PYRIDYL-2-AMIDOPHOSPHORIC DIETHYLENEIMIDES

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The synthesis of pyridyl-2-amidophosphoric diethyleneimides containing various substituents in the 3-, 5-, and 6-positions of the ring was undertaken as an extension of the study [1] to obtain antitumorigenic compounds.

The preparation of only the diethyleneimide of pyridyl-2-amidophosphoric acid by reaction of ethyleneimine with pyridyl-2-amidophosphoric dichloride is described in a British patent [2]. The starting phosphoric dichloride was prepared by reaction of 2-aminopyridine with phosphorus trichloride.

It was previously found [3,4] that pyrimidyl-2-and pyrimidyl-4-amidophosphoric chlorides are conveniently obtained by phosphorylation of aminopyrimidines with phosphorus pentachloride. Moreover, it was shown that the primary reaction products are monomeric trichlorophosphazopyrimidines which are converted in almost quantitative yield to pyrimidyl-2- and pyrimidyl-4-amidophosphoric dichlorides by reaction with anhydrous formic acid. In this paper, this reaction is extended to the aminopyridine series. It might be expected that since the electron density on the exocyclic nitrogen atom in the 2-aminopyridines is low [5], they will react with phosphorus pentachlorides in a manner similar to that of the amides of carboxylic acids [6], i.e., to form monomeric trichlorophosphazopyridines.

The reaction of 2-aminopyridines (I) with phosphorus pentachloride was carried out in refluxing benzene under nitrogen; the end point of the reaction was determined from cessation of the evolution of hydrogen chloride, which was trapped and back-titrated. In all cases, two equivalents of hydrogen chloride were evolved, while only one equivalent was evolved in the reaction of 2-amino- and 2-amino-6-methylpyridines with phosphorus pentachloride. In this case, trichlorophosphazopyridine hydrochlorides were apparently formed as in the aminopyrimidine series [4]. The trichlorophosphazopyridines (II) or their hydrochlorides

TABLE 1. Pyridyl-2-amidophosphoric Dichlorides [III]

No.	R_1	R_2	R_3	Yield, %	Crystallization solvent	Mp, deg	Found, %	Empirical formula	Cl calc., %
1	H	Cl	H	96,8	Ether	144—5	29,21*	$C_5H_4Cl_3N_2OP$	28,99
2	H	Br	H	97,2	»	157—8	24,65	$C_5H_4BrCl_2N_2OP$	24,46
3	H	I	H	99	Methanol	182—4	20,86	$C_5H_4ICl_2N_2OP$	21,05
4	CH_3	Br	H	98,5	Ether	165—7	22,79	$C_6H_6BrCl_2N_2OP$	23,33
5	H	Cl	Cl	90,4	»	169—71	25,20*	$C_5H_3Cl_4N_2OP$	25,34
6	H	Br	Br	96,8	»	167—9	18,89	$C_5H_3Br_2Cl_2N_2OP$	19,23
7	H	NO_2	H	91,8	»	147†	28,10	$C_5H_4Cl_2N_3O_3P$	27,70
8	H	H	NO_2	94,5	»	130—1	27,57	$C_5H_4Cl_2N_3O_3P$	27,70
9	CH_3	NO_2	H	97,2	Ether + benzene	166	26,20	$C_6H_6Cl_2N_3O_3P$	26,26
10	CH_3	H	NO_2	94,5	Ether	129—30	25,53	$C_6H_6Cl_2N_3O_3P$	26,26
11	H	Cl	NO_2	99,5	»	86—7	36,70	$C_5H_3Cl_3N_3O_3P$	36,62
12	CH_3	Br	Br	94	»	157—8	18,33	$C_6H_5Br_2Cl_2N_2OP$	18,52

*Hydrolyzable chlorine.

†Decomposition temperature.

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TABLE 2. Pyridyl-2-amidophosphoric Diethyleneimides (IV)

