THE REACTION OF PENTACHLOROPYRIDINE WITH ALIPHATIC AMINES

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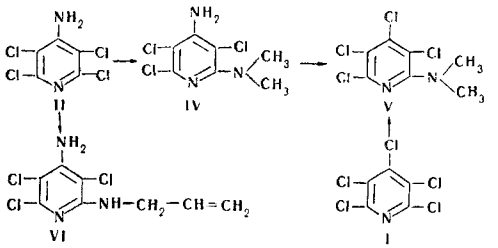
The reaction of pentachloropyridine with aliphatic amines has given a series of 2-alkylaminotetrachloropyridines.

In recent years, among polychloropyridine derivatives effective herbicides (4-amino-3,5,6-trichloropicolinic acid, 3,5,6-trichloropyridin-4-ol, and others) have been discovered which are finding use in agriculture [1]. In order to discover new plant growth regulators among amino derivatives of the polychloropyridines, we have synthesized a number of alkylaminotetrachloropyridines.

According to the information in the literature, the chlorine atom in position 4 of the pyridine nucleus possesses the greatest reactivity in reactions of pentachloropyridine (I) with nucleophilic reagents, the chlorine atoms in position 2 and 4 are less reactive, and those in position 3 and 5 still less [2-5].

In the reaction of I with the various aliphatic amines, and also with piperidine and morpholine, the predominant formation of 4-alkylaminotetrachloropyridines together with the corresponding 2,4-derivatives could have been expected. However, as was established in 1967 [6, 7] on the basis of NMR and mass spectroscopic studies, the main products of the reaction between I and aliphatic amines are 2-alkylaminotetrachloropyridine.

In addition to performing the reaction between I and aliphatic amines, we have also carried out directed synthesis of 2-alkylaminotetrachloropyridines. As the starting materials we used two substances: 4-amino-2,3,5,6-tetrachloropyridine (II) and 2,3,5,6-tetrachloro-4-ethoxypyridine (III) [2,8]. A comparison of the compounds obtained in the two cases showed that a nucleophilic attack of aliphatic amines is actually directed exclusively or predominantly to position 2 of the pyridine nucleus. The reaction of II with an aqueous ethanolic solution of dimethylamine in a sealed tube (125°C, 5 h) gave 4-amino-3,5,6-trichloro-2-dimethylaminopyridine (IV), the diazotization of which is hydrochloric acid leads to 3,4,5,6-tetrachloro-2-dimethylaminopyridine (V). An analogous product was obtained directly from I and dimethylamine.



The introduction of a dimethylamino group into position 2 of compound II facilitates its diazotization. When a weaker electron donor (alkylamino group) is introduced, it is impossible to diazotize the amino group. Consequently, the second key substance was III, with which a reaction with morpholine was carried out at 125°C. The 3,5,6-trichloro-4-ethoxy-2-morpholinopyridine (VII) isolated was converted by saponification

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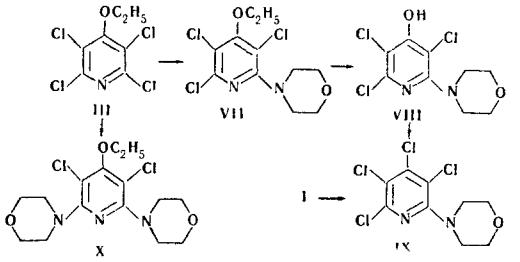
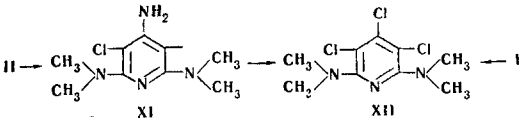
with 80% sulfuric acid into 3,5,6-trichloro-2-morpholinopyridin-4-ol (VIII), the action of phosphorous oxychloride on which gave 3,4,5,6-tetrachloro-2-morpholinopyridine (IX). A mixture of IX with the product obtained directly from I and morpholine gave no depression of the melting point. The reaction of III with morpholine at 170°C forms 3,5-dichloro-4-ethoxy-2,6-dimorpholinopyridine (X).



