PHOSPHORIC AND PHOSPHOROTHIOIC ESTERS CONTAINING HETEROCYCLIC GROUPS

COMMUNICATION 6. REACTION OF PHOSPHORIC AND PHOSPHOROTHIOIC CHLORIDES WITH BENZIMIDAZOLE AND WITH MORPHOLINE

(UDC 547.27+661.718)

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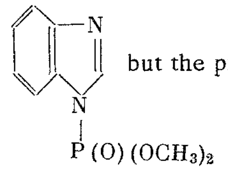
In the development of our investigations on organophosphorus compounds containing heterocyclic groups, which are of potential physiological activity [1], we have studied the reactions of dialkyl phosphorochloridates, dialkyl phosphorochloridothioates, and N,N,N',N'-tetraalkylphosphorodiamidic chlorides with the sodium salt of benzimidazole and with morpholine. The reaction of the acid chlorides with the sodium salt of benzimidazole was carried out in acetonitrile solution, because we have found previously that in other solvents reaction did not go or was very slow.

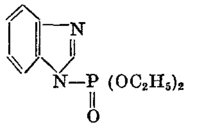
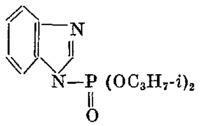
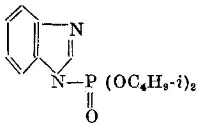
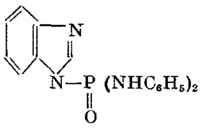
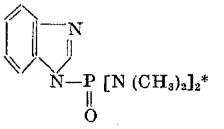
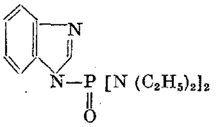
We obtained the products of the reaction of diethyl phosphorochloridate diisopropyl phosphorochloridate, diisobutyl phosphorochloridate, N,N'-diphenylphosphorodiamidic chloride, and N,N,N',N'-tetraethylphosphorodiamidic chloride with the sodium salt of benzimidazole (Table 1). The substances synthesized are readily soluble in methanol, ethanol, benzene, acetone, and chloroform; less soluble in petroleum ether. Many of them are readily soluble in water.

In the remaining cases (in the reactions of dimethyl phosphorochloridate, diethyl phosphorochloridothioate, and N,N,N',N'-tetramethylphosphorodiamidic chloride with the sodium salt of benzimidazole) we obtained viscous liquids which we could not cause to crystallize by the method used in the syntheses of all the above-described crystalline amido esters (cooling, rubbing with a glass rod, addition of petroleum ether). With the object of isolating these reaction products in the pure state, after the removal of solvent the reaction mixtures were vacuum-distilled. However, on distillation, even in a high vacuum, in almost every case we succeeded in isolating only a small amount of a liquid product which did not contain phosphorus. The greater part of the reaction product remained in the distilling flask as a hard glassy mass. Thus, in the distillation of the product of the reaction of dimethyl phosphorochloridate with the sodium salt of benzimidazole we isolated a product which, according to analysis, was not the expected amido ester  but the product of the thermal decomposition of this, i.e., somewhat impure 1-methylbenzimidazole. Confirmation of the structure of the product of b.p. 91.5-92° (0.015 mm) as 1-methylbenzimidazole was provided by the preparation of its picrate by the action of an alcoholic solution of picric acid. The melting point of this picrate was 245-246°, and the literature gives m.p. 246-247°.

When we attempted to distill the products of the reaction of $(C_2H_5O)_2P(O)Cl$ and of $(C_2H_5O)_2P(S)Cl$ with the sodium salt of benzimidazole we obtained alkylation products. The product was obtained in a purer state in the second case: b.p. 148° (6 mm); d_0^{20} 1.1146; n_D^{20} 1.5805; found MR 43.60; calculated MR for $C_9H_{10}N_2$ 43.60. The picrate obtained melted at 219-220°; according to the literature the picrate of 1-ethylbenzimidazole has m.p. 219-220°.

