THE NITRATION OF IODOIMIDAZOLES

S. S. Novikov, L. I. Khmel'nitskii,
O. V. Lebedev, L. V. Epishina,
and V. V. Sevost'yanova

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Treatment of iodoimidazoles with nitric acid of various concentrations results in replacement of the iodine atoms by nitro groups, including those in the 2-position, which is not activated towards electrophilic substitution in acid media. The use of a nitric acid–sulfuric acid nitrating mixture also results in the replacements of the iodine atom in the 4(5)-position.

We have described [1,2] some new methods for the nitration of imidazoles. Here we examine "substitutive" nitration in the imidazole series (the IR spectra of the salts of the compounds described here have already been published by us [3]. Proof of the structures of the salts was also given).

Replacement of halogen atoms by the nitro group in heteroaromatic compounds has been effected using various nitrating agents (nitric acid, sulfuric-nitric nitrating mixtures, and nitric acid-acetic anhydride mixtures [4-14]).

In examining substitutive nitration in the imidazole series, we have investigated the action of three different nitric acid concentrations (3, 50, and 100%), and a sulfuric acid-nitric acid nitrating mixture, on iodoimidazoles (as being the most accessible).

No nitro derivative was obtained on treating triiodoimidazole with 3% nitric acid.

On boiling tri- and tetraiodoimidazoles (I and II) with 50% nitric acid, replacement of two of the iodoatoms by nitro groups occurred to give the same dinitroiodoimidazole IV. In order to prove its stucture, it was methylated with dimethyl sulfate in alkaline solution, and with diazomethane. In both cases, methylation gave a mixture of the two isomers V and VI, one of them predominating. The formation of two isomers proves conclusively that IV is 2,4(5)-dinitro-5(4)-iodoimidazole, since the other possible isomer (2-iodo-4,5-dinitroimidazole) would have given only a single isomer.

On careful heating of 2,4,5-triiodo- (I) and 1,2,4,5-tetraiodoimidazole (II) in 50% nitric acid, the intermediate reaction product 1,2,4(5?)-triiodo-5(4?)-nitroimidazole (III) may be isolated, whose structure is proved by its chemical reactions (with potassium iodide it is readily converted into 2,4(5)-diiodo-5(4)-nitroimidazole (VII), and methylation of this gives the two isomers VIII and IX).

Proof of the structures of the intermediate and final products shows that the iodine atoms are replaced successively in the polyiodoimidazoles. The first atom to be replaced is that in the 4(5)-position, followed by that in the 2-position.

Treatment of 2,4(5)diiodoimidazole (X) with boiling 50% nitric acid results, in addition to replacement of the 2-iodine atom, in nitration at the free 5(4)-position (X→IV).

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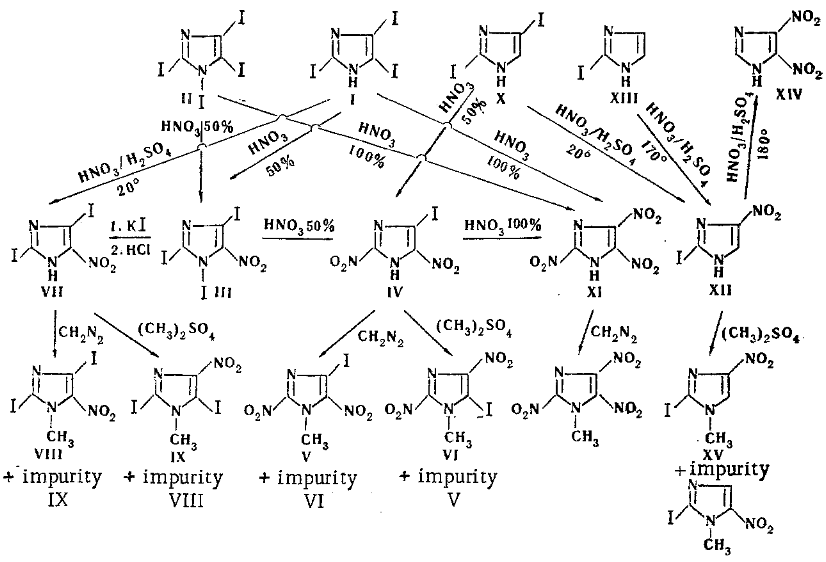

The iodine atom in 2,4(5)-dinitro-5(4)-iodoimidazole (IV) is replaced by the nitro group only on boiling with nitric acid (d 1.5), giving the previously described [2], full nitrated 2,4,5-trinitroimidazole (XI) in 80% yield. When nitric acid of d 1.5 is used, the trinitroimidazole XI may be obtained not only from IV, but also from triiodo- (I) and tetraiodoimidazole (II), without isolating the less nitrated intermediate products.

