NITRATION OF IMIDAZOLES WITH VARIOUS NITRATING AGENTS

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The nitration of imidazole and its derivatives has been studied. The action of sulfuric-nitric nitrating mixture on imidazole and its nitro derivatives has given di- and trinitroimidazoles. The action of a mixture of nitric acid and acetic anhydride on the mononitroimidazoles has given the corresponding N-nitro derivatives, and some of their properties have been studied.

Until recently it was believed that the nitration of imidazole with sulfuric-nitric nitrating mixture forms 4(5)-mononitroimidazole which does not nitrate further [1]. The nitro group never enters the position 2, like other substituents in electrophilic substitution reactions taking place in an acid medium. In 1964, 2,4(5)-dinitroimidazole was synthesized [2] but this was obtained by the nitration of a natural antibiotic, 2-nitroimidazole, already containing a nitro group in position 2.

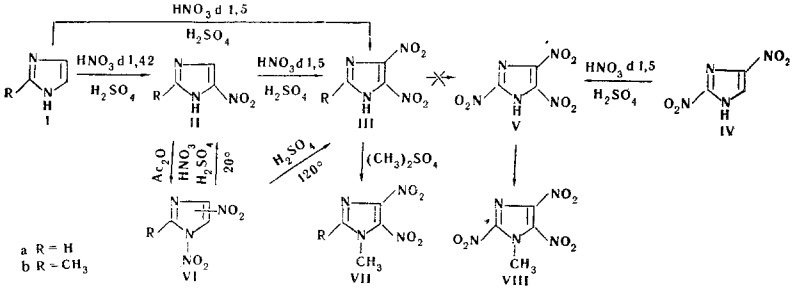
We have shown [3] that under certain special conditions it is possible to introduce a nitro group into position 2 and also to obtain polynitroimidazoles. In view of this and of certain properties of the polynitromidazoles (their ready solubility in water and therefore the possibility of their loss on isolation), a critical consideration of the literature on the nitration of imidazole is called for.

Among the numerous investigations there are papers by Lehmstedt and his co-workers on the nitration of 2,2'-bisimidazole and its bromo derivatives [4-6]. By using somewhat unusual nitration conditions, namely heating the substance first with nitric acid alone and then with sulfuric-nitric nitrating mixture, the authors obtained nitro derivatives of 2,2'-bisimidazole. The di-, tri-, and tetranitro derivatives were ascribed the structure of N-nitroamines.

A comparison of the properties of these compounds with the properties of the polynitroimidazoles that we have obtained [3] and certain literature information gave grounds for assuming that the polynitrobisimidazoles are C-nitro derivatives. Consequently, it might be expected that, under the conditions of the nitration of 2,2'-bisimidazole, imidazole itself and its derivatives will be nitrated to form polynitroimidazoles.

In actual fact it was found that under these conditions imidazole (Ia) gives a mixture of 4(5)-nitroimidazole (IIa) (30%), and the dinitroimidazole IIIa (20%). Since the dinitroimidazole obtained has physical properties differing from those of the known 2,4(5)-dinitroimidazole [2, 3], it must be ascribed the structure of 4,5-dinitroimidazole (IIIa).

Under Lehmstedt's conditions, the 4(5)-mononitroimidazoles (II) nitrate to give 4,5-dinitroimidazoles (III). Renitration of 4,5-dinitroimidazole (IIIa) did not give a trinitroimidazole, but under these conditions 2,4(5)-dinitroimidazole (IV) gave a 26% yield of 2,4,5-trinitroimidazole (V).



We have shown that the preliminary boiling of the starting materials with nitric acid is an unnecessary operation. Nitration takes place only when sulfuric acid is added, and also when the substances are heated with previously-prepared

sulfuric-nitric nitrating mixture. The failure to obtain polynitroimidazoles in the nitration of imidazole [1] can be explained by the use of relatively dilute nitric acid in this reaction.

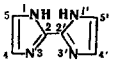
The di- and trinitroimidazoles, like dinitropyrrole, dinitrotriazole, and the trinitromethyl derivatives of nitroimidazole, are strong acids [7]; they dissolve comparatively readily in water and polar solvents and are methylated with the formation of substances no longer possessing acidic properties and soluble in nonpolar solvents.

We have also shown that under the conditions for the N-nitration of pyrazoles [8] (the action of nitric acid in acetic anhydride), the mononitroimidazoles II form the N-nitro derivatives VI. It was found by chromatography (TLC) that in each case only one of the two possible isomers is formed. The position of the C-nitro group in them was not established. These substances, like the N-nitropyrazoles, having no free imine hydrogen, no longer possess acidic properties. The action of concentrated sulfuric acid in the cold on the N-nitroimidazoles VI leads to the splitting off of the nitro group from the nitrogen atom with the formation of 4(5)-nitroimidazoles (II), while when they are heated with sulfuric acid the nitro group migrates from the nitrogen atom to the carbon in position 4(5).

