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RESEARCHES ON IMIDAZOLES
XIX. Nitrochloroimidazoles*

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Nitration of 1-alkyl(1,2-dialkyl)-5-chloro- and 1-alkyl(1,2-dialkyl)-4-chloroimidazoles with mixed concentrated nitric and sulfuric acids is investigated. A number of known and new 1-alkyl(1,2-dialkyl)-4-nitro-5-chloro- and 1-alkyl(1,2-dialkyl)-4-chloro-5-nitro-imidazoles are prepared.

4(5)-Nitro-5(4)-chloroimidazoles have received little attention. Only a few such compounds are described in the literature [1-4]. Among other things, nitrochloroimidazoles are of definite interest in connection with biological research [4,5], and as starting materials for synthesizing bi- and polycyclic heterocyclic ring systems containing an imidazole ring. The literature describes the preparation of nitrochloroimidazoles by heating chloroimidazole nitrates with concentrated sulfuric acid [1-3], or by a more complicated method, from 2-nitroimidazole [4].

Examination of the first method showed that it was unsuitable. The yield of nitrochloroimidazoles did not exceed 71%, and on account of losses arising in the preparation and purification of chloroimidazole nitrates, it was 50-65% of the theoretical based on the chloroimidazoles or bases. To simplify the process and raise the yields of nitrochloroimidazoles, a study was made of the direct nitration of chloroimidazoles, without conversion to nitrates.

The starting materials used were the previously prepared 1-alkyl(1,2-dialkyl)-5-chloro- and 1-alkyl(1,2-dialkyl)-4-chloro-imidazoles [6,7]. It was found that even at 70° nitric acid (d 1.5) alone does not nitrate chloroimidazoles, only the nitrates being formed. Nitration of chloroimidazoles with mixed sulfuric and nitric acids made it possible to work out a simpler method of preparing 4(5)-nitro-5(4)-chloroimidazoles [8]. The best results (75-98% yields of nitroimidazoles) were obtained by using 10-30% more nitric acid than that theoretically required, and running the reaction at 90-100°. Two variants of the method were tried. In one, method A, the chloroimidazole was dissolved in concentrated sulfuric acid, nitric acid added to this solution, and the reactants heated at 100°. In the other, method B, the chloroimidazoles were added to a previously prepared nitrating mixture. The other conditions were the same.

The method was used to prepare a number of known and new 1-alkyl-(1,2-dialkyl)-4-nitro-5-chloro- and 1-alkyl(1,2-dialkyl)-4-chloro-5-nitroimidazoles (I-XIII). The Table gives yields, physical constants, and analytical data. Due to the presence of a strongly electronegative group, the basic properties of the nitrochloroimidazoles are very weak. They do not form methiodides, picrates, or salts even with dilute aqueous and alcohol solutions of strong mineral acids.

Experimental

Synthesis of the starting 1-alkyl(1,2-dialkyl)-5-chloro- and 1-alkyl(1,2-dialkyl)-4-chloroimidazoles has previously been described [6,7].

Preparation of nitrochloroimidazoles.

Method A. 118.3 g 1-methyl-5-chloroimidazole was added with stirring and cooling to 350 ml 96-98% sulfuric acid at such a rate that the temperature did not exceed 30°. 55 ml 98% nitric acid (d 1.5) was added gradually, with stirring, to this solution, which was kept at 30-40° by cooling the flask externally. After all the nitric acid had been added, the reaction mixture was heated to 98-100° over a period of 30 min, then stirred at that temperature for 1 hr, cooled to 18-22° and stirred into cold water (3500 ml). After cooling the mixture, the precipitate which formed was filtered off, washed with water until the washings were no longer acid to congo red, and dried. Yield 130.3 g (79.6%) 1-methyl-4-nitro-5-chloroimidazole (I), pale yellow prisms mp 147-148°. A few more grams of the substance could be obtained by extracting the mother liquors with dichloroethane, chloroform, or methylene chloride. Compounds II, III, IV, and IX were prepared similarly.