The alkylation of amines with dialkyl phosphorochloridates has been observed previously in the work of B. A. Arbuzov and co-workers [2] in the case of 2-aminopyridine and other amines. By distillation in a high vacuum we succeeded in isolating the product of the reaction of N,N,N',N'-tetramethylphosphorodiamidic chloride with the so-

TABLE 1

No.	Formula	M.p., °C	P, % Found	P, % Calc.	Yield, %
1		80—82	12,05	12,2	42
2		107	10,84	10,98	39
3		73—75	9,98	9,99	77,4
4		Softens at 212° and melts at 222°	9,46	8,91	75
5		B.p. 160-167° (0.015 mm); n_D^{20} 1.5521	—	—	59
6		84—88	10,43	10,06	68

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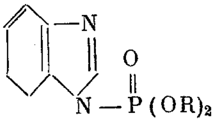
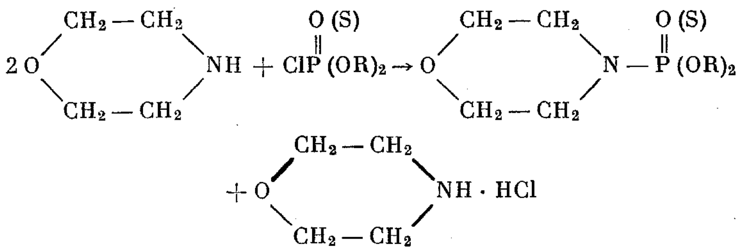
* A known substance, which has been prepared by Dutch chemists. The authors give b.p. 179-180° (1 mm) [3].

dium salt of benzimidazole (No. 5, Table 1). This substance was synthesized by the Dutch chemists Van Den Bos and co-workers in 1960 [3].*

When we treated the amido ester  with picric acid in alcoholic solution we encountered an interesting fact: we then obtained the picrate of benzimidazole itself, m.p. 223-224° (the literature gives m.p. 223°). The ease with which benzimidazole picrate is formed in the reaction with picric acid would appear to indicate the weakness of the N—P bond in the amido esters studied. The reactions of dialkyl phosphorochloridates with morpholine were carried out in a dry ether medium. To bind the hydrogen chloride liberated in the reaction we took a second molecule of morpholine:



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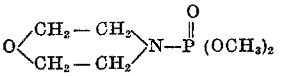
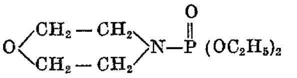
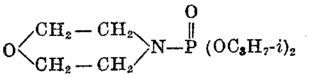
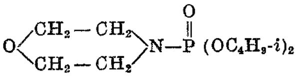
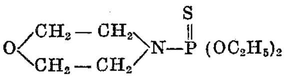
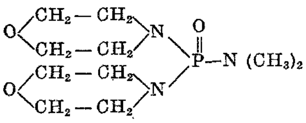
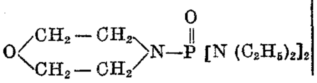
* The authors gave b.p. 179-180° (1 mm). The phosphorus content found differed by 1% from the calculated value. The authors gave no other data.

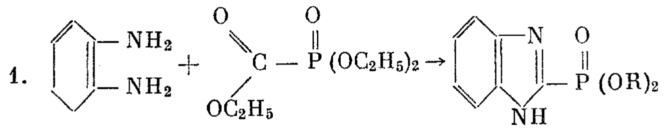
TABLE 2

Formula	B.p., °C (p, mm)	d_0^{20}	n_D^{20}	MR		P, %		Yield, %
				Found	Calc.	Found	Calc.	
	108—109 (3)	1,2300	1,4526	42,81	43,63	15,87	15,88	60
	114—115 (3,5)	1,1385	1,4478	52,41	52,87	13,84	13,89	68,3
	105 (1)	1,0742	1,4418	61,83	62,11	12,32	12,34	68,4
	147—147,5 (4)	1,0485	1,4464	71,01	71,34	11,18	11,10	55,1
	122—125 (5)	1,1425	1,4880	60,26	58,73	13,05	12,95	50
	172 (3); m.p.64—66	—	—	—	—	11,76	11,77	50
	152—153 (3)	1,0686	1,4808	73,76	75,94	11,05	11,18	68,8