Thus, the results obtained confirm our hypothesis on the structure of Lehmstedt's nitrobisimidazoles as C-nitro derivatives.

In actual fact, salt formation of the nitrobisimidazoles not alkylated at the nitrogen atoms obviously takes place in a similar manner to salt formation in the nitroimidazoles [9] and is a consequence of the increase in the mobility of the hydrogens attached to the "pyrrole" nitrogen atoms as a result of the accumulation of C-nitro groups. The products of the alkylation of the nitrobisimidazoles are generally N-alkyl derivatives, with properties similar to those of other N-alkyl nitroazoles. In their turn, the capacity of some of the nitro groups in the nitrobisimidazoles for being replaced by OH, OR, and NH_2 groups under the action of nucleophilic reagents is analogous, for example, to the capacity of 1,2,-3,5-tetranitrobenzene for being converted under the action of ammonia into picramide and under the action of alkali into picric acid [10]. The products of replacement by OH and NH_2 groups have properties similar to those of the known N-methyl-4-nitroimidazolone and 5-amino-N-methyl-4-nitroimidazole [11-12]. In the N-alkyl-substituted nitrobisimidazoles, of the two nitro groups it must be that in position 4, which is activated by the nitro group in position 5 and by the "pyridine" nitrogen atom, that is replaced.

Table 1



Structure of the substances according to Lehmstedt	Structure proposed by us
1,5-Dinitro-	4,5-Dinitro- or 4(5), 4′(5′)-dinitro-
1,1′, 5-Trinitro-	4,5,4′(5′)-Trinitro-
1,1′,5,5′-Tetranitro-	4,5,4′,5′-Tetranitro-
4-Alkyl-1,1′,5,5′-tetranitro-	1-Alkyl-4,5,4′,5′-tetranitro-
4,4′-Dialkyl-1,1′,5,5′-tetranitro-	1,1′-Dialkyl-4,5,4′,5′-tetranitro-
Disodium salt of 1,1′-dihydroxy-5,5′-dinitro-	Disodium salt of the 5,5′-dinitro-4,4′-dione
Disodium salt of 1,1′-dihydroxy-4,4′-dimethyl-5,5′-dinitro-	Disodium salt of the 1,1′-dimethyl-5,5′-dinitro-4,4′-dione
1,1′-Dimethoxy-4,4′-dimethyl-5,5′-dinitro-	4,4′Dimethoxy-1,1′-dimethyl-5,5′-dinitro-
Disodium salt of 1,1′-diamino-4-methyl-5,5′-dinitro-	Disodium salt of 4,4′-diamino-1-methyl-5, 5,5′-dinitro-

In the dinitrobisimidazole, both nitro groups are most probably present in the same imidazole nucleus, since after the introduction of the first nitro group, of course, the basicity of the nitrated imidazole ring falls sharply and the non-nitrated nucleus must be protonated preferentially. This should lead to a lower reactivity of the non-nitrated nucleus. In addition to this, it is known [1, 13] that the protonated imidazole ring is para-directing. In the nitration of various phenylimidazoles, the first nitro group enters the para position of the phenyl ring. Thus, the protonation of the imidazole ring must favor the entry of a nitro group into the substituted ring when mononitro-2,2'-bisimidazole is nitrated further.

Table 1 gives the structures that we propose for some of the nitrobisimidazoles synthesized by Lehmstedt.

EXPERIMENTAL

4(5)-Nitroimidazole (IIa) and 2-methyl-4(5)-nitroimidazole (IIb) were obtained from imidazole [14] (Ia) (mp 88-90°C) and from 2-methylimidazole [15] (Ib) (mp 141-143°C), respectively, by a published method [15] as modified by us: 0.44 mole of I was dissolved in 6 ml of HNO_3 (d 1.42) at 30-40°C (cooling with ice). With stirring and cooling, 5 ml of conc. H_2SO_4 was slowly added to the resulting solution (the temperature rose gradually to 75°C). The reaction mixture was boiled for 1 hr. Then it was cooled, 8 ml of a mixture of sulfuric and nitric acids (1 : 1) was added, and it was heated to a boil for a further 1 hr. After this it was poured onto ice, and the nitro derivative that precipitated was filtered off, washed three times with water, and dried in the air. 4(5)-Nitroimidazole: yield 73%, mp 308-310°C. Literature data [15]: mp 312-313°C. 2-Methyl-4(5)nitroimidazole: yield 60%, mp 254-256°C. Literature data [15]: mp 254°C.