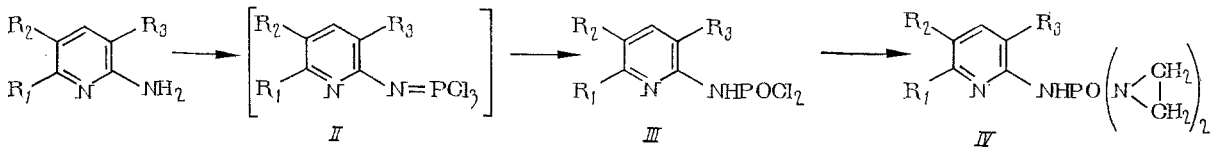
No.	R_1	R_2	R_3	Yield, %	Crystallization solvent	mp, deg	Found, %					Empirical formula	Calc., %				
							C	H	Cl (Br, I)	N	P		C	H	Cl (Br, I)	N	P
1	H	H	H	82	Ethyl acetate	148,5—149	48,21	6,13	—	24,85	13,73	$C_9H_{13}N_4OP$	48,21	5,84	—	24,99	13,82
2	CH_3	H	H	83,3	»	122,5—124,5	50,79	6,10	—	23,54	13,02	$C_{10}H_{15}N_4OP$	50,42	6,34	—	23,52	13,00
3	H	Cl	H	78,8	»	156,5—157	42,09	4,99	13,71	21,53	11,82	$C_9H_{12}ClN_4OP$	41,79	4,68	13,71	21,66	11,98
4	H	Br	H	75,3	»	163,5—164	35,98	4,10	25,99	18,25	10,00	$C_9H_{12}BrN_4P$	35,66	3,99	26,37	18,48	10,22
5	H	I	H	78,1	»	167,5—168,5 (161)†	31,03	3,46	36,88	16,30	9,03	$C_9H_{12}IN_4OP$	30,87	3,46	36,25	16,00	8,85
6	CH_3	Br	H	85	»	155,5—156	37,79	4,30	24,97	17,64	9,96	$C_{10}H_{14}BrN_4OP$	37,87	4,45	25,20	17,67	9,77
7	H	Cl	Cl	90	»	141,5—142	36,82	3,81	24,41	19,52	10,73	$C_9H_{11}Cl_2N_4OP$	36,88	3,78	24,19	19,12	10,53
8	H	Br	Br	95,4	»	135—6	28,29	2,89	—	14,72	8,20	$C_9H_{11}Br_2N_4OP$	28,29	2,90	—	14,67	8,11
9	H	NO_2	H	77,8	Methanol	167—167,5 (162) *	40,24	4,64	—	25,97	11,00	$C_9H_{12}N_5O_3P$	40,15	4,49	—	26,02	11,51
10	H	H	NO_2	88,5	Ethyl acetate	120—121,5	40,25	4,70	—	25,76	11,80	$C_9H_{12}N_5O_3P$	40,15	4,49	—	26,02	11,51
11	CH_3	NO_2	H	66,2	»	176—176,5‡ (172)†	42,74	4,91	—	25,00	10,86	$C_{10}H_{14}N_5O_3P$	42,40	4,98	—	24,73	10,94
12	CH_3	H	NO_2	69	»	151—2 ‡	42,38	4,99	—	24,43	11,11	$C_{10}H_{14}N_5O_3P$	42,40	4,98	—	24,73	10,94
13	H	Cl	NO_2	90,5	»	123—4	36,00	3,38	11,81	22,41	10,14	$C_9H_{11}ClN_5O_3P$	35,60	3,65	11,68	23,07	10,20
14	CH_3	Br	Br	96,2	»	132,5—133,5	30,09	3,53	—	14,02	7,76	$C_{10}H_{13}Br_2N_4OP$	30,32	3,31	—	14,15	7,82

*Yield of crude product, 10-20% less on crystallization.

†Temperature at which the capillary was introduced.

‡Decomposition temperature.

were treated (without isolation) with an equimolecular amount of anhydrous formic acid, and the corresponding pyridyl-2-amidophosphoric dichlorides (III) were isolated. The 5-chloropyridyl-2-amidophosphoric dichloride obtained by this method was identical to the compounds synthesized by reaction of phosphorus oxychloride with 2-amino-5-chloropyridine. The preparation of the corresponding pyridyl-2-amido phosphoric dichlorides by reaction of anhydrous formic acid with the trichlorophosphazopyridines is an indirect proof of the formation, during the reaction of monomeric 2-trichlorophosphazopyridines since the dimers do not give the corresponding dichlorides under these conditions [7]:



II III IV

Dichlorides (III) are crystalline substances which are readily soluble in chloroform and are gradually hydrolyzed by moist air (Table 1).

On heating with water, compounds (III) form the corresponding 2-aminopyridines on their hydrochloride salts. The diethyleneimides of the corresponding pyridyl-2-amidophosphoric acids (IV) are obtained by reaction of (III) with ethyleneimine in the presence of triethylamine. The diethyleneimides (IV) are crystalline substances which are stable under the usual conditions, and are soluble in chloroform, alcohol, and acetone. Compounds Nos. 1, 2, 10, and 13 (Table 2) are soluble in water.

EXPERIMENTAL

Pyridyl-2-amidophosphoric Dichloride (III, $R_1 = R_2 = R_3 = H$)

A suspension of 3 g of 2-aminopyridine and 6.65 g of phosphorus pentachloride in 50 ml of benzene was refluxed for 2 h with stirring under nitrogen. The reaction mass was cooled and filtered under nitrogen. The precipitate was washed with ether, 100 ml of ether was added, and the mixture was treated with 1.47 g of anhydrous formic acid in 20 ml of ether with cooling (10-15°). The mixture was then stirred for 3 h and allowed to stand for 12 h. The precipitate was filtered and washed with ether to give 5.86 g (87%) of a substance with mp 177-180°. Found %: Cl 33.65. $C_5H_5Cl_2N_2OP$. Calculated %: Cl 33.61.

