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RESEARCHES ON IMIDAZOLES

XVI. Preparation of 1-Methyl-4, 5-Dihalogeno- and 1-Methyl-2, 4, 5-Trihalogenoimidazoles*

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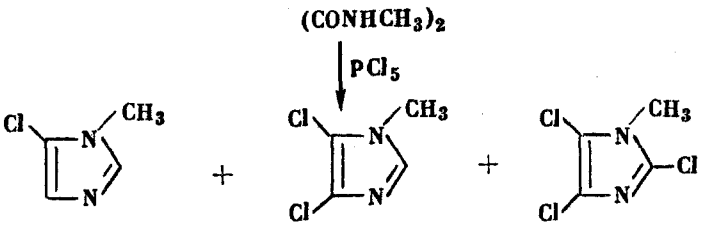
The 1-methyl-4, 5-dihalogeno- and 1-methyl-2, 4, 5-trihalogenoimidazoles resulting from reacting N, N'-dimethyloxamide with phosphorus pentachloride or pentabromide, are formed by secondary reaction, halogenation of 1-methyl-5-halogenoimidazoles by the phosphorus pentahalides, which also halogenate other imidazoles derivatives, e. g., 1, 2-dialkyl-5-chloroimidazole and 2-alkylimidazoles at the free position in the nucleus.

In a previous paper it was pointed out that heating N, N'-dimethyloxamide with phosphorus pentahalides gives mixtures of 1-methyl-5-halogeno-, 1-methyl-4, 5-dihalogeno-, and 1-methyl-2, 4, 5-trihalogenoimidazoles, e. g.:



Formation of monohalogenoimidazoles [2, 3] proceeds according to an equation established by Wallach and Boehringer [2]. It was of interest to elucidate the causes of formation of dihalogeno- and trihalogenoimidazoles. It was assumed that these compounds are formed by partial halogenation of the primary products of the reaction, 1-methyl-5-halogenoimidazoles. This is indicated by the low yields (6-20%) of 1-methyl-4, 5-dichloro(dibromo)imidazoles when reaction is carried out under the usual conditions (2 moles PCl_5 or PBr_5 to 1 mole dimethyloxamide), and the formation of appreciable amounts (3-6%) of 1-methyl-2, 4, 5-trichloro(tribromo) imidazoles when 4-5 moles of phosphorus pentahalide are used to 1 mole of dimethyloxamide.

For this the halogenation of 1-methyl-5-chloro- and 1-methyl-4, 5-dichloro(dibromo) imidazoles by phosphorus pentahalides was investigated. Reaction was effected by refluxing in phosphorus oxychloride and phosphorus triahlides do not halogenate the above-mentioned monochloro- and dichloro(dibromo)imidazoles.

Reaction of 1-methyl-5-chloroimidazole with phosphorus pentachloride (1: 1 molar ratio) gave a mixture of compounds, from which the starting compound, 1-methyl-2, 4, 5-trichloroimidazole (I), and 1-methyl-4, 5-dichloroimidazole (II) were separated. The compound I was formed in good yield (82. 1%) by chlorinating II with phosphorus pentachloride. Similarly the compound 1-methyl-2, 4, 5-tribromoimidazole (III, 51. 9% yield) was obtained by heating II with phosphorus pentabromide. Inorganic products of this reaction were hydrogen halide and phosphorus trihalide.

Thus it was shown that under the conditions of reaction, the 1-methyl-halogenoimidazoles formed from dimethyloxamide and phosphorus pentahalides can undergo halogenation at positions 4 and 2 of the imidazole ring, this also being the reason for formation of 1-methyl-4, 5-dihalogeno- and 1-methyl-2, 4, 5-trihalogenoimidazoles.

Apparently the imidazole ring is halogenated in a stepwise manner, first at position 4, then at position 2. With the reverse order of entry in the synthesis of 1-methyl-2, 4, 5-trihalogenoimidazoles the intermediates would not be 1-methyl-4, 5-dihalogenoimidazoles, but 1-methyl-2, 5-dihalogenoimidazoles, but these could not be isolated in a single case.

