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REACTION OF 2-AMINOPYRIMIDINES WITH PHOSPHORUS PENTACHLORIDE

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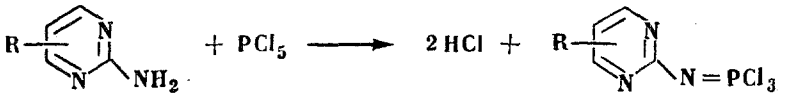
A study has been made of the reaction of phosphorus pentachloride in boiling benzene with 2-aminopyrimidines substituted at positions 4, 5, and 6. It was found that, depending on the basicity of the starting amine, reaction led to formation of phosphazo- compounds, or tetrachlorophosphopyrimidines. The formation of these compounds was confirmed by conversion of the latter into pyrimidyl-2-amidophosphoric dichloroanhydrides.

Continuing work previously begun on the phosphorylation of 2-aminopyrimidines [1, 2], a study has been made of the reaction of this compound with phosphorus pentachloride. It was of interest to investigate whether it was possible to extend the Kirsanov [3-6] phosphazo reaction to the 2-aminopyrimidine series, with a view to future use of this reaction to produce pyrimidyl-2-aminophosphoric acid dichloroanhydrides. The present work made use of 2-aminopyrimidine and a number of its derivatives with substituents at positions 4 and 5, as well as at 4, 5 and 4, 6 in the pyrimidine ring. The reaction was carried out using equimolecular amounts of phosphorus pentachloride and 2-aminopyrimidines* in boiling benzene. The reaction was judged to have finished when evolution of hydrogen chloride ceased.

The work carried out led to the conclusion that the reaction between phosphorus pentachloride and 2-aminopyrimidines proceeds in the way suggested by Kirsanov and coworkers [7].

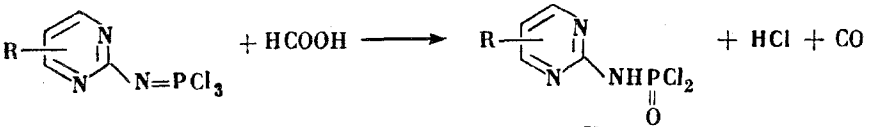
However, depending on the basicity of the 2-aminopyrimidine** the end-product of the reaction is either a pyrimidylamidotetrachlorophorphorus (III), or a trichlorophosphazopyrimidine (IV). 2-Aminopyrimidines of low basicity [pK_a less than 3.6 (compounds 1-8 in the table)] react with phosphorus pentachloride like amides and anhydrides of acids, with liberation of two equivalents of hydrogen chloride, and formation of benzene-soluble trichlorophosphazopyrimidines IV.



IV

R = 4-chloro; 5-chloro; 5-bromo; 4, 6-dichloro; 4, 6-dimethoxy; 4-chloro-6-methyl; 4-chloromethoxy; 4-methyl-5-bromo.

Formation of the phosphazo- compound IV was proved by formolysis of the reaction products of 2-aminopyrimidines and phosphorus pentachloride. Each time a benzene solution of the reaction products was treated with anhydrous formic acid under the usual conditions; this formolysis gave pyrimidyl-2-amidophosphoric chloroanhydrides in almost quantitative yields, and in a high degree of purity:



V

Reaction of phosphorus pentachloride with 2-aminopyrimidines of high basicity [pK_a greater than 3.6 (compounds 9-16 in the table)] leads to liberation of only one equivalent of hydrogen chloride, and formation of benzene-insoluble pyrimidylamidotetrachlorophosphorus compounds.

The results of formolysis of reaction products, as well as their reaction with acetic anhydride, gives evidence in favor of formation of pyrimidylamidotetrachlorophosphorus compounds (III). The action of one equivalent of anhydrous

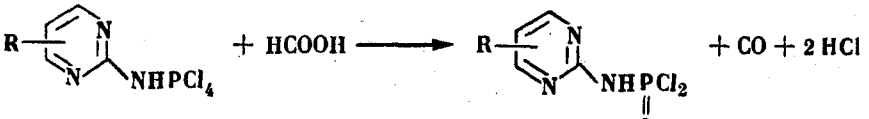
*Two equivalents of phosphorus pentachloride were used with 2-amino-4, 6-dimethylpyrimidine monohydrate.

