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RESEARCHES ON IMIDAZOLES

# XVII. Chlorination of 1-Methyl-5-Chloro-, 1-Methyl-4, 5-Dichloro-, and 1, 2-Dialkyl-5-Chloroimidazoles*

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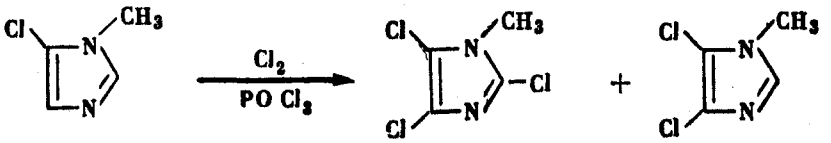
It is found that when 1-methyl-5-chloroimidazole is chlorinated in phosphorus oxychloride, there is electrophilic substitution of hydrogen atoms by chlorine in the imidazole ring. Chlorination of 1-methyl-5-chloro-, 1-methyl-4, 5-dichloro, and 1, 2-dialkyl-5-chloroimidazoles with chlorine in glacial acetic acid leads to their oxidation to oxygenated derivatives of imidazole or alkyloxamides.

The compounds mentioned in the title of the paper are chlorinated by phosphorus pentachloride to the corresponding dichloro- or trichloroimidazole derivatives [1]. It was of interest to investigate the chlorination of these compounds by chlorine; hitherto chlorination of mono- and dichloroalkylimidazoles has not been described. Only bromination of 1-ethyl-2-methyl-5-chloroimidazole with bromine is known, this apparently giving 1-ethyl-2-methyl-4-bromo-5-chloroimidazole (Wallach's bromochloroxaloethyline).

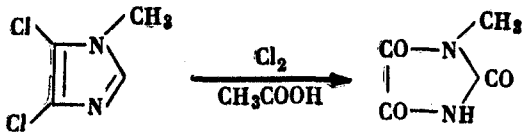
First of all, the chlorination of 1-methyl-5-chloroimidazole with chlorine in phosphorus oxychloride was investigated. It was found that the usual reaction of electrophilic substitution of hydrogen atoms in the imidazole ring by chlorine atoms occurs, and that reaction does not go to completion, as in the reaction with phosphorus pentachloride [1]. 1-Methyl-2, 4, 5-trichloroimidazole (I) was isolated, and along with it 1-methyl-4, 5-dichloroimidazole (II) and the starting compound.




I II

Chlorination of 1-methyl-5-chloroimidazole in chloroform was also ambiguous, since even at the beginning of reaction a chloroform-insoluble precipitate of 1-methyl-5-chloroimidazole hydrochloride separated.

In an attempt to carry out chlorination under homogeneous conditions, glacial acetic acid was used as solvent, but it was then found that chlorination of mono- and dichloroimidazoles resulted in more profound changes in the imidazole ring, to formation of oxygen-containing derivatives of imidazole and alkyloxamides, apparently due to the oxidizing action of chlorine. Thus chlorination of 1-methyl-4, 5-dichloroimidazole (II) gave a high yield (90%) of methylparabanic acid (III).




III

On chlorinating 1-methyl-5-chloroimidazole, its salt with methylparabanic acid and hydrogen chloride (IV) was obtained. Treatment of salt IV with sodium carbonate gave 1-methyl-5-chloroimidazole methylparabanate (V). Treatment of the latter with picric acid gave 1-methyl-5-chloroimidazole picrate. The compositions of salts IV and V are proved by their preparation from substances of known structure.

Chlorination of 1-ethyl-2-methyl-5-chloroimidazole in acetic acid with chlorine led, judging by elementary analysis, to formation of a salt of the starting compound with 1-ethyl-2-trichloromethyl-4, 5-dioxoimidazole (VI). Treatment of this salt with picric acid gave the picrate of 1-ethyl-2-methyl-5-chloroimidazole, while treatment with hydrochloric acid gave a crystalline substance VII, which actually seemed to be 1-ethyl-2-trichloromethyl-dioxoimidazoline, but its structure was not definitely proved.

*For Part XVI see [1].

Chlorination of 1-propyl-2-ethyl-5-chloro- and 1-butyl-2-propyl-5-chloroimidazoles gave products resulting from oxidative fission of the imidazole ring, the propyloxamide VIII, and the butyloxamide IX.