The reaction of I with aliphatic amines was carried out in ethanolic dioxane solution at 60-70°C for 4-5 h. Under these conditions all the primary alkylamines gave the corresponding 2-alkylamino-3,4,5,6-tetrachloropyridines and dimethylamine gave 3,4,5-trichloro-2,6-bis(dimethylamino)pyridine (XII). The preparation of V required milder reaction conditions (45°C, 2 h 30 min). To prove the structure of XII, compound II was treated with dimethylamine (170°C, 4 h). The 4-amino-3,5-dichloro-2,6-bis-(dimethylamino)pyridine (XI) so formed was converted into XII by diazotization in hydrochloric acid. A mixture of this product with the product obtained from I and dimethylamine at 60-70°C gave no depression of the melting point.



The preferential direction of the reaction of I with aliphatic amines at position 2 is explained, in all probability, by the fact that the α position in I is sterically less blocked than the γ position.

EXPERIMENTAL

4-Amino-3,5,6-trichloro-2-dimethylaminopyridine (IV). A mixture of 1.2 g (0.005 mole) of II, 1.7 g (0.012 mole) of 33% aqueous dimethylamine, and 5 ml of ethanol was placed in a glass tube and heated at 125°C for 5 h. After cooling, the tube was opened and the contents were poured into water, the crystals that deposited being filtered off. Yield 1 g (86%), mp 69-70°C (from ethanol). Found %: Cl 44.47; N 17.95. $C_7H_8Cl_3N_3$. Calculated %: Cl 44.28; N 17.46.

3,4,5,6-Tetrachloro-2-dimethylaminopyridine (V). a. A solution of 1.2 g (0.05 mole) of IV in 15 ml of concentrated hydrochloric acid was cooled to 0°C. The mixture was saturated for another 10 min with hydrogen chloride at this temperature and then, with vigorous stirring and cooling, a saturated aqueous solution of 0.4 g (0.006 mole) of $NaNO_2$ was added in portions. The solution acquired a blue coloration immediately after the addition of the first portions of sodium nitrite and retained it until the end of the reaction. Then the mixture was kept in the refrigerator for 1 h, diluted with water, and left overnight at room temperature. The crystals that deposited were filtered off. Yield 1.1 g (83%), mp 48-50°C (from aqueous ethanol). Found %: Cl 54.59; N 10.93. $C_7H_6Cl_4N_2$. Calculated %: Cl 54.61; N 10.77.

b. Five grams (0.02 mole) of I was dissolved in 60 ml of dioxane–ethanol (1 : 1), 7 ml (0.05 mole) of 33% aqueous dimethylamine was added, the mixture was heated at 45°C for 2 h 30 min, the bulk of the solvent was distilled off, and the residue was cooled and diluted with a large amount of water. The oil that separated out was extracted several times with ether, the extract was dried with sodium sulfate, the ether was distilled off, and the oil was distilled in vacuum. Yield 3.6 g (70%), bp 107-109°C (1 mm), mp 48°C (from aqueous ethanol). Found %: Cl 54.41; N 10.75. $C_7H_6Cl_4N_2$. Calculated %: Cl 54.61; N 10.77.

3,4,5,6-Tetrachloro-2-diethylaminopyridine was obtained similarly; yield 65%, bp 109-110°C (1 mm). Found %: Cl 49.78; N 9.63. $C_9H_{10}Cl_4N_2$. Calculated %: Cl 49.30; N 9.72.