**Measurement carried out by I. V. Persianova.

III

R = H; 4-methyl; 4-methoxy; 4-methoxy-6-methyl; 4-morpholyl; 4-piperidyl; 4-diethylamino.

formic acid on the reaction products from the indicated 2-aminopyrimidines and phosphorus pentachloride gives high yields (80-100%) of pyrimidyl-2-amidophosphoric dichloroanhydrides (V)



III V

Reaction of III with acetic anhydride also gives V, identical with that obtained by formolysis. Attempts to split off a further equivalent of hydrogen chloride by prolonged boiling in benzene (10-12 hr), or using a higher-boiling solvent (toluene) were not successful.

Pyrimidyl-2-amidophosphoric dichloroanhydrides (V) are colorless crystalling substances, gradually giving off hydrogen chloride on standing in air. Usually, specimens for analysis were purified by recrystallization. Because of the insolubility of compounds 13, 14, and 15 in inert organic solvents, they were washed with ice water, acetone, and ether, then vacuum-dried over P_2O_5. Analytical data are given in the table.

Experimental

The reaction between 2-aminopyrimidines and phosphorus pentachloride was carried out in a current of nitrogen.

1. Formation of phosphazo-compounds by reacting 2-aminopyrimidines with phosphorus pentachloride.

Typical experiment. A mixture of 1 g (7.71 mmole) 2-amino-5-chloropyrimidine and 1.61 g (7.71 mmole) phosphorus pentachloride in 30 ml dry benzene was refluxed in an oil bath, until evolution of hydrogen chloride ceased, (2 hr). Towards the end of the heating the 2-amino-5-chloropyrimidine went into solution. The hydrogen chloride evolved in the reaction was absorbed in 200 ml water, and then titrated with 0.1 N NaOH, using phenolphthalein. Found: HCl 93.6%. Calculated: 2 equivalents.

Phosphazo-compound formolysis. 0.36 g (7.71 mmole) anhydrous formic acid in 10 ml dry ether were added, with stirring, to the benzene solution obtained after reacting 2-amino-5-chloropyrimidine with PCl_5, the temperature being kept at 10-15°, stirring continued for 2 hr more, at room temperature, and the products allowed to stand overnight. The benzene was then distilled off in a vacuum, and the residue washed with petroleum ether, to give 1.86 g (97.7%) 5-chloropyrimidyl-2-amidophosphoric dichloroanhydride. In the cases of the 2-aminopyrimidines 2-8 (see table), reaction with phosphorus pentachloride, and formolysis of the phosphazo-compound proceeded similarly.

2. Formation of pyrimidylamidotetrachlorophosphorus compounds by reacting 2-aminopyrimidines with phosphorus pentachloride. A mixture of 1 g (10.5 mmole) 2-aminopyrimidine and 2.19 g (10.5 mmole) phosphorus pentachloride in 40 ml benzene was refluxed in an oil bath, until evolution of HCl ceased (2 hr 30 min). The hydrogen chloride evolved in the reaction was absorbed in 200 ml water, and then titrated with 0.1 N NaOH, using phenolphthalein. Found: HCl 93.5%. Calculated: 1 equivalent.

A. Formolysis of the pyrimidylamidotetrachlorophosphorus compounds. 0.48 g (10.5 mmole) anhydrous formic acid in 10 ml dry ether was added gradually, with stirring and at room temperature, to the benzene-insoluble product of the reaction between 2-aminopyrimidine and phosphorus pentachloride. After addition was finished, the reactants were stirred for 1 hr at room temperature, then for 2 hr at 30-35°, and allowed to stand overnight. The precipitate was filtered off and, washed on the funnel with petroleum ether. Yield 2.05 g (92%) pyrimidyl-2-amidophosphoric dichloroanhydride.

