ETHYLENIMINE DERIVATIVES. VI. DIETHYLENIMIDES OF PYRIMIDYL-5-AMIDOPHOSPHORIC ACID*

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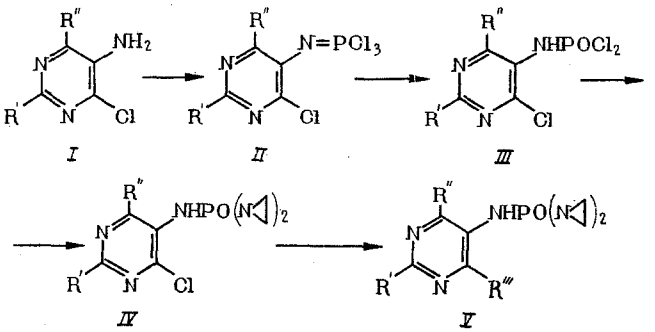
We have shown earlier, that 5-aminopyrimidines (I) containing a chlorine atom in the 4-position on the pyrimidine ring, react with PCl_5 to form monomeric 5-trichlorophosphazopyrimidines (II).

Our present work indicates that 5-trichlorophosphazopyrimidines are analogous to the trichlorophosphazo compounds of amides of carboxylic acids [2, 3], of sulfanilamides [4], of 2-aminopyrimidines [5], in their reactions with formic acid to form dichloroanhydrides of the corresponding amidophosphoric acids (III). The dichloroanhydrides of pyrimidyl-5-amidophosphoric acids (III) are crystalline substances, easily hydrolyzed in moist air. Various derivatives of pyrimidyl-5-amidophosphoric acid can be obtained from them by nucleophilic substitution of the chlorine bonded to phosphorus. We used these compounds, in part, for the synthesis of diethylenimides of the corresponding pyrimidyl-5-amidophosphoric acids (IV).



Diethylenimides of pyrimidyl-5-amidophosphoric acids (IV) having two chlorine atoms on the pyrimidine ring exchange one of them for the amine residue. We encountered two examples. In the first case (IV, R' = H, R" = Cl) one chlorine atom was replaced by a secondary aliphatic amine residue (dimethyl- and diethylamine), by a heterocyclic amine (piperidine, pyrrolidine, and ethylenimine) and by an aralkyl amine (benzylamine). In the second case, (IV, R' = CH_3, R" = Cl) the chlorine was replaced by a residue of piperidine, morpholine and ethylenimine, respectively. The substitution reaction proceeds in methanol at 20°C.

The diethylenimides of pyrimidyl-5-phosphoric acids (IV), having one or two chlorine atoms on the pyrimidine ring, are dehalogenated by a palladium catalyst at normal pressure and 20° in methanol, in the presence of triethylamine, We dehalogenated the diethylenimides of IV, where R' = H, and R" = Cl, $-OCH_3$, $-NC_5H_{10}$, $-NC_2H_4$ (see Table 1).

Diethylenimides of pyrimidyl-5-amidophosphoric acids are colorless crystalline compounds, stable under normal conditions, soluble in water, alcohol and chloroform.

EXPERIMENTAL PART

Dichloroanhydride of 4,6-Dichlorpyrimidyl-5-amidophosphoric acid (III, R' = H, R" = Cl). A suspension of 7 g (0.0427 mole) of 5-amino-4,6-dichloropyrimidine and 8.9 g (0.0427 mole) of PCl_5 in 60 ml of benzene was stirred and heated to 70° in a stream of nitrogen for 1.5 h. The benzene solution was stirred with carbon and filtered under nitrogen. After the benzene was evaporated under vacuum, the residue was

*For paper V in this series, see [1].

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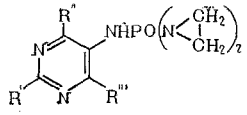
TABLE 1. Properties of Compounds (V) Synthesized