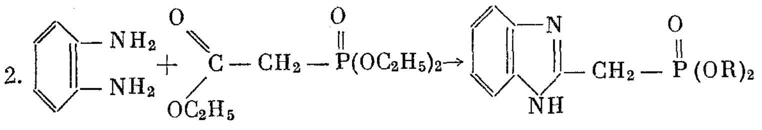
In the reactions of morpholine with dialkyl phosphorochloridates we obtained oils in all cases. The physical constants of the amido esters obtained are presented in Table 2. These compounds have a weak characteristic smell; they are readily soluble, both in the usual organic solvents and in water.

All the compounds that we synthesized—amido esters of phosphorus acids containing benzimidazole and morpholine groups—were sent to the Toxicological Laboratory of the Kazan' Chemical Institute for a study of their insecticidal and toxic properties and also to the Kazan' State Medical Institute for tests on their bacterial properties.

We also made attempts to synthesize phosphonic esters containing the benzimidazole group. It was thought to be interesting and possible to form a benzimidazole ring by the reaction of o-phenylenediamine with esters of phosphonoformic and phosphonoacetic acids:



(A)



(B)

The experiments were carried out under various conditions: in neutral and acid media and in xylene solution. When o-phenylenediamine was heated with the triethyl ester of phosphonoformic acid in presence of a catalyst (HCl) the phosphonoformic ester was hydrolyzed and condensation did not take place. In experiments with phosphonoacetic triester in neutral and acid media, in each case a little of a substance of m.p. 255-257° was obtained. Determination of the molecular weight by the cryoscopic method in glacial acetic acid and analysis for phosphorus content showed that the compound obtained was of the expected structure (B), but was not altogether pure.

EXPERIMENTAL

Reactions of Phosphorus Acid Chlorides with Benzimidazole

Reaction of Dimethyl Phosphorochloridate with the Sodium Salt of Benzimidazole. The sodium salt of benzimidazole was prepared by the reaction of benzimidazole with sodium dissolved in absolute methanol. Alcohol was removed in a vacuum, and the carefully dried salt formed a colorless crystalline mass. 6.6 g of dimethyl phosphorochloridate was added dropwise with mechanical stirring to a suspension of 6.4 g of the sodium salt of benzimidazole in 50 ml of dry acetonitrile. The reaction mixture became warm, and a fine precipitate of sodium chloride formed.

The reaction mixture was heated for three hours at a bath temperature of 50-55°. It was then cooled, and the precipitate of sodium chloride was filtered off (2.4 g). Acetonitrile was vacuum-distilled from the filtrate. We obtained a thick yellowish liquid, which we did not succeed in crystallizing. It was distilled in a high vacuum. At a bath temperature of 180-195° about 2 g of a substance came over; it had: b.p. 91.5-92° (0.015 mm); n_D^{20} 1.5925; d_0^{20} 1.1397. Found: P 0.8; C 69.33; H 6.61%. $C_9H_{11}N_2PO_3$. Calculated: P 13.71; C 47.78; H 4.86%. In analysis the product did not correspond to the expected amido ester, but was not the entirely pure product of the alkylation of benzimidazole (1-methylbenzimidazole) ($C_8H_8N_2$), for which we calculated: C 72.69; H 6.10%; MR 39.02; found MR 39.03.

Picrate. A saturated solution of picric acid was added to an alcoholic solution of the product of b.p. 91.5-92° (0.015 mm). Yellow crystals of the picrate came down immediately; m.p. 245-246° (from alcohol). For the picrate of 1-methylbenzimidazole the literature gives m.p. 246-247°.