Nitration of imidazole derivatives under the conditions for the nitration of 2,2'-bisimidazole [4]. A solution of 0.1 mole of the substance in 33.5 ml of HNO_3 (d 1.5) was boiled under reflux. After cooling, 50 ml of conc. H_2SO_4 was added and the mixture was boiled for 2 hr 30 min, cooled, and poured onto ice. For 2,4(5)-dinitroimidazole, the time of heating with HNO_3 was 5 min and with the sulfuric-nitric nitrating mixture 15 min. The aqueous acid solution was neutralized with sodium bicarbonate, and the precipitate of sodium sulfate was filtered off and washed with water. The filtrate, together with the wash-water, was acidified with HNO_3 (d 1.32) until it was acid (to Congo Red), after which another 5 ml of HNO_3 (d 1.32) was added and extraction was carried out with ether (5 × 250 ml). The ethereal extracts were evaporated. The reaction product, which deposited in the form of yellow crystals, was filtered off, washed with water, and dried in the air.

The reaction mixture obtained in the nitration of Ia was poured onto ice, whereupon the 4(5)-nitroimidazole precipitated; it was filtered off and then the IIIa was isolated. The identity of the substances obtained was established by chromatography with authentic products and by the absence of a depression of the melting point of mixtures.

The isolation of V was carried out in a similar manner to that of III. After the ethereal extracts had been evaporated, the residual oil was dissolved in 200 ml of water, and the solution was neutralized with potassium carbonate and saturated with potassium chloride. The potassium salt of V that deposited was filtered off, washed with water, and dried. Then it was dissolved in 200 ml of dil. HCl (1 : 1), and the solution was extracted with ether (4 × 50 ml). On evaporation an oil remained which crystallized on standing over $CaCl_2$.

The results of nitration are given in Table 2.

Table 2. Nitration of Imidazole Derivatives under the Conditions for the Nitration of 2,2'-bisimidazole

Initial imidazole	Reaction product	Mp, °C	R_f[1]*	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
IIa	IIIa[2]*	187—188[3]*	0,75	$C_3H_2N_4O_4$	23.05 22.91	1.42 1.39	35.25 35.01	22.79	1.28	35.44	45
IIb	IIIb	207—208[3]*	0,67	$C_4H_4N_4O_4$	28.12 28.20	2.39 2.43		27.91	2.34		55
Ia	IIIa	187—188[3]*									31
	IIa	308—310[3]*									21
IV	V[4]*	136—138		$C_3HN_5O_6 \cdot C_3H_4N_2$[5]*	26.26 26.50	1.94 2.03	35.67 35.78	26.57	1.86	36.16	26

[1]*Acid alumina (obtained by washing commercial alumina with 3% HCl and then with distilled water until free from chloride ions; benzene methanol (4 : 1) system.

[2]*Gave a depression of the melting point with 2,4(5)-dinitroimidazole; K salt, mp 255-258°C (decomp., from water); salt with imidazole, mp 227-228°C (from water).

[3]*From water.

[4]*Hygroscopic yellow substance soluble in water, ethanol, and acetone. K salt, mp 238-240°C (from water).

[5]*Salt of V with imidazole, mp 210-211.5°C (from water).

1-Methyl-4,5-dinitroimidazole (VIIa). When 0.44 g (2.5 mM) of IIIa was methylated with dimethyl sulfate in the presence of sodium bicarbonate [3], the yield of the methyldinitroimidazole VIIa was 0.3 g (63%). Mp 73-75°C (from methanol). R_f 0.65 [Al_2O_3; benzene-methanol (25 : 1)]. Found %: C 27.93, 28.07; H 2.34, 2.38; N 32.31, 32.35. $C_4H_4N_4O_4$. Calculated %: C 27.91; H 2.34; N 32.56.

When 4,5-dinitroimidazole (IIIa) was methylated with diazomethane [3], the yield of the imidazole VIIa was 0.4 g (72%), mp 73-75°C (from methanol). The chromatogram showed the presence of a single substance identical with the 1-methyl-4,5-dinitroimidazole obtained by the methylation of 4,5-dinitroimidazole with dimethyl sulfate in an alkaline medium.

1,2-Dimethyl-4,5-dinitroimidazole (VIIb). Compound IIIb was methylated with dimethyl sulfate in the presence of sodium bicarbonate. The yield of VIIb was 65%. Mp 49-50°C (from ethanol). R_f 0.62 [Al_2O_3; benzene-methanol (25 : 1)]. Found %: C 31.85, 31.97; H 3.48, 3.36; N 29.93, 30.08. $C_5H_6N_4O_4$. Calculated %: C 32.26; H 3.25; N 30.10.

1-Methyl-2,4,5-trinitroimidazole (VIII). The trinitroimidazole V obtained from 10 g (40 mM) of the potassium salt was methylated with diazomethane in ether. The yield of VIII was 3.54 g (65%) of a yellow crystalline substance readily soluble in ether, dichloroethane, and alcohols, and sparingly soluble in carbon tetrachloride, benzene, hexane, and water; mp 81.5-82.5°C [from dichloroethane-carbon tetrachloride (1 : 1)]. Found %: C 22.11; 22.22; H 1.47, 1.57. $C_4H_3N_5O_6$. Calculated %: C 22.13; H 1.39.