Serial No.	R′	R″	R‴	Yield, %	Mp (°C)	Recrystallization solvent	Found, %					Empirical formula	Calculated, %				
							C	H	Cl	N	P		C	H	Cl	N	P
1	CH_3	Cl	Cl	65	147,5—8	Acetone	34,74	4,20	22,81	22,46	10,0	$C_9H_{12}Cl_2N_5OP$	35,08	3,92	23,02	22,73	10,06
2	H	$N(CH_3)_2$	Cl	38,5	169—9,5	Acetone and methanol (10:1)	39,57	5,08	11,42	27,56	10,54	$C_{10}H_{16}ClN_6OP$	39,68	5,32	11,71	27,76	10,23
3	H	$N(C_2H_5)_2$	Cl	40,17	169,5[1] (155)[2]	Ethyl acetate	43,85	6,08	10,38	25,68	9,3	$C_{12}H_{20}ClN_6OP$	43,57	6,09	10,72	25,41	9,37
4	H		Cl	69,8	177-8	Acetone and methanol (3:1)	45,29	5,92	10,04	24,30	9,50	$C_{13}H_{20}ClN_6OP$	45,55	5,88	10,34	24,52	9,04
5	H		Cl	68	184,5—5	Acetone and methanol (1:1)	43,97	5,72	10,89	25,49	9,38	$C_{12}H_{18}ClN_6OP$	43,84	5,52	10,80	25,56	9,42
6	H		Cl	63,5	188[1] (186)[2]	Acetone and methanol	40,20	5,25	11,41	27,72	10,14	$C_{10}H_{14}ClN_6OP$	39,94	4,69	11,79	27,92	10,3
7	H	$NHCH_2C_6H_5$	Cl	50	149,5—50,5	Ethyl acetate	49,77	5,20	9,17	23,17	8,59	$C_{15}H_{18}ClN_6OP$	49,38	4,97	9,72	23,04	8,49
8	CH_3	morpholyl	Cl	65	168,5—9,5	Acetone	43,85	5,65	10,21	23,36	8,89	$C_{13}H_{20}ClN_6O_2P$	43,52	5,62	9,88	23,43	8,64
9	CH_3	piperidyl	Cl	53,6	178—8,5	Acetone	47,30	6,36	10,22	23,65	8,80	$C_{14}H_{22}ClN_6OP$	47,12	6,23	9,94	23,56	8,68
10	CH_3	ethylenimyl	Cl	63	171,5[1] (170)[2]	Acetone and methanol (10:1)	41,73	5,25	11,10	26,55	9,81	$C_{11}H_{16}ClN_6OP$	41,98	5,12	11,27	26,71	9,84
11	H	OCH_3	H	54,4	130—30,5	Ethyl acetate	42,26	5,77	—	27,40	12,30	$C_9H_{14}N_5O_2P$	42,35	5,53	—	27,44	12,12
12	H		H	48,8	125—5,5	Ethyl acetate	50,41	6,80	—	26,98	9,65	$C_{13}H_{21}N_6OP$	50,64	6,86	—	27,26	10,05
13	H		H	65,3	119[1] (115)[2]	Ethyl acetate	45,15	5,88	—	31,46	11,66	$C_{10}H_{15}N_6OP$	45,12	5,68	—	31,57	11,63

[1]Decomposition temperature.

[2]Capillary insertion temperature.

dissolved in a mixture of dry ether and petroleum ether. To this solution was added a solution of 1.97 g (0.0427 mole) of anhydrous formic acid in 20 ml of ether at 10-15°. After the resulting reaction mixture was stirred for 1.5 h at 20°, and allowed to stand overnight, the solvent was evaporated under vacuum, yielding 11.45 g (95.5%) of the dichloroanhydride of 4,6-dichloropyrimidyl-5-amidophosphoric acid, mp 121-125°. Found, %: $Cl_{(hydrol.)}$ 25.42. $C_4H_2Cl_4N_3OP$. Calculated, %: $Cl_{(hydrol.)}$ 25.25.

By analogous procedures, the dichloroanhydride of 4,6-dichloro-2-methyl-5-amidophosphoric acid (III, R' = CH_3, R" = Cl) was obtained in 91.6% yield, mp 139-140.5°. Found, %: $Cl_{(hydrol.)}$ 23.46. $C_5H_4Cl_4N_3OP$. Calculated, %: Cl 24.05.