Reaction of Diethyl Phosphorochloridate with the Sodium Salt of Benzimidazole. 8.63 g of diethyl phosphorochloridate diluted with an equal volume of acetonitrile was added dropwise with stirring to 7 g of the sodium salt of benzimidazole in 50 ml of acetonitrile. The reaction mixture was warmed to 52°. A finer and heavier precipitate of sodium chloride appeared. To complete reaction the mixture was heated in a water bath at 60° for 3.5 h. After the separation of the precipitate and vacuum evaporation of part of the acetonitrile, gleaming crystals of benzimidazole appeared on the walls of the flask (m.p. 169-170°). These crystals were filtered off. When acetonitrile was evaporated further, the whole reaction mixture solidified. The product was recrystallized from acetonitrile; it may also be recrystallized from a mixture of benzene and petroleum ether (b.p. 40-50°). The crystals had m.p. 80-82°; yield 5.3 g (42.0%). The product was readily soluble in methanol, ethanol, acetone, benzene, and toluene—somewhat less soluble in ether; it was also soluble in water. Found: P 11.92; 12.05%. $C_{11}H_{15}N_2O_3P$. Calculated: P 12.19%. According to analysis the product was the expected phosphoric amido ester [1-phosphonobenzimidazole diethyl ester].

Hydrolysis. A mixture of 0.2 g of the product and 12 ml of dilute (1: 1) hydrochloric acid was heated under reflux in a boiling water bath for six hours. The colorless contents of the flask were evaporated on the water bath with repeated additions of water until hydrogen chloride had been removed completely. By the action of an alcoholic solution of picric acid on the hydrolysis products we obtained orange needles of the picrate of benzimidazole, m.p. 222-223°. Found: C 44.94; H 2.69%. $C_{13}H_9N_5O_7$. Calculated: C 44.94; H 2.61%.

Action of Picric Acid on 1-Phosphonobenzimidazole Diethyl Ester. When alcoholic solutions of the amido ester and picric acid were mixed, a homogeneous solution was formed at first, but after a few seconds orange needles of a picrate came down. After being recrystallized from alcohol the picrate had m.p. 223-224°, undepressed by admixture of known benzimidazole picrate.

Thermal Decomposition of 1-Phosphonobenzimidazole Diethyl Ester. We took 6.24 g of the sodium salt of benzimidazole and 6.2 g of the acid chloride and carried out the reaction as described above. After the removal of acetonitrile the reaction products were distilled in a high vacuum. We obtained 4.5 g of a substance: b.p. 109-167° (0.02 mm); n_D^{20} 1.5492; d_0^{20} 1.1325. It was an oily liquid which darkened when kept in a sealed tube; it contained traces of phosphorus. The greater part of the reaction products remained in the distilling flask as a dark-yellow solid mass.

The addition of an alcoholic solution of picric acid to the oily distillate gave a yellow picrate, m.p. 219-220° (from alcohol). Found: C 47.98; H 3.39%. $C_{15}H_{13}N_5O_7$. Calculated: C 47.98; H 3.46%. This picrate was found to be 1-ethylbenzimidazole picrate, for which the literature gives m.p. 219-220°.

Reaction of Diethyl Phosphorochloridothioate with the Sodium Salt of Benzimidazole. The reaction was carried out as in the preceding experiments. We took 6.5 g of the sodium salt of benzimidazole, 8.7 g of diethyl phosphorochloridothioate, and about 60 ml of acetonitrile. The mixture was heated in a water bath at 80-85° for 2.5 h. 2.5 g of sodium chloride was filtered off. Acetonitrile was distilled off, and the residue was distilled in a high vacuum. At a bath temperature of 200-210°, 1.52 g of a product of b.p. 90-94° (0.017 mm) was distilled off. This product was again vacuum-distilled: b.p. 148° (6 mm); n_D^{20} 1.5805; d_0^{20} 1.1147. According to the analytical figures (P 2.03; C 68.77; H 7.69%) this product was not the expected phosphorothioic amido ester, but was impure alkylation product. The picrate was prepared as indicated above: yellow needles, m.p. 220° (from alcohol).