B. Reaction of pyrimidylamidotetrachlorophosphorus compounds with acetic anhydride. 1.07 g (10.5 mmole) acetic anhydride was added to the reaction product from 2-aminopyrimidine and phosphorus pentachloride, and the whole heated at 80° for 2 hr. The precipitate formed on cooling was filtered off, and washed on the funnel with petroleum ether. Yield 1.66 g (74.5%) pyrimidyl-2-amidophosphoric dichloroanhydride. In the cases of the 2-aminopyrimidines 10-15 (see table), reaction with phosphorus pentachloride, formylation of the pyrimidylamidotetrachlorophospho-

Substituted Pyrimidyl-2-Amidophosphoric Dichloroanhydrides (V)

Compound no.	Substituent	pK_a of the starting amines	Reaction time, hr	Method of preparing V	Mp, °C	Crystallizing solvent	Formula	Cl, %		Yield V, %
								Found	Calculated	
1	5-Chloro	2.38	2	1	163—165	Ether	$C_4H_3Cl_3N_3OP$	42.70	43.16	97.7
2	4-Chloro	3.29	2	1	167—169 (150)*	"	$C_4H_3Cl_3N_3OP$	43.26	43.16	88.2
3	5-Bromo	2.38	2.5	1	180—181** (170)*	Benzene	$C_4H_3BrCl_2N_3OP$	24.15***	24.38	86.3
4	4, 6-Dichloro	3.04	1.5	1	184—186	"	$C_4H_2Cl_4N_3OP$	50.44	50.49	93.2
5	4-Chloro-6-methoxy	3.00	1.5	1	150—152	"	$C_5H_5Cl_3N_3O_2P$	38.46	38.48	93.6
6	4, 6-Dimethoxy	3.00	3	1	133.5—135.5**	Ether + benzene (8 : 1)	$C_6H_8Cl_2N_3O_3P$	25.66	26.07	100
7	4-Chloro-6-methyl	3.12	3	1	166—168	Ether	$C_5H_5Cl_3N_3OP$	40.99	40.84	95.6
8	5-Bromo-4-methyl	3.25	3	1	173—174** (160)*	Benzene	$C_5H_5BrCl_2N_3OP$	23.04***	23.26	94.3
9	H	3.62	2.5	2A	182—184** (170)*	"	$C_4H_4Cl_2N_3OP$	33.69	33.45	92
10	4-Methyl	3.93	2.5	2A	165—167** (163)*	"	$C_5H_6Cl_2N_3OP$	31.37	31.38	81.3
11	4-Methoxy	4.93	2	2A, 2B	199—200** (196)*	"	$C_5H_6Cl_2N_3O_2P$	29.06	29.30	95.8
12	4-Methoxy-6-methyl	5.49	3.5	2A, 2B	168—171	"	$C_6H_8Cl_2N_3O_2P$	27.33	27.70	96
13	4-(1-Morpholyl)	6.93	6	2B	228—230**	—	$C_8H_{11}Cl_2N_4O_2P$	24.05	23.87	100
14	4-(1-Piperidyl)	7.57	5	2B	226—228**	—	$C_9H_{13}Cl_2N_4OP$	23.72	24.03	96.3
15	4-Diethylamino	7.64	5	2A, 2B	212—215**	—	$C_8H_{13}Cl_2N_4OP$	25.00	25.05	95.6
16	4, 6-Dimethyl	4.33	3	2A	161—163**	Ether	$C_6H_8Cl_2N_3OP$	28.99	29.24	98.3

*Temperature at which the capillary descends.

**Decomposition temperature.

***Chlorine hydrolyzed.

rus compounds, and reaction of the latter with acetic anhydride, all took place similarly.

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