Method B. 25.5 g 1-methyl-4-chloroimidazole was added in 25 min to a stirred mixture of 77 ml 94-98% sulfuric acid and 11 ml 98% nitric acid, the temperature being held at 30-35° by cooling the flask externally with ice. Then, over a period of 40-60 min, the reaction mixture was gradually heated to 98-100°, stirred at that temperature for 1 hr, cooled to 18-20°, and poured, with stirring, into 770 ml cold water. After cooling the mixture to 0-10° the precipitate was filtered off, and washed with water until the washings were neutral to congo red, to give 32.7 g moist 1-methyl-4-chloro-5-nitroimidazole (IX, dry specimen had mp 76-77°), which was recrystallized from 66 ml ethanol, 20.9 g pure compound IX mp 78-79° was obtained. Extraction of the mother liquors and wash waters with dichloroethane (5

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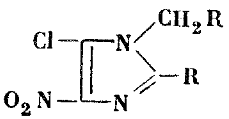
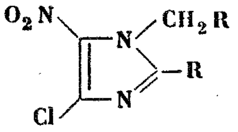
*For Part XVIII see [7].

Nitrochloroimidazoles



I-VII



IX—XIII

Compound No.	R	Method	Mp, °C	Molecular formula	Found, %				Calculated, %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
I	H	A B	148—149	$C_4H_4ClN_3O_2$*									79.6 83
II	CH_3	A B	90—91	$C_6H_8ClN_3O_2$									73.9 89.2
III	C_2H_5	A	60—61	$C_8H_{12}ClN_3O_2$**	43.77	5.35	16.46	18.89	44.14	5.56	16.29	19.31	90.5
IV	C_3H_7-*n*	A	34.5—35	$C_{10}H_{16}ClN_3O_2$	48.63	6.40	14.36	17.20	48.88	6.56	14.43	17.10	90.1
V	C_3H_7-*i*	B	110—111	$C_{10}H_{16}ClN_3O_2$	48.88	6.51	14.72	17.20	48.88	6.56	14.43	17.10	94
VI	C_4H_9-*n*	B	T. Bp 188—189 (1 mm)	$C_{12}H_{20}ClN_3O_2$	52.99	7.28	13.10	15.30	52.65	7.36	12.95	15.35	98
VII	C_4H_9-*i*	B	T. Bp 206—209 (1. 5 mm)	$C_{12}H_{20}ClN_3O_2$	53.09	7.29	13.13	15.35	52.65	7.36	12.95	15.35	98
VIII	C_5H_{11}-*n*	B	***	$C_{14}H_{24}ClN_3O_2$	55.76	7.78	12.13	13.75	55.71	8.01	11.75	13.92	90.8
IX	H	A B	78.5—79	$C_4H_4ClN_3O_2$									70 83
X	CH_3	B	67—68	$C_6H_8ClN_3O_2$									77.5
XI	C_2H_5	B	58—59	$C_8H_{12}ClN_3O_2$	44.13	5.42	16.34	19.24	44.14	5.56	16.29	19.31	74.6
XII	C_3H_7-*n*	B	T. Bp 164 (3 mm)	$C_{10}H_{16}ClN_3O_2$	49.38	6.45	16.87	14.37	48.88	6.56	14.43	17.10	83
XIII	C_4H_9-*i*	B	T. Bp 150—151 (1 mm)	$C_{12}H_{20}ClN_3O_2$	52.59	7.66	13.12	15.68	52.65	7.36	12.95	15.35	80.5

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* According to [1, 2] I, II, IX, and X have respectively mp 147-148°, 88°, 77-78°, and 67°.

**Analytically pure specimens of compounds I, II, V, IX, and X were obtained by crystallizing from ethanol, of compound XI from 75% ethanol, of compound III from ethyl acetate-petrol ether, and of compound IV, from ethanol-petrol ether.

***Compound VIII decomposes on distilling under reduced pressure. The technical product was used for analysis.

times with 50 ml portions), followed by distilling off the solvent and crystallization of the residue from 15 ml alcohol gave a further 8.6 g compound IX mp 77-79°. Total yield 29.5 (83%). Compounds I, II, V-VIII, X-XIII were obtained similarly. After decomposing the reaction products with water, the liquid nitrochloroimidazoles (VI-VIII, XII and XIII) were extracted with dichloroethane or methylene chloride.

Properties of the nitrochloroimidazoles: pale yellow crystalline or liquid substances, readily soluble in most organic solvents, almost insoluble in cold water and cold petrol ether. Undecomposed after standing for some years. Both the crystalline and liquid technical products can be used for most syntheses without further purification.

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