Reaction of Diisopropyl Phosphorochloridate with the Sodium Salt of Benzimidazole. From 2.8 g of the sodium salt of benzimidazole and 4 g of diisopropyl phosphorochloridate, after the usual treatment of the reaction mixture, we obtained 2.2 g (39%) of colorless needles. After being recrystallized from a mixture of benzene and petroleum ether (b.p. 40-60°) the crystals melted at 107°. Found: P 10.84%. $C_{12}H_{19}O_3N_2P$. Calculated: P 10.98%. The product was 1-phosphonobenzimidazole diisopropyl ester; in its properties it was reminescent of the analogous amido ester with ethyl groups. By the action of picric acid in alcohol solution we obtained orange needles of the picrate of benzimidazole, m.p. 223°.

Hydrolysis. This was carried out as for the ethyl ester. The picrate of the hydrolysis product melted without depression when mixed with the picrate prepared indirectly from the amido ester.

Reaction of Diisobutyl Phosphorochloridate with the Sodium Salt of Benzimidazole. For reaction we took 7 g of the sodium salt of benzimidazole in 60 ml of acetonitrile and 11.43 g of diisobutyl phosphorochloridate. The mixture was heated for one hour at 55-60°. After the removal of sodium chloride, a small amount of benzimidazole crystals (m.p. 170°) formed on the walls of the flask after a time. The solution was poured into another flask. As acetonitrile evaporated further, the whole mass crystallized out. The product was recrystallized from ether (with activated charcoal); m.p. 47-49°; yield 12 g (77.4%). The amido ester is readily soluble in methanol, ethanol, benzene, and toluene, but sparingly soluble in ether; it is soluble in water. Found: P 9.92; 9.98%. $C_{15}H_{23}O_3N_2P$. Calculated: P 9.99%. Treatment with an alcoholic solution of picric acid gave orange needles of benzimidazole picrate, m.p. 223°.

Reaction of N,N'-Diphenylphosphorodiamidic Chloride with the Sodium Salt of Benzimidazole. A mixture of 0.28 g of the sodium salt of benzimidazole and 0.5 g of the acid chloride in 25 ml of acetonitrile was boiled for 30 min. The precipitate of sodium chloride was filtered off, and much of the acetonitrile was distilled from the filtrate. When the solution was cooled, a precipitate formed which we were unable to recrystallize from the usual solvents. The precipitate was analyzed after repeated washing with a mixture of benzene and petroleum ether and vacuum-drying; yield 0.51 g (75%); m.p. 222° (softened at 212°). Found: P 9.46%. $C_{19}H_{17}ON_4P$. Calculated: P 8.91%.

Reaction of N,N,N',N'-Tetraethylphosphorodiamidic Chloride with the Sodium Salt of Benzimidazole. A solution of 6.44 g of the acid chloride in an equal volume of acetonitrile was added dropwise with stirring to a suspension of 5 g of the sodium salt of benzimidazole in 35 ml of acetonitrile (the temperature rose spontaneously from 20 to 30°). To complete the reaction the mixture was heated at 60° for three hours. After the usual treatment the reaction product crystallized. 6.8 g (68%) of crystals were filtered off; m.p. 84-88°. We were unable to recrystallize them from benzene and petroleum ether. The crystals were analyzed after being vacuum-dried. Found: P 10.43; $C_{15}H_{25}N_2OP$. Calculated: P 10.06%.

Reaction of N,N,N',N'-Tetramethylphosphorodiamidic Chloride with the Sodium Salt of Benzimidazole. A mixture of 4.2 g of the sodium salt of benzimidazole, 5.1 g of N,N,N',N'-tetramethylphosphorodiamidic chloride, and 25 ml of acetonitrile was heated for three hours at a bath temperature of 60°. The precipitate of sodium chloride was filtered off (2.5 g). The residue remaining after the removal of acetonitrile was distilled in a high vacuum. We obtained 4.5 g (59%) of a product of b.p. 160-167° (0.015 mm); n_D^{20} 1.5521. It was a very thick colorless liquid with a weak amine odor.