A sulfuric acid–nitric acid nitrating mixture is also an effective reagent for the replacement of the iodine atom in iodoimidazoles by the nitro group. Thus, treatment of a solution of I in concentrated sulfuric acid with nitric acid (d 1.5) resulted in replacement of the iodine atom in the 4(5)-position, even in the cold (I → VII). A similar result was obtained when 2,4(5)-diiodoimidazole was treated with a sulfuric acid-nitric acid nitrating mixture to give 2-iodo-4(5)-nitroimidazole (XII). (The preparation of this compound by a similar method was described in 1966 [15].) The structure of this compound was confirmed by its preparation from 2-iodoimidazole (XIII) with a hot sulfuric acid-nitric acid nitrating mixture. Heating XII with the same nitrating mixture at 180° C gave 4,5-dinitroimidazole (XIV), which was identical with the compound which we obtained by nitration of imidazole [2].

In order to prove the structure of some of the nitroiodoimidazoles, they were methylated with dimethyl sulfate in alkaline solution, and with diazomethane. According to the mechanism for the methylation of 4(5)-nitroimidazoles with dimethyl sulfate in alkali [16–18], the 4-nitro isomers should predominate. Methylation of imidazoles with diazomethane does not result in a definite orientation of the methyl group [19].

Methylation of iodonitroimidazoles with dimethyl sulfate and diazomethane gave predominantly different products.

The methylation of IV, VII, and XII with dimethyl sulfate gave products whose structure must be VI, IX, and XV respectively, since methylation of IV and VII with diazomethane gave mainly those isomers which occurred only as impurities in the dimethyl sulfate methylation products. Therefore these isomers possess a nitro group in the 5-position, and the principal diazomethane methylation products of IV and VII must be assigned the structures V and VIII, respectively.

Comparison of the mp's and chromatographic distribution coefficients (here and elsewhere, referring to thin layer chromatography without binders) of the methylation products of IV, VII, and XII, and of 4(5)-nitroimidazole (Table 1) also support the structures assigned. The 4-nitro isomers have much higher mp's and smaller distribution coefficients than the 5-nitro isomers.

EXPERIMENTAL

2,4(5)-Dinitro-5(4)-iodoimidazole (IV). A) A 1-g (2 mmole) quantity of 2,4,5-triiodoimidazole (I) [20] (mp 191–192° C) was added to 40 ml of hot nitric acid (d 1.32), and the mixture was boiled until iodine vapor no longer evolved. The reaction mixture from 14 reactions was poured into 400 g of ice, and neu-

TABLE 1. Comparison of the Properties of the Methylnitroimidazoles

R_f	mp, °C	Isomer obtained by methylation with dimethyl sulfate	Isomer obtained by methylation with diazomethane	mp, °C	R_f
0.38	134	1-Methyl-4-nitro	1-Methyl-5-nitro	53	0.60
0.60	259—261	1-Methyl-2,5-diiodo-4-nitro	1-Methyl-2,4-diiodo-5-nitro	206—207	0.79
0.53	216—218	1-Methyl-2,4-dinitro-5-iodo	1-Methyl-2,5-dinitro-4-iodo	113—115	0.84
0.25	236—238	1-Methyl-2-iodo-4-nitro	1-Methyl-2-iodo-5-nitro	*	0.59

* This isomer was not obtained in the pure state.