Dichloroanhydride of 4-Chloro-6-methoxypyrimidyl-5-amidophosphoric Acid (III, R' = H, R" = OCH_3). A suspension of 2 g (0.0125 mole) of 5-amino-4-chloro-6-methoxypyrimidine and 2.61 g (0.0125 mole) of PCl_5 in 40 ml of benzene was stirred 1.5 h at 70° in a stream of nitrogen. The solution was then stirred with carbon, filtered under nitrogen. To the mother liquor, cooled to 15-20°, 0.57 g (0.0125 mole) of anhydrous formic acid in 10 ml of ether, was added with stirring. After stirring for 2 h at 20°, the mixture was allowed to stand overnight. The residue was filtered off and washed with ether, yielding 2.62 g (72.5%) of the dichloroanhydride of 4-chloro-6-methoxypyrimidyl-5-amidophosphoric acid, decomposition temperature 85°. Found, %: $Cl_{(hydrol.)}$ 25.46. $C_5H_5Cl_3N_3O_2P$. Calculated, %: $Cl_{(hydrol)}$ 25.65.

In an analogous manner, after treatment of an anhydrous solution of the trichlorophosphazo compound with anhydrous acetic acid and evaporating the solvent under vacuum, we obtained the dichloride of 4-chloro-6-morpholinopyrimidyl-5-amidophosphoric acid in 87.4% yield, decomposition temperature 119°. Found, %: $Cl_{(hydrol.)}$ 21.28. $C_8H_{10}Cl_3N_4O_2P$. Calculated, %: $Cl_{(hydrol.)}$ 21.39.

Diethylenimide of 4,6-Dichloropyrimidyl-5-amidophosphoric Acid (IV, R' = H, R" = Cl). To a solution of 2.71 g (0.0628 mole) of ethylenimine and 6.3 g (0.0628 mole) of triethylamine in 150 ml, with stirring and cooling (8-10°) was added 8.82 g (0.0314 mole) of the dichloroanhydride of 4,6-dichloropyrimidyl-5-amidophosphoric acid. After this reaction mixture was stirred for 1 h in the cold, and then 1 h at 20°, the residue was filtered off, washed with ether, dried on the filter, and then washed with 5 ml of water and with acetone. The resulting diethylenimide crystallizes from an acetone-methanol (5:1) mixture. The yield was 6.36 g (69%), decomposition temperature 161.5° (when the capillary insertion temperature was 154°). Found, %: C 33.19; H 3.44; N 23.67; P 10.03. $C_8H_{10}Cl_2N_5OP$. Calculated, %: C 32.67; H 3.43; N 23.82; P 10.53.

Diethylenimide of 4-Chloro-6-Morpholinopyrimidyl-5-amidophosphoric Acid (IV, R' = H, R" - Morpholino). A solution of 2.5 g (0.0085 mole) of the diethylenimide of 4,6-dichloropyrimidyl-5-amidophosphoric acid and 1.48 g (0.017 mole) of morpholine in 40 ml of methanol was allowed to stand for two days at 20°. The solvent was evaporated and the residue boiled with 150 ml of ethyl acetate and filtered off. The ethyl acetate was evaporated in vacuum, and the residue recrystallized from ethyl acetate. The yield was 1.17 g (40.4%), mp 163.5-164°. Found, %: C 41.91; H 5.22; Cl 10.29; N 24.38; P 8.99. $C_{12}H_{18}ClN_6O_2P$. Calculated, %: C 41.80; H 5.26; Cl 10.29; N 24.38; P 8.99.

By analogous procedures, we prepared compounds 2-10 shown in Table 1.

Diethylenimide of Pyrimidyl-5-amidophosphoric Acid (V, R' = R" = H). A hydrogenation flask was charged with 1.65 g (0.0056 mole) of the ethylenimide of 4,6-dichloropyrimidyl-5-amidophosphoric acid, 1.15 g (0.0112 mole) of triethylamine, 0.4 g of 5% Pd on C (BAU brand) and 80 ml of absolute methanol. Dehalogenation proceeds at 20° at atmospheric pressure. The calculated amount of hydrogen was absorbed in $3^1/_2$ h. The catalyst was filtered off and washed with methanol, the solvent evaporated under vacuum and the residue boiled with ethyl acetate (80 ml × 2) and filtered off. The ethyl acetate was evaporated and the residue recrystallized from ethyl acetate. The yield was 0.6 g (48.5%), decomposition temperature 153.5° (at a capillary insertion temperature of 145°). Found, %: C 42.98; H 5.28; N 31.49. $C_8H_{12}N_5OP$. Calculated, %: C 42.66; H 5.37; N 31.10.

By analogous procedures, we prepared the diethylenimides of the pyrimidyl-5-aminophosphoric acids shown in the table under Nos. 11-13.

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