RESEARCH ON FIVE-MEMBERED HETEROCYCLES.

II.* HALONITROIMIDAZOLES

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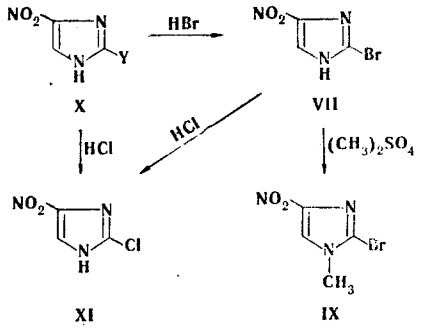
UDC 547.781.4.5:542.944

Replacement of the nitro group in polynitroimidazoles by a halogen atom by the action of $POBr_3$ in dimethylformamide or by means of hydrohalic acids was studied. It is shown that the second method is the most convenient method in the preparation of chloro- and bromonitroimidazoles.

Nitrohalo derivatives of imidazole are usually synthesized by nitration of haloimidazoles [2-4] or by halogenation of nitroimidazoles [3]. The first method is fraught with certain difficulties associated with the preparation of the starting halo derivatives [5]. Only dibromonitroimidazole has been obtained by the second method.

Since convenient methods for the preparation of dinitroimidazoles have been developed [6, 7] and interest in halonitroimidazoles as starting compounds in the synthesis of medicinal preparations [8] and amino- [9] and mercaptoimidazoles [10] has grown, we studied the possibility of replacement of the nitro group by halogen in 4,5-dinitro- (I) and 2,4-dinitroimidazoles (II) and their 1-methyl-substituted derivatives (III and IV, respectively), and 2,4,5-trinitroimidazole (V). It was found that the nitro group in these compounds is replaced by a halogen atom under the influence of $POBr_3$ in dimethylformamide (DMF) (method A).

We used this method to synthesize 4(5)-bromo-5(4)-nitro- (VI) [3], 2-bromo-4(5)-nitro- (VII), 1-methyl-4-nitro-5-bromo- (VIII) [11], and 1-methyl-2-bromo-4-nitroimidazole (IX). The structures of VII and IX were proved by alternative synthesis from the known 2-iodo-4(5)-nitroimidazole (X) [4].



The location of the bromine atom in VI and VIII was confirmed by synthesis from them of the known 4(5)-chloro-5(4)-nitro- (XII) [12] and 1-methyl-5-chloro-4-nitroimidazole (XIII) [2].

The ease of replacement of the nitro group in dinitroimidazoles by bromine and chlorine by the action of $POBr_3$ and $POCl_3$ [12] provided a basis for the assumption of the possibility of the synthesis of halonitroimidazoles under milder conditions. In fact, brief refluxing of I-IV in hydrobromic and hydrochloric acids (method B) leads to bromonitro- (VI-IX) and chloronitroimidazoles (XI-XIII).

The reaction of dinitroimidazoles I-III with hydriodic acid constitutes a certain exception. In this case II reacts with concentrated HI at room temperature to give 2-iodo-4(5)-nitroimidazole (X), whereas the reaction of I and III under similar conditions proceeds very exothermically and terminates with resinification of the reaction mixture.

*See [1] for communication I.

S. M. Kirov Kazan Chemical-Technological Institute, Kazan 420015. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1666-1668, December, 1977. Original article submitted November 2, 1976.

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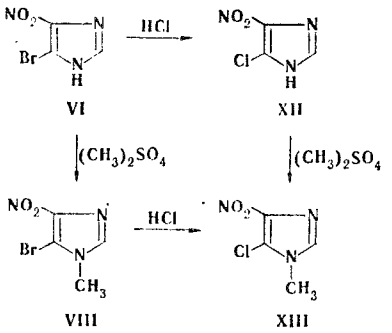
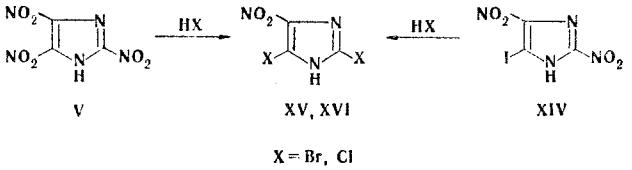


2,4(5)-Dibromo-5(4)-nitro- (XV) [3] and 2,4(5)-dichloro-5(4)-nitroimidazole (XVI) were synthesized by treatment of 2,4,5-trinitroimidazole (V) and 5(4)-iodo-2,4(5)-dinitroimidazole (XIV) with hydrohalic acids.



