EXPERIMENTAL

The mass spectra of the investigated compounds were recorded with an MKh-1303 spectrometer with a system for introduction of the samples directly into the ion source at an ionizing-electron energy of 70 eV and 80-100°. The high-resolution mass spectra were recorded with a JEOL JMS-10SG2 spectrometer with recording on a photographic plate and subsequent processing with a microphotometer—JEC-6 computer system.

Compound XI was obtained by refluxing (three times) I in CH_3OD, which made it possible to achieve 70% deuteration.

LITERATURE CITED

1. R. A.Khmel'nitskii, V. I. Vysotskii, and I. I. Grandberg, Zh. Org. Khim., No. 5, 417 (1969).
2. H. Budzikiewicz, C. Djerassi, and D. M. Williams, Structure Elucidation of Natural Products by Mass Spectrometry of Alkaloids, Holden-Day (1964).
3. V. I. Vysotskii, R. A. Khmel'nitskii, I. I. Grandberg, and V. A. Budylin, Izv. Timiryazev, Sel'skokhoz. Akad., No. 4, 221 (1970).
4. V. I. Vysotskii, R. A. Khmel'nitskii, and I. I. Grandberg, Izv. Timiryazev. Sel'skokhoz. Akad., No. 5, 217 (1970).

RESEARCH ON FIVE-MEMBERED HETEROCYCLES.

I. SYNTHESIS OF NITROCHLOROIMIDAZOLES

G. P. Sharnin, R. Kh. Fassakhov, T. A. Eneikina, and P. P. Orlov

UDC 547.781.4.5:542.944

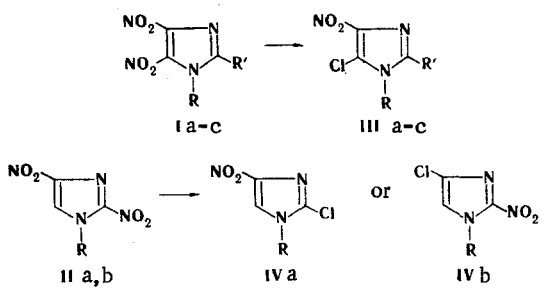
Nitrochloroimidazoles were synthesized by replacement of the nitro group in dinitroimidazoles by chlorine by the action of $POCl_3$. It is shown that in the case of 4,5-dinitroimidazoles substitution takes place when both dimethylformamide (DMF) and pyridine are used as the solvents, while only DMF is suitable for 2,4-dinitroimidazoles. The location of the halogen in the synthesized nitrochloroimidazoles was confirmed by alternative synthesis.

Very little information on nitrochloroimidazoles is available in the literature. The synthesis of 1-alkyl-, (1,2-dialkyl)-4-nitro-5-chloro-, 1-alkyl-, and (1,2-dialkyl)-5-nitro-4-chloroimidazoles [1] and 2-chloro-4(5)-nitro-5(4)-chloroimidazole, to which the isomeric 4(5)-nitro-5(4)-chloroimidazole structure was incorrectly assigned [2], has been described. Chloronitroimidazoles are of definite interest as subjects for biological studies [2] and as intermediates for the preparation of amino- [3] and mercaptoimidazoles [4] and heterocyclic compounds containing an imidazole fragment.

In the present research we investigated the possibility of the synthesis of the previously undescribed nitrochloroimidazoles IIIa-c and IVa,b by reaction of dinitroimidazoles Ia-c and IIa,b with $POCl_3$ in dimethylformamide (DMF) or pyridine.

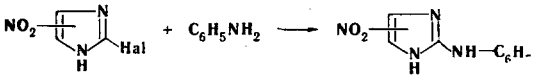
We have shown that the ease of replacement of a nitro group by chlorine in Ia-c and IIa-b depends on the nature of the solvent and the structure of the dinitroimidazoles. Thus similar substitution occurs in 4,5-dinitroimidazoles Ia-c under the influence of $POCl_3$ in DMF at 80-85°C (method A) or in pyridine at 90-95° (method B). 2,4-Dinitroimidazoles (IIa,b) form the corresponding chloronitroimidazoles IVa,b only via method A. Despite variations in

S. M. Kirov Kazan Chemical-Engineering Institute, Kazan 420015. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, May, 1977. Original article submitted May 14, 1976; revision submitted August 26, 1976.



I, III a R = R′ = H; b R = CH_3, R′ = H; c R = H, R′ = CH_3; II, IV a R = H; b R = CH_3

the conditions (reaction temperatures up to 105°, reaction times up to 8 h, and changes in the $POCl_3$ to pyridine ratio from 1:1 to 6.4:1), we were unable to replace a nitro group in IIa,b by method B. The location of the halogen in IIIa and IVa was confirmed by alternative synthesis. Thus 1-methyl-5-chloro-4-nitroimidazole (IIIb), which was described in [1] and was also obtained from 1-methyl-4,5-dinitroimidazole (Ib), was synthesized by methylation of chloronitroimidazole IIIa with dimethyl sulfate. A substance identical to the compound obtained by refluxing dinitroimidazole IIa in ethylene chlorohydrin [2] was obtained by treatment of 2,4-dinitroimidazole IIa under the conditions of method A. Lancini and co-workers [2] erroneously assigned a 4(5)-chloro-5(4)-nitroimidazole structure to it. However, our condensations of aniline with IVa and 2-iodo-4(5)-nitroimidazole [5] in ethanol led to the same 2-phenylamino-4(5)-nitroimidazole:



Hal = Cl, I

This demonstrated convincingly that IVa corresponds to the 2-chloro-4(5)-nitroimidazole structure. To confirm the structure of IVb we synthesized the isomeric 1-methyl-2-chloro-4-nitroimidazole (V) by methylation of IVa with dimethyl sulfate.