## Experimental

Chlorination of 1-methyl-4, 5-dichloroimidazole. A slow stream of chlorine was passed for 1 hr 15 min through a solution of 4 g 1-methyl-4, 5-dichloroimidazole [3] in 50 ml glacial acetic acid heated to 60°, then the solution evaporated to dryness in a vacuum, and the colorless crystalline residue washed with ether and dried. Yield of methylparabanic acid (III) mp 152.5-153°, 2.8 g. A further 0.25 g of the same substance, mp 153-153.5°, was obtained by evaporating the ether mother liquor to dryness, washing the crystals with petroleum ether, and then with ether. Colorless long prisms, mp 153-154° (from ethanol). Mixed mp with authentic methylparabanic acid (mp 153-154°) [4], undepressed.

Chlorination of 1-methyl-5-chloroimidazole.

a) Chlorine was passed for 1 hr 30 min into a solution of 11.6 g 1-methyl-5-chloroimidazole [5] in 20 ml phosphorus oxychloride at 15-16° (the gas was made from 6.4 g potassium permanganate and 40 ml concentrated HCl). A brown precipitate quickly separated from the solution. The phosphorus oxychloride was distilled off under vacuum, 35 ml water added to the residue, the precipitate filtered off, washed with water, and dried. Yield of 1-methyl-2, 4, 5-trichloroimidazole (I), mp 73-74°, 2.48 g. Colorless needles mp 75.5-76° (from 40% aqueous alcohol). Mixed mp with a previously prepared specimen of this compound (mp 75.5-76°) undepressed. The mother liquor was neutralized with sodium bicarbonate, and extracted with chloroform (150 ml), the extract washed with water, dried with magnesium sulfate, and the solvent evaporated under vacuum. Yield 7.08 g dark brown liquid, which on vacuum distillation gave 3.97 g of the starting 1-methyl-5-chloroimidazole mp 64-69° (1 mm), $n_D^{20}$ 1.5111. The picrate formed yellow crystals mp 166-168° (from alcohol), mixed mp with the picrate of the starting material [5] (mp 167-168°) undepressed. The residue in the flask was warmed with water, and extracted with ether (20 ml, 6 times), the extract washed with water, dried over magnesium sulfate, and the solvent evaporated in a vacuum. Yield 0.15 g oily material, containing 1-methyl-4, 5-dichloroimidazole (II). The picrate formed yellow crystals, mp 130-131° (from alcohol). Mixed mp with the picrate of II (mp 130.5-131.5°) undepressed [3].

b) A slow stream of chlorine was passed for 2 hr into a solution of 14.2 g 1-methyl-5-chloroimidazole in 40 ml glacial acetic acid at 14-16°, after which the acetic acid was distilled off in a vacuum. The crystalline residue was washed with acetone and dried. Yield of 1-methyl-5-chloroimidazole methylparabanate hydrochloride (IV) mp 162-163°, 10.09 g. Colorless prisms mp 162.5-164.5° (from ethanol), soluble in water and alcohol, sparingly soluble in acetone. Mixed mp with 1-methyl-4, 5-dichloroimidazole hydrochloride (mp 161-163°) [3], 128-130°. Mixed mp with methylparabanic acid (mp 153-154°) 131.5-133°. Found: C 34.54; H 3.72; Cl 25.58; N 20.25%. Calculated for $C_4H_5ClN_2 \cdot C_4H_4N_2O_3 \cdot HCl$: C 34.18; H 3.58; Cl 25.23; N 19.93%.

A portion of salt IV was dissolved in water, the solution neutralized with sodium carbonate, and a precipitate of 1-methyl-5-chloroimidazole methylparabanate (V) separated. This was filtered and crystallized twice from water. Long colorless prisms, mp 120-121.5°, easily soluble in organic solvents and in hot water, sparingly soluble in cold water. Found: C 39.20; H 3.85; Cl 14.56; N 22.47%. Calculated for $C_4H_5ClN_2 \cdot C_4H_4N_2O_3$: C 39.28; H 3.71; Cl 14.49; N 22.90%.