TABLE 1. Characteristics of the Compounds Obtained

R	bp, °C (pressure, mm)	mp, °C	Solvent for crystallization	Empirical formula	Found, %		Calc., %		Yield, %
					Cl	N	Cl	N	
CH_3	—	125—126	Hexane	$C_6H_4Cl_4N_2$	57,70	11,45	57,72	11,38	50
C_2H_5	—	68—69	Petroleum ether	$C_7H_6Cl_4N_2$	54,83	10,61	54,61	10,76	62
$CH_2—CH_2—OH$	—	127—128	Benzene	$C_7H_6Cl_4N_2O$	51,91	10,16	51,44	10,14	78
$CH_2—CH=CH_2$	135—136 (1)	56—57	Ethanol	$C_8H_6Cl_4N_2$	52,02	10,22	52,20	10,29	80
n-C_3H_7	133—135 (1)	—	—	$C_8H_8Cl_4N_2$	51,87	—	51,82	—	65
i-C_3H_7	130—132 (1)	65—66	Ethanol	$C_8H_8Cl_4N_2$	52,31	10,02	51,82	10,21	64
n-C_4H_9	128 (0,5)	—	—	$C_9H_{10}Cl_4N_2$	49,03	9,70	49,30	9,72	55
i-C_4H_9	130—132 (1)	—	—	$C_9H_{10}Cl_4N_2$	49,07	9,67	49,30	9,72	75

2-Allylamino-4-amino-3,5,6-trichloropyridine (VI). A mixture of 1.2 g (0.005 mole) of II, 0.85 g (0.015 mole) of allylamine, and 5 ml of ethanol was sealed in a tube and heated at 180°C for 4 h. After cooling, the tube was opened and the contents were poured into water; the oil that separated out crystallized on cooling. Yield 1.1 g (88%), mp 72-74°C (from petroleum ether). Found %: Cl 42.48; N 16.53. $C_8H_8Cl_3N_3$. Calculated %: Cl 42.17; N 16.63.

3,5,6-Trichloro-4-ethoxy-2-morpholinopyridine (VII). A mixture of 1.3 g (0.005 mole) of III, 1 g (0.011 mole) of freshly distilled morpholine, and 5 ml of ethanol was charged into a tube and heated at 120-125°C for 4 h. After the ethanol had been driven off in vacuum, the residue was diluted with water and an oil separated out which crystallized on cooling. Yield 1.4 g (92%), mp 51-52°C (from aqueous ethanol). Found %: Cl 34.06; N 9.04. $C_{11}H_{13}Cl_3N_2O_2$. Calculated %: Cl 34.18; N 8.98.

3,5,6-Trichloro-4-hydroxy-2-morpholinopyridine (VIII). A solution of 1.5 g (0.005 mole) of VI in 3 ml of 80% H_2SO_4 was heated at 150-160°C for 20 min. Then it was poured into ice water and the crystals that separated out were filtered off. Yield 1.3 g (92%), mp 224-225°C (from ethanol). Found %: Cl 37.29; N 10.18. $C_9H_9Cl_3N_2O_2$. Calculated %: Cl 37.56; N 9.87.

3,4,5,6-Tetrachloro-2-morpholinopyridine (IX). a. A mixture of 1.4 g (0.005 mole) of VIII and 5 ml of $POCl_3$ was heated in a sealed tube at 170°C for 4 h. After cooling, the contents were poured onto ice, and the crystals that deposited were filtered off. Yield 1.2 g (80%), mp 83°C (from ethanol). Found %: Cl 46.56. $C_9H_8Cl_4N_2O$. Calculated %: Cl 47.02.

b. An ethanolic solution of 1.3 g (0.015 mole) of freshly distilled morpholine was added to 1.2 g (0.005 mole) of I in 20 ml of dioxane and the mixture was heated at the boil for 1 h. The solvent was distilled off in vacuum and the residue was treated with water and extracted with ether, and the oil remaining after the evaporation of the ether crystallized. Yield 1.3 g (86%), mp 84°C (from ethanol). Found %: Cl 46.80; N 9.17. $C_9H_8Cl_4N_2O$. Calculated %: Cl 47.02; N 9.27.