EXPERIMENTAL

Starting dinitroimidazoles Ia-c and IIb were obtained by the methods in [6], and 2,4-dinitroimidazole was synthesized by the method in [7].

Halonitroimidazoles (IIIa-c, IVa,b). A) An 0.114-mole sample of $POCl_3$ was added dropwise to 0.228 mole of DMF at 2-8°, and 0.038 mole of the starting dinitroimidazole was added to the resulting solution. The mixture was heated to 80-85° and maintained at this temperature for 2-6 h, after which it was cooled to room temperature and poured into 200 g of ice. The resulting precipitate was removed by filtration, washed to neutrality with ice water (four 15-ml portions), and dried. The filtrate and wash waters were combined, neutralized with the calculated amount of alkali, acidified to pH 4 with hydrochloric acid, and extracted with ether (four 50-ml portions). The ether extracts were evaporated to give an additional amount of the chloronitroimidazoles.

TABLE 1. Replacement of a Nitro Group by Chlorine in Dinitroimidazoles (method A)

Compound	Reaction time, h	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
IIIa*	2	260—261	24,4	1,4	23,6	27,2	$C_3H_2ClN_3O_2$	24,5	1,4	24,0	28,5	75
IIIb*	6	147—148 †										70
IIIc	6	234—235	29,7	2,7	22,1	26,0	$C_4H_4ClN_3O_2$	29,8	2,5	22,0	26,0	71
IVa	2	216—217 †	24,4	1,3	23,9	28,2	$C_3H_2ClN_3O_2$	24,5	1,4	24,0	28,5	68
IVb	6	158—159	29,9	2,4	22,3	26,3	$C_4H_4ClN_3O_2$	29,8	2,5	22,0	26,0	60

*Compounds IIIa,b were also obtained by method B in 75 and 70% yields, respectively.
†Compounds IIIb and IVa were described in [1, 2].

B) An 0.022-mole sample of pyridine was added with stirring at 10-15° to 0.14 mole of $POCl_3$, after which 0.02 mole of dinitroimidazole was added in portions. The temperature of the reaction mixture was raised to 90-95° and maintained at this temperature for 2-4 h, after which the resulting solution was cooled to 10° and poured over ice. The resulting precipitate was removed by filtration, washed to neutrality with water (four 15-ml portions), and dried.

The chloronitroimidazoles obtained by methods A and B were purified by recrystallization from water. Compounds IIIb and IVb were identified by mixed-melting-point determinations. The characteristics of the nitrochloroimidazoles are presented in Table 1.

1-Methyl-2-chloro-4-nitroimidazole (V). An 0.01-mole sample of 2-chloro-4(5)-nitroimidazole was added to a solution of 0.1 mole of $NaHCO_3$ in 60 ml of water at room temperature, after which the mixture was stirred for 15 min. Dimethyl sulfate (5.5 ml) was then added, and the mixture was allowed to stand for 24 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.8 g (54.4%) of 1-methyl-2-chloro-4-nitroimidazole with mp 141-142° (from water). The product was quite soluble in hot water and alcohol but only slightly soluble in organic solvents. Found, %: C 22.1; H 2.4; Cl 21.5; N 25.8. $C_3H_4ClN_3O_2$. Calculated, %: C 22.3; H 2.5; Cl 22.0; N 26.0.

2-Phenylamino-4(5)-nitroimidazole. A solution of 0.0064 mole of aniline in 5 ml of alcohol was added to a suspension of 0.0063 mole of 2-chloro- or 2-iodo-4(5)-nitroimidazoles in 5 ml of alcohol at room temperature, after which the mixture was allowed to stand at this temperature for 30 min. The precipitated crystals were removed by filtration, washed, and dried to give 1 g of a substance with mp 158-160°. Recrystallization from water gave 2-phenylamino-4(5)-nitroimidazole with mp 159-160°. Found,%: C 52.6; H 3.8; N 27.4. $C_9H_8N_4O_2$. Calculated, %: C 53.0; H 3.9; N 27.4.

LITERATURE CITED

1. P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 5, 761 (1965).
2. G. G. Lancini, N. Maggi, P. Sensi, Farmaco (Pavia), Ed. Sci., 18, 390 (1963); Ref. Zh. Khim., 23Zh, 226 (1963).
3. P. M. Kochergin and S. G. Verenikina, Khim. Geterotsikl. Soedin., No. 5, 770.
4. P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 5, 749 (1966).
5. S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, L. V. Epishina, and V. V. Sevost'yanova, Khim. Geterotsikl. Soedin., No. 5, 664 (1970).
6. S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, V. V. Sevost'yanova, and L. V. Epishina, Khim. Geterotsikl. Soedin., No. 4, 503 (1970).
7. G. P. Sharnin, R. Kh. Fassakhov, and P. P. Orlov, USSR Author's Certificate No. 458,553; Byul. Izobr., No. 4, 52 (1975).