Reactions of Phosphorus Acid Chlorides with Morpholine

Reaction of Dimethyl Phosphorochloridate with Morpholine. An ethereal solution of 10.44 g of morpholine was added with cooling (cold water) and mechanical stirring to a solution of 8.67 g of dimethyl phosphorochloridate in 50 ml of dry ether. There was an immediate white precipitate of morpholine hydrochloride and the reaction mixture became warm. When it was cool, we filtered off 7.3 g of morpholine hydrochloride; the filtrate was vacuum-distilled twice from an Arbuzov flask. We obtained 7 g (about 60%) of a product having: b.p. 108-109° (3 mm);

n_D^{20} 1.4526; d_0^{20} 1.2300; found MR 42.81; calculated MR 43.63. Found: P 15.87%. $C_6H_{14}O_4NP$. Calculated: P 15.88%. According to analysis the product was 4-phosphonomorpholine dimethyl ester. It was a colorless liquid with a weak amine odor, readily soluble in organic solvents and in water.

Reaction of Diethyl Phosphorochloridate with Morpholine. To 22 g of morpholine in 100 ml of dry ether a solution of 21 g (2: 1) of diethyl phosphorochloridate in an equal volume of ether was added dropwise. Slight warming was observed with the precipitation of the morpholine salt. To complete the reaction the mixture was heated in a water bath at 55-60° for two hours. After the separation of the precipitate the reaction products were vacuum-distilled twice. We obtained 27.25 g (68.3%) of a substance of b.p. 114-115° (3.5 mm) [the literature [4] gives b.p. 137° (11 mm)]; n_D^{20} 1.4478; d_0^{20} 1.1385. Found: P 13.84; 13.79%; MR 52.41. $C_8H_{18}O_4NP$. Calculated: P 13.89%; MR 52.87.

Reaction of Diisopropyl Phosphorochloridate with Morpholine. The reaction was carried out as described above. An ethereal solution of 11.5 g of the acid chloride was added with stirring and cooling with cold water to 10 g of morpholine dissolved in 75 ml of dry ether. Slight warming occurred, and a crystalline precipitate of the morpholine salt was formed. The reaction mixture was stirred for one hour and then left overnight at room temperature. 6.8 g of the morpholine salt was filtered off. The filtrate was vacuum-distilled twice. We obtained 9.85 g (68.4%) of a substance having: b.p. 105° (<1 mm); n_D^{20} 1.4418; d_0^{20} 1.0753. Found: C 47.70; H 8.73; P 12.32%; MR 61.83. $T_{10}H_{22}O_4NP$. Calculated: C 47.77; H 8.82; P 12.34%. MR 62.11. The product was 4-phosphonomorpholine diisopropyl ester.

Reaction of Diisobutyl Phosphorochloridate with Morpholine. For reaction we took 20.09 g of diisobutyl phosphorochloridate and 15.33 g of morpholine (1: 2). The ethereal solution was heated with mechanical stirring in a water bath at 60-70° for 2.5 h. As a result of fractionations we obtained 13.5 g (55.1%) of product; b.p. 147-147.5° (4 mm); n_D^{20} 1.4464; d_0^{20} 1.0485. Found: P 11.18%; MR 71.01. $C_{12}H_{26}O_4NP$. Calculated: P 11.10%; MR 71.34. This was an oily liquid of characteristic odor, thicker than the preceding products, soluble in the usual organic solvents and also in water.