TABLE 2. Methylation of Iodonitroimidazoles

Starting compound	Method	Main reaction product	R_f[a]	mp, °C	Molecular formula	Found, %				Calculated, %				Overall yield, %
						C	H	I	N	C	H	I	N	
IV	A	V	0.84	111—113[b]	$C_4H_3IN_4O_4$	16.32 16.25	1.13 1.32	42.50 42.44	18.64 19.09	16.12	1.02	42.59	18.80	82
	B	VI	0.53	219—221[c]		16.34 16.29	1.15 1.12	42.76 42.76						74
VII	A	VIII	0.79	206—208[d]	$C_4H_3I_2N_3O_2$			67.31 67.37	11.23 11.37			67.02	11.09	85
	B	IX	0.60	259—261[e]				67.25 67.36	10.48 10.52					85
XII	B	XV	0.25	236—238[f]	$C_4H_4IN_3O_2$	19.19 19.37	1.59 1.59	50.08 50.06	16.56 16.52	19.06	1.60	50.37	16.67	68

[a] Al_2O_3, grade II activity, benzene—methanol = 25 : 1. [b] From CCl_4. [c] From dichloroethane. [d] From benzene—petroleum ether (3 : 1). [e] From benzene. [f] From alcohol; literature mp [15], 240° C.

tralized with sodium bicarbonate. Nitric acid (d 1.32) (20 ml) was then added, and the mixture was extracted with 12 × 150 ml of ether. The ether extracts were evaporated, and the residual yellow crystals of 2,4(5)-dinitro-5(4)-iodoimidazole (IV) were filtered off, washed with water, and dried in air to give 8 g (80%) of product, mp 216-218° C (from water). R_f 0.43 ["acid" alumina (obtained by washing commercial alumina with 3% HCl and then with distilled water until chloride ion was absent) grade II activity, benzene : methanol = 20 : 5]. Found, %: C 12.01, 12.03; H 0.99, 1.00; I 42.10, 42.05; N 18.31, 18.22. Calculated for $C_3HIN_4 \cdot H_2O$, %: C 11.94; H 1.00; I 42.02; N 18.55. IV is readily soluble in ether and alcohol, but sparingly soluble in dichloroethane. With hydroxides, carbonates, and bicarbonates of the alkali metals, readily water-soluble salts are formed. With imidazole, it gives a salt, mp 252-253° C (from water).

B) A 0.8-g (1.5 mmole) quantity of 1,2,4,5-tetraiodoimidazole (II) [21] was introduced into 50 ml of nitric acid (d 1.32), and heated to boiling. Iodine was liberated, II dissolved, and a yellow precipitate of 1,2,4(5?)-triiodo-5(4?)-nitroimidazole (III) separated. This in turn gradually dissolved. The reaction mixture was heated until iodine vapor was no longer evolved, and poured on to 20 g of ice compound. IV was isolated as in A) above to give 0.2 g (50%) of product, mp 216-218° C (from water).

C) Reaction of 2,4(5)-diiodoimidazole (X) [22] (mp 180-181° C) with nitric acid (d 1.32) under conditions similar to those in A) above gave IV in 40% yield, mp 216-218° C (from water).

D) A 0.43-g (1.1 mmole) quantity of 2,4(5)-diiodo-5(4)-nitroimidazole (VII) was introduced into 20 ml of nitric acid (d 1.32), and the mixture was heated until evolution of iodine vapor ceased. The reaction mixture was poured onto 20 g of ice, neutralized with sodium bicarbonate, then 1 ml of nitric acid (d 1.32) added, and the mixture was extracted with 12 × 10 ml of ether. The ether extracts were evaporated, and the crystals of IV which separated were filtered off, washed with water, and dried in air to give 0.23 g (70%), mp 216-218° C (from water).

The identity of IV as obtained in B-D above, and its methylation products, with the authentic compound and its N-methyl derivatives was established by chromatography and mixed mp's.

1,2,4(5?)-Triiodo-5(4?)-nitroimidazole (III). A 1-g (2 mmole) quantity of I was mixed with 40 ml of nitric acid (d 1.32), and the mixture heated slowly. The solid dissolved, the mixture became brown in color, and a yellow solid separated. Heating was discontinued. After 3 hr, III was filtered off and washed with water, alcohol, and ether to give 0.22 g (20%) of yellow powder, insoluble in organic solvents and in water. It did not melt up to 350° C, and did not chromatograph on alumina.