It has also been established that other imidazole derivatives are halogenated by phosphorus pentahalides. Thus chlorination of 1-butyl-2-propyl-5-chloroimidazole with phosphorus pentachloride gave 1-butyl-2-propyl-4, 5-dichloroimidazole (IV), while bromination, with phosphorus pentabromide, of 2-methyl- and 2-ethylimidazoles gave the corresponding 2-alkyl-4, 5-dibromoimidazoles (V and VI).

It may be mentioned that the literature does not describe the electrophilic substitution of hydrogen atoms by phosphorus pentahalide halogen atoms for imidazoles, though the reaction is known for a number of other heterocyclic systems, e. g., thiazole [4, 5], benzothiazole [6], and indole [7].

*For Part XV see [1].

Experimental

Chlorination of 1-methyl-5-chloroimidazole. A mixture of 11.6 g (0.1 mole) 1-methyl-5-chloroimidazole [3], 20.8 g (0.1 mole) phosphorus pentachloride, and 120 ml phosphorus oxychloride was refluxed for 8 hr 30 min, then left overnight. The phosphorus oxychloride and phosphorus trichloride formed in the reaction were distilled under atmospheric pressure (the distillate came over at 50-102°), 125 ml water were added (with cooling) to the residue in the flask, the precipitate filtered off, washed with water, and dried. A 3.18 g yield of 1-methyl-2, 4, 5-trichloroimidazole (I) was obtained, mp 73-74.5°. Colorless needles mp 75.5-76° (from 40% alcohol) mixed mp with I undepressed, as previously stated [1]. The mother liquor was extracted with chloroform, (20 ml, twice), the extracts dried over sodium sulfate, and the solvent distilled off in a vacuum. 0.6 g material was obtained, which on cooling partly crystallized. The crystals were filtered off, washed with a small amount of cooled 50% ethanol, and dried. Yield of impure 1-methyl-4, 5-dichloroimidazole (II), mp 54-55°, 0.22 g. Mixed mp with a specimen of the compound (mp 58.5-59.5°) [1] undepressed. Picrate, yellow crystals mp 130-131°, mixed mp with the picrate of compound II (mp 130.5-131.5°) [1] undepressed. After extracting with chloroform, the acid mother liquor was neutralized with sodium carbonate to pH 7.5-8, then extracted with chloroform (45 ml, 7 times), the extracts washed with water (20 ml), dried with sodium sulfate, and the solvent distilled off in a vacuum. Yield 7.6 g dark brown liquid n_D^{20} 1.5110. Distillation gave 4.95 g of the starting 1-methyl-5-chloroimidazole, bp 79° (1 mm), 50° (0.6 mm), n_D^{21} 1.5100. Picrate, yellow crystals, mp 167-168° (from alcohol), mixed mp with a previous known specimen of this compound (mp 167-168°) [3] undepressed. The residue (0.51 g) remaining in the flask after distilling off the 1-methyl-5-chloroimidazole was dissolved in dilute alcohol (about 3 ml), the solution warmed, filtered off, and evaporated in a vacuum. Yield 0.4 g material, which on cooling partly crystallized; the crystals were filtered off, washed with water, and dried. Yield 0.2 g II, mp 55-57°, mixed mp with a pure specimen of II, 57-58°. Picrate, yellow crystals mp 129-130°, mixed mp with the pure picrate of compound II [1], undepressed.

Chlorination of 1-methyl-4, 5-dichloroimidazole. A solution of 1.51 g (0.1 mole) 1-methyl-4, 5-dichloroimidazole [1] and 2.3 g (0.11 mole) phosphorus pentachloride in 15 ml phosphorus oxychloride was refluxed for 3 hr, the solvent distilled off in a vacuum, 20 ml water added to the residue (with cooling), the colorless precipitate filtered off, washed with water, and dried. Yield of impure 1-methyl-2, 4, 5-trichloroimidazole (I) mp 65-67°, 1.52 g (82.1%). Colorless long needles, mp 75.5-76° (from 40% aqueous alcohol), mixed mp with a specimen of compound I obtained as described in the previous experiment, undepressed.