The second method for the preparation of chloro- and bromonitroimidazoles (method B) was found to be more convenient, since it does not require the application of scarce starting compounds, reduces the reaction time by a factor of four to six as compared with method A, simplifies the isolation of the desired products, and increases their purity.

EXPERIMENTAL

The starting nitroimidazoles I-V were obtained by the methods in [6, 7].

4(5)-Bromo-5(4)-nitroimidazole (VI). Method A. A mixture of 9.6 ml of DMF (0.114 mole), 10.9 g (0.038 mole) of $POBr_3$, and 3 g (0.019 mole) of 4,5-dinitroimidazole was refluxed on a water bath for 2.5 h, after which it was cooled to room temperature and poured over 300 g of ice. The precipitate was removed by filtration and washed with water and alcohol. The yield of product with mp 279-280°C (from water or dilute HBr) was 3.54 g (97%). The product was identical to 4(5)-bromo-5(4)-nitroimidazole obtained by the method in [3].

Method B. A 0.01-mole sample of 4,5-dinitroimidazole was refluxed in 20 ml of hydrobromic acid for 15-20 min, after which the mixture was cooled and diluted with water. The precipitate was removed by filtration and washed with water.

The other nitro- (II-V) and halonitroimidazoles (VI-VIII and X) react with HBr and HCl similarly. The reaction of II (0.01 mole) with freshly prepared HI (10 ml) was carried out at room temperature for 2-2.5 h. The yields and melting points of the halonitroimidazoles

TABLE 1. Reaction of Hydrohalic Acids with Nitroimidazoles

Starting compound	Product	mp, °C	Yield, %
I	VI	278—279	75
II	VII	238—239	82
III	VIII	178—179	80
IV	IX	157—158	70
II	X	278—280	50
VII, X	XI	216—217	78
VI	XII	259—260	82
VIII	XIII	147—148	75
V, XIV	XV	270	80
V, XIV	XVI*	194—195	76

*Found: C 19.6; H 0.4; Cl 38.7; N 23.3%. $C_3HCl_2N_3O_2$. Calculated: C 19.8; H 0.5; Cl 39.0; N 23.1%.

obtained are presented in Table 1. The compounds were purified by crystallization from water or the corresponding hydrohalic acids.

2-Bromo-4(5)-nitroimidazole (VII). This compound was obtained as white crystals with mp 238-239°C (from dilute HBr) in 60% yield by method A (the reaction time was 4 h). Found, %: C 18.0; H 1.0; Br 41.5; N 21.9. $C_3H_2BrN_3O_2$. Calculated, %: C 18.8; H 1.0; Br 41.7; N 21.9.

1-Methyl-5-bromo-4-nitroimidazole (VIII). This compound, with mp 179-180°C (from water), was obtained in 75% yield by method A (the reaction time was 6 h). The product was identical to a genuine sample [11] with respect to its IR spectrum and melting point.

1-Methyl-2-bromo-4-nitroimidazole (IX). This compound was obtained in 76% yield by the method A (the reaction time was 3.5 h) and also in 56% yield by methylation of VII with dimethyl sulfate in alkaline media as in [13]. The product had mp 157-158°C (from water). Found, %: C 23.0; H 1.9; Br 38.6; N 20.5. $C_4H_4BrN_3O_2$. Calculated, %: C 23.3; H 1.9; Br 38.8; N 20.4.

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