2,4(5)-Diiodo-5(4)-nitroimidazole (VII). A) A 5.7-g (11 mmole) quantity of III was placed in 100 ml of a 10% solution of potassium iodide. Solution of III was accompanied by the separation of iodine. The filtered reaction mixture was extracted with toluene until all the iodine had been removed, and acidified with dilute HCl (1 : 1). The precipitated VII was filtered off, washed with water, and air dried to give 1.9 g (45%), mp 225-226.5° C (from dichloroethane). R_f 0.49 (acid alumina, benzene : methanol = 20 : 5). Compound, readily soluble in alcohols, moderately soluble in ether and dichloroethane, and sparingly soluble in water and hydrocarbons. With hydroxides, carbonates, and bicarbonates of the alkali metals, it gave salts which were readily water soluble.

B) To a solution of 4.46 g (10 mmole) of I in 40 ml of conc. H_2SO_4 was added dropwise in the cold 0.4 ml (10 mmole) of nitric acid (d 1.5). Iodine was liberated. The mixture was diluted with five times its volume of ice, and the precipitate of iodine and the iodonitroimidazole VII was washed with potassium iodide solution until the iodine had been completely removed, then with water, and air dried. Yield, 2 g (55%) of product, mp 225-226.5° C (from dichloroethane), identical by chromatography with the material obtained from III, and giving no depression of mp with this material.

2,4,5-Trinitroimidazole (XI). A) A mixture of 5 g (16 mmole) of IV and 40 ml of nitric acid (d 1.5) was boiled for 10 min. A precipitate of iodic acid separated. The mixture was poured into 100 g of ice, neutralized with sodium bicarbonate, 5 ml of nitric acid (d 1.32) was added, and it was extracted with 6 × 50 ml of ether. The ether extracts were evaporated, and the residual oil dissolved in 20 ml of water. The solution was adjusted to pH 8-9 by adding potassium carbonate, and saturated with potassium chloride. The precipitated potassium salt of the trinitroimidazole XI was filtered off, washed with water, and dried, mp 232-235° C (from water). Yield 67%.

B) Under conditions similar to those in A) above, the trinitroimidazole XI was obtained from I in 26% yield, and from II in 15% yield.

The N-methyl derivative of XI was obtained as in A) and B) and gave no depression of mp on mixing with authentic 1-methyl-2,4,5-trinitroimidazole [2].

2-Iodo-4(5)-nitroimidazole (XII). A) To a solution of 3.2 g (10 mmole) of 2,4(5)-diiodoimidazole (X) in 40 ml of conc. H_2SO_4 was added dropwise in the cold, 0.4 ml (10 mmole) of nitric acid (d 1.5). Iodine was liberated only on decomposition of the reaction mixture with ice. The precipitate of XII was washed with potassium iodide solution until the iodine was completely removed, then with water, and finally air dried to give 1.5 g (62%), mp 277-280° C (from ethanol, then dioxane). Literature mp [15], 281° C. R_f 0.47 (acid alumina, benzene: methanol = 20: 5). Yellow crystalline solid, moderately soluble in alcohols, less soluble in dichloroethane, and sparingly soluble in water and ether. Treatment with alkali gave salts.

B) To a solution of 0.5 g (2.6 mmole) of 2-iodoimidazole (XIII) [22] (mp 135-136° C) in 30 ml of conc. H_2SO_4 was added dropwise 3 ml (7 mmole) of nitric acid (d 1.5). The reaction mixture was heated to 170° C, and poured into a fivefold quantity of ice. The precipitate of XII was filtered off, washed with water, and air dried to give 0.25 g (40%) of product, mp 277-280° C (from ethanol and dioxane). The XII obtained was identical chromatographically with 2-iodo-4(5)-nitroimidazole (XII) obtained from X, and gave no depression of the mp when mixed with it.

4,5-Dinitroimidazole (XIV). On heating XII with a sulfuric acid-nitric acid nitrating mixture [as in B) above] at 180° C for 20 min, 20% of 4,5-dinitroimidazole (XIV), was obtained mp 187-188° C (from water). The identity of XIV with an authentic sample of 4,5-dinitroimidazole [2] was established by chromatography and mixed mp.

Methylation of the nitration products was carried out with diazomethane [1] (method A), and with dimethyl sulfate in alkaline solution [1] (method B). The isomers were separated by fractional crystallization. Results are given in Table 2.

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