6-Methylpyridyl-2-amidophosphoric Dichloride (III, $R_1 = CH_3$, $R_2 = R_3 = H$)

A suspension of 2 g of 2-amino-6-methylpyridine and 3.86 g of phosphorus pentachloride in 30 ml of benzene was refluxed for 5 h with stirring under nitrogen. The reaction mixture was then cooled and treated with 0.85 g of anhydrous formic acid in 10 ml of ether with cooling (10-15°). The mixture was then stirred for 4.5 h, and the precipitate was filtered and washed with ether to give 4.34 g (91.7%) of 6-methylpyridyl-2-amidophosphoric dichloride hydrochloride with mp 127-129° (decomposition). Found %: Cl 39.78. $C_6H_7Cl_2N_2OP \cdot HCl$. Calculated %: Cl 40.68.

Standard Experiment. A mixture of 0.01 mole of the corresponding 2-aminopyridine and 0.01 mole of phosphorus pentachloride in 30-50 ml of benzene was refluxed with stirring under nitrogen until hydrogen chloride evolution ceased. The reaction mass was cooled and treated with 0.01 mole of anhydrous formic acid with cooling (10-15°). The mixture was then stirred for 2-3 h at 20°, after which the precipitate was either filtered or the solvent removed to obtain the corresponding pyridyl-2-amidophosphoric dichloride. For analysis, a sample was dissolved in an organic solvent, the solution shaken with carbon black and filtered, and the filtrate evaporated to 3/4 of its initial volume. The compound crystallized out on standing. The data are presented in Table 1.

5-Chloropyridyl-2-amidophosphoric Dichloride (III, $R_1 = R_3 = H$, $R_2 = Cl$)

A suspension of 1 g of 2-amino-5-chloropyridine in 10 ml of freshly distilled phosphorus oxychloride was refluxed for 1 h. The phosphorus oxychloride was removed in vacuo and the residue was washed with petroleum ether to give 1.91 g (99.4%) of 5-chloropyridyl-2-amidophosphoric dichloride which was identical to the dichloride obtained from 2-amino-5-chloropyridine by reaction with phosphorus pentachloride (see Table 1, compound No. 1).

Pyridyl-2-amidophosphoric Diethyleneimides (IV)

The dichloride (0.03 mole) of the corresponding pyridyl-2-amidophosphoric acid was added with stirring and cooling (8-12°) to a solution of 0.06 mole of ethyleneimine and 0.06 mole of triethylamine in 100 ml of benzene. The mixture was stirred at this temperature for 0.5 h and for 2-3 h at 20°, and then allowed to stand for 12 h. The precipitate was filtered and extracted twice with boiling benzene (2 · 80 ml). The mother liquors were combined, the solvent was removed in vacuo, and the residue was washed with ether and recrystallized. The data are presented in Table 2.

5-Nitropyridyl-2-amidophosphoric Diethyleneimide (IV, $R_1 = R_3 = H$, $R_2 = NO_2$)

The dichloride (0.02 mole) of 5-nitro-pyridyl-2-amidophosphoric acid was added with stirring and cooling (8-12°) to a solution of 0.04 mole of ethyleneimine and 0.04 mole of triethylamine in 80 ml of benzene. The reaction mass was then stirred for 0.5 h at the same temperature and then for 2 h at 20°. The precipitate was filtered and washed with ether and then with 5 ml of water. The residue was dried in vacuo over phosphorus pentachloride and recrystallized.

LITERATURE CITED

1. I. E. Mamaeva, N. V. Sazonov, and A. A. Kropacheva, Khim.-Farmats. Zh., Vol. 2, No. 2, 31 (1968).
2. British Patent No. 885,370; Chem. Abstr., 58, 7949e (1963).
3. A. A. Kropacheva and N. V. Sazonov, Khim. Geterotsikl. Soed., No. 3, 433 (1965).
4. N. V. Sazonov and A. A. Kropacheva, Khim. Geterotsikl. Soed., No. 1, 55 (1970).
5. A. Katritskii and J. Logovskaya, Chemistry of Heterocyclic Compounds [in Russian], Moscow (1953), p. 73.
6. A. V. Kirsanov and G. I. Derkach, Zh. Obshch. Khim., 26, 2009 (1956); 27, 3248 (1957); 28, 1887 (1958).
7. I. N. Zhmurova and A. V. Kirsanov, Zh. Obshch. Khim., 30, 4048 (1960).