9 9	5,20	11,50
IV	47,0	$\frac{117-8}{0,08}$	134	56,61	7,01	9,80	10,11	C ₁₄ H ₂₁ N ₂ OPS	56,74	7,14	9,45	10,45
V VI VII VIII	78,2 82,7 63,0 87,0	(90-2) (78-9) (110-1) (162-3)	80 82 35 28	43,81 47,71 40,70 58,05	4,30 5,20 3,41 4,28	5,43 4,91 4,82 6,70	11,02 10,08 10,27 7,50	C ₁₀ H ₁₂ NO ₂ PS ₂ C ₁₂ H ₁₆ NO ₂ PS ₂ C ₁₀ H ₁₀ NCI ₂ OPS ₂ C ₂₀ H ₁₈ N ₂ O ₂ PS ₂	43,94 47,82 40,83 58,17	4,43 5,35 3,43 4,30	5,12 4,64 4,76 6,77	11,33 10,27 10,53 7,50
I X	45,0	$\frac{54-6}{0.08}$	105	65,68	8,83	14,25	10,47	C ₁₆ H ₂₆ N ₃ PS	65,71	8,96	14,37	10,59
Х	36,2	<u>83-5</u> 0,09	128	53,41	5,88	5,47	11,20	C ₁₂ H ₁₆ NO ₂ PS	53,5 2	5,99	5,20	11,50
XI	30,7	$\frac{117-9}{0,08}$	122	56,63	7,03	9,14	10,53	C ₁₄ H ₂₁ N ₂ OPS	56,74	7,14	9,45	10,43

TABLE 1. Chemical Characteristic of Phosphonylthioindoles

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TAE	SLE	2.	Ant:	imicr	obia]	L Act	civity
of	3 - I	Phos	hon	vlthi	oindo	les	V-VIII

punoc	Menin- gococ- cus	Staphyl- ococcus-	Strepto- coccus	Diphteria bacillus		
Comp	minima tion, g/	l b acte ri /ml	cidal cor	ncentra-		
V VI VII VIII	$0,0005 \\ 0,0005 \\ 0,0025 \\ 0,0025 \\ 0,0025$	 0,001 	 0,001 0,001	0,005 0,001 0,001 0,001		

In the PMR spectra of II and VII there are resonance signals, δ , ppm: for II at 1.05 t (CH₃, J_{HH} = 5 Hz); 3.32 q (CH₂, J_{HH} = 5 Hz); 7.05 (C₂-H), 7.22-8.10 m (benzene ring); for VII, 4.4 q (CH₂, J_{PH} = 10.1 Hz); 6.8 (CH₂-H); 7.3-8.1 m (benzene ring). The resonance of the N-H proton does not appear in the spectrum because of great broadening and partial deutero exchange with the deutero solvent.

In the IR spectra of IV-VII there are appear absorption bands, v_{max} , cm⁻¹: at 3415, 3250 (NH), 1615-1617 (indole ring), 1193 (P=0), 1010, 1017 (P-O-C), 675 (P=S).

EXPERIMENTAL CHEMISTRY

The IR spectra were run on the UR-20 spectrophotometer and the NMR spectra on the WP-80 spectrometer. The chemical shifts of the ¹H nuclei were measured with reference to TMS and of the ³¹P nuclei with reference to H_3PO_4 .

3-S-(0,0-Diethylthiophosphitoyl)indole (III) and 1-(0,0-diethylphosphitoyl)-3-thioindole (X). An ethereal solution of 15.65 g of diethyl chlorophosphite is added dropwise at -15° C in an inert atmosphere to 300 ml of an ethereal solution of 7.45 g of 3-mercaptoindole and 10.1 g of Et₃N. The reaction mixture in held at the above temperature for 3 h, and at room temperature for 4 h. After separation of the Et₃N·HCl precipitate and removal of the solvent, 8.31 g (61.8%) of III and 4.87 g (36.2%) of X are chromatographically isolated on a column with SiO₂. A 3:1 mixture of absolute benzene and ether serves as eluent. The products are distilled *in vacuo*. Compounds II, IV, IX, and XI are obtained in a similar way (Table 1).

<u>3-S-(Bis-chloromethylphosphinatoyl)indole (VII).</u> A mixture of 11.15 g of 3-mercaptoindole, 7.5 g of Et₃N and 13.35 g of bis(chloromethyl)phosphinyl chloride in 250 ml of absolute benzene is heated for 3.5 h in a dry atmosphere, while maintaining the temperature in the bath at 120-130°C. After the removal of Et₃N·HCl and distillation of the solvent *in vacuo*, the residue is recrystallized from CHCl₃. Yield, 17.48 g (63%) of VII. Compounds V and VI are obtained in a similar way.

EXPERIMENTAL BIOLOGY

The antimicrobial activity was studied on the example of the more stable compounds V-VIII by the method of serial dilutions in a liquid serial medium [1] with respect to four types of bacteria. The compounds studied were found to be slightly active toward gram-positive and gram-negative bacteria (Table 2).

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