Bromination of 1-methyl-4, 5-dibromoimidazole. A solution of 1.2 g (0.05 mole) 1-methyl-4, 5-dibomoimidazole [1] and 2.25 g (0.052 mole) phosphorus pentabromide in 20 ml phosphorus oxychloride was refluxed for 1 hr 30 min, the phosphorus oxychloride distilled off in a vacuum, 15 ml water added to the residue (with cooling), the precipitate filtered off, washed with water, and dried. Yield of 1-methyl-2, 4, 5-tribromoimidazole (III), mp 88-90°, 0.92 g (51.9%). Colorless prisms (from aqueous alcohol), mp 88-89° (using an ordinary thermometer), and 93-94° (using a short Anschütz thermometer). The literature gives 88-89° [9, 10], and 93-94.5° [11].

Chlorination of 1-butyl-2-propyl-5-chloroimidazole. A mixture of 20 g (0.1 mole) 1-butyl-2-propyl-5-chloroimidazole [3], 22.8 g (0.1 mole) phosphorus pentachloride, and 150 ml phosphorus oxychloride was refluxed for 3 hr, then left overnight, the solvent distilled off in a vacuum, and 50 ml water added (with cooling) to the residue, the oily product extracted with chloroform (150 ml), the extract washed with water, and dried over sodium sulfate. After distilling off the solvent, the yield of impure 1-butyl-2-propyl-4, 5-dichloroimidazole (IV), was 22.5 g (97.5%), n_D^{18} 1.5115. Two distillations in a vacuum gave a colorless liquid bp 152-154° (0.5 mm), n_D^{20} 1.5100, d_{20}^{20} 1.1304, readily soluble in most organic solvents, insoluble in water, petroleum ether, and dilute hydrochloric acid. The substance did not react with picric acid. Found: C 51.41; H 7.03; N 11.80%. Calculated for $C_{10}H_{16}Cl_2N_2$: C 51.08; H 6.86; N 11.91%.

Bromination of 2-methylimidazole. A mixture of 1.7 g (0.0207 mole) 2-methylimidazole [12], 10.1 g (0.0235 mole) phosphorus pentabromide and 50 ml phosphorus oxychloride was refluxed for 2 hr, then the phosphorus oxychloride distilled off in a vacuum, and 125 ml water added (with cooling) to the residue, along with 50 ml saturated sodium acette solution, the precipitate filtered off, washed with water, and dried. Yield of impure 2-methyl-4, 5-dibromoimidazole (V) mp 214-216°, 1.5 g (49.7%). Colorless crystals, mp 236-239° (from 50% aqueous ethanol). The literature gives [13] mp 236-240°.

Bromination of 2-ethylimidazole. A mixture of 2.4 g (0.25 mole) 2-ethylimidazole [12], 23.6 (0.055 mole) phosphorus pentabromide and 60 ml phosphorus oxychloride was heated for 3 hr at 98-102°. The phosphorus oxychloride was distilled off in a vacuum, the residue dissolved in water, heated with active carbon, and filtered. The filtrate was neutralized with an aqueous solution of sodium bicarbonate and made alkaline, the precipitate filtered off, washed with water, and dried. Yield of impure 2-ethyl-4, 5-dibromoimidazole (VI), mp 147-154.5°, 2.0 g (31.5%). Colorless crystals mp 157-158° (from 40% aqueous alcohol), readily soluble in most organic solvents, insoluble in cold water. Found: C 23.77; H 2.68; Br 63.47; N 11.31%. Calculated for $C_5H_6Br_2N_2$: C 23.65; H 2.38; Br 62.94; N 11.03%.

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