An aqueous solution of picric acid was added to an aqueous solution of salt V, the precipitate of 1-methyl-5-chloroimidazole picrate filtered off, and crystallized from water. Yellow prisms mp 167.5-168°, mixed mp with a known specimen of the picrate (mp 167-168°) undepressed [5].

A mixture of 0.4 g 1-methyl-5-chloroimidazole, 0.4 g methylparabanic acid, and 1 ml water was boiled (with active carbon), the solution filtered, cooled, the precipitate filtered off, washed with a small amount of water, and dried. Yield of 1-methyl-5-chloroimidazole methylparabanate (V) mp 121-122°, 0.4 g. Mixed mp with V prepared in the way previously described, undepressed. An alcoholic solution of hydrogenchloride was added to an aqueous solution of V, the precipitate of 1-methyl-5-chloroimidazole methylparabanate hydrochloride (IV) was filtered off, and recrystallized from alcohol. Color less crystals mp 161-163°. Mixed mp with IV prepared as previously described, undepressed.

Chlorination of 1-ethyl-2-methyl-5-chloroimidazole. A slow stream of chlorine was passed for 2 hr into a solution of 11.5 g 1-ethyl-2-methyl-5-chloroimidazole [5], in 45 ml glacial acetic acid at 10-12°, after which the acetic acid was distilled off in a vacuum, an aqueous solution of sodium bicarbonate added to the residue, and on standing the oily material crystallized. The precipitate was filtered off, washed with water, then with petroleum ether, and dried. Yield 5.4 g material mp 99-101°. Two recrystallizations from ethyl acetate-petroleum ether, followed by one from aqueous alcohol gave colorless plates mp 130-136°, readily soluble in most organic solvents, slightly soluble in water, insoluble in petroleum ether. The elementary composition agreed best with that of a salt between 1-ethyl-2-methyl-5-chloroimidazole and 1-ethyl-2-trichloromethyl-4, 5-dioxoimidazole (VI). Found: C 34.90; H 4.08; Cl 36.47; N 13.75%. Calculated for $C_6H_9ClN_2 \cdot C_6H_5Cl_3N_2O_2$: C 35.49; H 3.97; Cl 34.92; N 13.80%.

An ether solution of picric acid was added to an alcohol solution of VI, the precipitate formed filtered off, and recrystallized from alcohol. Yellow prisms mp 154-155°, mixed mp with 1-ethyl-2-methyl-5-chloroimidazole picrate (mp 154.5-155°) [5] undepressed. A portion of VI was warmed with dilute hydrochloric acid, the solution filtered, cooled, and the precipitate filtered off and recrystallized from water. Colorless crystals mp 183.5-184.5° (sublimation), readily soluble in alcohol, sparingly soluble in cold water. The elementary composition of the substance corresponds to a hydrate of 1-ethyl-2-trichloromethyl-4,5-dioxoimidazole (VII). Found: C 27.68; H 2.57; Cl 41.09; N 10.54%. Calculated for $C_6H_5ClN_2O_2 \cdot H_2O$: C 27.56; H 2.70; Cl 40.68; N 10.71%.

Chlorination of 1-propyl-2-ethyl-5-chloroimidazole. A slow stream of chlorine was passed for 1 hr into a solution of 2.3 g 1-propyl-2-ethyl-5-chloroimidazole [5] in 45 ml glacial acetic acid at 70-90°. Then the acetic acid was evaporated in a vacuum, and the residue heated with an aqueous solution of sodium carbonate, when it precipitated. The precipitate was filtered off, washed with water, and recrystallized from alcohol, using active carbon. Colorless crystals mp 196-196.5°. Mixed mp with propyloxamide VIII (mp 196.5-197°) undepressed [6].

Chlorination of 1-butyl-2-propyl-5-chloroimidazole. A small stream of chlorine was passed for 2 hr into a solution of 8.1 g 1-butyl-2-propyl-5-chloroimidazole [5] in 45 ml glacial acetic acid at 50-65°, after which the acetic acid was distilled off in a vacuum, the residue dissolved in chloroform, the solution washed with an aqueous soda solution, then with water, dried over sodium sulfate, the solvent distilled off under vacuum, when it gave butyloxamide IX. Colorless crystals mp 197.5-198.5° (from ethyl acetate). Mixed mp with authentic specimen of the compound (mp 197.5-198.5°) [6] undepressed.

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