Reaction of Diethyl Phosphorochloridothioate with Morpholine. 7.6 g of diethyl phosphorochloridothioate was added with stirring to a solution of 7.01 g of morpholine in 50 ml of dry ether. The mixture was heated for 30 min in a water bath and then filtered. The ethereal solution was washed twice with a little water and then dried with sodium sulfate. After three vacuum distillations we obtained a product having: b.p. 122-124° (5 mm); n_D^{20} 1.488; d_0^{20} 1.1425; found MR 60.31; calculated MR 58.73. Yield 4.85 g (50%). The resulting phosphorothioic amido ester was similar in appearance to the analogous oxygen compound, but it had a smell characteristic for sulfurous compounds. Unlike its oxygen analog, it was sparingly soluble in water. Found: P 13.07; 13.10; S 13.08%. $C_8H_{18}O_3NPS$. Calculated: P 12.95; S 13.40%.

Reaction of N,N-Dimethylphosphoramidic Dichloride with Morpholine. To 24.4 g of morpholine in 80 ml of dry ether we added an ethereal solution of 11.5 g of N,N-dimethylphosphoramidic dichloride (1 mole to 4 moles of morpholine). The reaction mixture was stirred at room temperature for two hours. After the separation of the morpholine salt the filtrate rapidly began to crystallize, and the temperature rose from 21 to 33°. To separate the product from residual morpholine salt the reaction products were vacuum-fractionated twice. The product obtained boiled at 172° (3 mm) and melted at 64-66°. Colorless crystals, readily soluble in the usual organic solvents; highly hygroscopic; yield 9.85 g (53%). Found: C 45.72; H 8.35; P 11.76%. $C_{10}H_{22}O_3N_3P$. Calculated: C 45.59; H 8.38; P 11.77%.

Reaction of N,N,N',N'-Tetraethylphosphorodiamidic Chloride with Morpholine. To a solution of 13.2 g of morpholine in 80 ml of dry ether we added an ethereal solution of 15.9 g (1 mole to 2 moles of morpholine) of N,N,N',N'-tetraethylphosphorodiamidic chloride. No liberation of heat was observed; the mixture became turbid. When the mixture was heated to the boil, the amount of precipitate gradually increased. The theoretical amount (6 g) of morpholine hydrochloride was filtered off. After two distillations we obtained 7.3 g (68.8%) of the phosphoric triamide; b.p. 152-153° (3 mm); n_D^{20} 1.4808; d_0^{20} 1.0686. Found: P 11.05; 11.35%; MR 73.76. $C_{12}H_{28}O_2N_3P$. Calculated: P 11.18%; MR 75.94. It was a thick colorless liquid with an amine odor, soluble in the usual organic solvents and in water.

SUMMARY

1. A study was made of the reactions of diethyl, diisopropyl, and diisobutyl phosphorochloridates, diethyl phosphorochloridothioate, and N,N,N',N'-tetraethyl-, N,N,N',N'-tetramethyl-, and N,N'-diphenylphosphorodiamidic chlorides with the sodium salt of benzimidazole. The corresponding phosphoric amido esters were obtained, and their properties were studied.

2. In the thermal decomposition of the phosphoric amido esters synthesized, products of the alkylation of benzimidazole were formed.

3. By the reaction of dimethyl, diethyl, diisopropyl, and diisobutyl phosphorochloridates, diethyl phosphorochloridothioate, N,N-dimethylphosphoroamidic dichloride, and N,N,N',N'-tetraethylphosphorodiamidic chloride with morpholine phosphoric amido esters and triamides containing morpholine groups were obtained. Their properties were studied.

LITERATURE CITED

1. B. A. Arbuzov, V. M. Zoroastrova, and M. P. Osipova, Izv. AN SSSR, Otd. khim. n. 1961, 2163.
2. B. P. Lugovkin and B. A. Arbuzov, Zh. obshch. khimii 22, 2041 (1952).
3. B. F. Van Den Bos and C. J. Schoot, Recueil 80, 9/10, 1060 (1961).
4. G. M. Kosolapoff, Organophosphorus Compounds, N.Y. (1950), p. 309.