3,4,5,6-Tetrachloro-2-piperidinopyridine. A solution of 5 g (0.02 mole) of I in 60 ml of a mixture of dioxane and ethanol (1 : 1) was treated with 4 g (0.042 mole) of piperidine, and the mixture was heated in the water at 70-75°C for 4 h. The bulk of the solvent was distilled off and the residue was diluted with water and made faintly acid with hydrochloric acid. The oil that separated out was extracted several times with ether, the extract was dried with sodium sulfate, the ether was evaporated off, and the residue was distilled in vacuum. Yield 4.1 g (68%), bp 174-175°C (1 mm), mp 44°C (from aqueous ethanol). Found %: Cl 47.88. $C_{10}H_{10}Cl_4N_2$. Calculated %: Cl 47.33.

3,5-Dichloro-4-ethoxy-2,6-dimorpholinopyridine (X). A mixture of 1.3 g (0.005 mole) of III, 2.6 g (0.03 mole) of freshly distilled morpholine, and 5 ml of ethanol was heated in a tube at 170°C for 4 h. Then the mixture was poured into water and the crystals that separated out were filtered off and boiled with carbon in ethanol. Yield 1.3 g (70%), mp 117-119°C (from aqueous ethanol). Found %: Cl 19.25; N 11.68. $C_{15}H_{21}Cl_2N_3O_3$. Calculated %: Cl 19.61; N 11.60.

4-Amino-3,5-dichloro-2,6-bis(dimethylamino)pyridine (XI). A mixture of 1.2 g (0.005 mole) of II, 4.2 g (0.03) mole of 33% aqueous dimethylamine, and 8 ml of dioxane was heated in a tube at 170°C for 4 h, and was then poured into water . Yield 1 g (84%), mp 55°C (from ethanol). Found %: Cl 28.86; N 22.53. $C_9H_{14}Cl_2N_4$. Calculated %: Cl 28.35; N 22.49.

3,4,5-Trichloro-2,6-bis(dimethylamino)pyridine (XII). a. A solution of 0.5 g (0.002 mole) of XI in 10 ml of concentrated hydrochloric acid was cooled to 0°C and the mixture was saturated for another 10 min with hydrogen chloride, after which a saturated aqueous solution of 0.15 g (0.0021 mole) of $NaNO_2$ was added dropwise, the temperature being kept at from 0 to −10°C throughout. The mixture was first left in the refrigerator for 1 h and then at room temperature for 12 h. Then it was made alkaline, whereupon crystals deposited. Yield 0.4 g (74%), bp 72-73°C (from aqueous ethanol). Found %: Cl 39.56; N 15.70. $C_9H_{12}Cl_3N_3$. Calculated %: Cl 39.66; N 15.60.

b. A solution of 5 g (0.02 mole) of I in 50 ml of dioxane was treated with 14 ml (0.01 mole) of 33% aqueous dimethylamine and 20 ml of ethanol and was heated at 55-60°C for 6 h. During the reaction, another two 5-ml portions of 33% dimethylamine were added. After cooling, the reaction mixture was diluted with water, the oil that separated out was extracted with ether and dried with sodium sulfate, the ether was driven off, and the residual oil was distilled in vacuum. Yield 3.2 g (60%), bp 114-115°C (1 mm), mp 71-73°C. Found %: Cl 40.16; N 15.40. $C_9H_{12}Cl_3N_3$. Calculated %: Cl 39.66; N 15.60.

General Method of Preparing 2-Alkylamino-3,4,5,6-tetrachloropyridines (Table 1). To a solution of 5 g (0.02 mole) of I in 60 ml of a mixture of dioxane and ethanol (1 : 1) was added 0.042 mole of the appropriate alkylamine and the mixture was heated at 70°C for 3-5 h. The bulk of the solvent was distilled off, and the residue was cooled and diluted with water. The crystals that deposited were filtered off. In the case of a low-melting product, the oil that separated out was extracted with ether, the ethereal extracts were dried with sodium sulfate, the ether was driven off, and the oil was distilled in vacuum.

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