1,4(5?)-Dinitroimidazole (VIa). A suspension of 0.5 g of 4(5)-nitroimidazole (IIa) in 18.2 ml of acetic acid was treated dropwise with 4.25 ml of nitric acid (d 1.5). The temperature rose to 50°C and the suspension of IIa dissolved. Then 12.1 ml of acetic anhydride was added to the mixture and it was left to stand for an hour. After this it was poured onto ice and the acid solution was extracted with dichloroethane. The dichloroethane extracts were washed twice with aqueous sodium bicarbonate solution and evaporated. The yield of the dinitroimidazole VIa was 0.5 g (71.5%). Mp 91.5-92.5°C (from carbon tetrachloride), R_f 0.33 ("acid" alumina; benzene). Found %: C 23.11, 23.22; H 1.44, 1.47; N 35.32, 35.38. $C_3H_2N_4O_4$. Calculated %: C 22.79; H 1.28; N 35.34. The substance consisted of colorless elongated needles dissolving slowly in aqueous sodium carbonate solution and reacting instantaneously with an aqueous solution of caustic potash with the appearance of an orange coloration. The substance is readily soluble in dichloroethane, chloroform, benzene, and ether, and sparingly soluble in petroleum ether.

2-Methyl-1,4(5?)-dinitroimidazole (VIb). This was obtained with a yield of 80% from 2-methyl-4(5?)nitroimidazole (IIb) in a similar manner to VIa, mp 121.5-122°C (from carbon tetrachloride), R_f 0.44 ("acid", alumina; benzene). Found %: C 28.26, 28.41; H 2.28, 2.21; N 32.33, 32.14. $C_4H_4N_4O_4$. Calculated %: C 27.91; H 2.34; N 32.56. The properties of VIb are similar to those of VIa.

Action of Concentrated Sulfuric Acid in the Cold on N-Nitroimidazoles.

1,4(5?)-Dinitroimidazole (VIa). A solution of 0.5 g (3 mM) of VIa in 5 ml of conc. H_2SO_4 was left overnight. Then it was decomposed with a fivefold amount of ice. The IIa that deposited was filtered off, washed with sodium bicarbonate solution and with water, and dried in the air. Yield 0.23 g (66%), mp 308-310°C (from 20% ethanol). It was chromatographically identical with authentic 4(5)-nitroimidazole and gave no depression of the melting point in admixture with it.

2-Methyl-1,4(5?)-dinitroimidazole (VIb). Compound IIb was obtained with a yield of 58% from VIb under similar conditions. Mp 254-256°C (from ethanol). It was chromatographically identical with authentic IIb and gave no depression of the melting point in admixture with it.

Action of Concentrated Sulfuric Acid on N-Nitroimidazoles with Heating.

1,4(5?)-Dinitroimidazole (VIa). A solution of 0.5 g (0.003 mole) of VIa in 5 ml of conc. H_2SO_4 was treated at 120-125°C for 2 hr. The reaction mixture was cooled and was poured into a fivefold amount of ice. The solution was washed with 20 ml of dichloroethane and was then neutralized with sodium bicarbonate. The precipitate of sodium sulfate was filtered off and washed with water. The combined filtrate and wash-waters were acidified with HNO_3 (d 1.32) and extracted with ether (5 × 50 ml). The ethereal extracts were evaporated. The crystals of 4,5-dinitroimidazole (IIIa) that deposited were filtered off, washed with water, and dried in the air. Yield 0.25 g (50%), mp 187-188°C (from water). The substance was chromatographically identical with the 4,5-dinitroimidazole obtained by the nitration of 4(5)-nitroimidazole, and gave no depression of the melting point in admixture with it. The product of methylation with dimethyl sulfate

was also chromatographically identical with the 1-methyl-4,5-dinitroimidazole obtained by the methylation of authentic 4,5-dinitroimidazoles and gave no depression of the melting point in admixture with it.

2-Methyl-1,4(5)-dinitroimidazole (VIb). When VIb was heated in conc. H_2SO_4 for 4 hr, 2-methyl-4,5-dinitroimidazole (IIIb) was obtained, in a similar manner to IIIa, with a yield of 40%. Mp 207-208°C (from water). The substance was chromatographically identical with the 2-methyl-4,5-dinitroimidazole obtained by the nitration of 2-methyl-4(5)-nitroimidazole and gave no depression of the melting point in admixture with it. The product of methylation with dimethyl sulfate was also chromatographically identical with the 1,2-dimethyl-4,5-dinitroimidazole obtained by the methylation of authentic 2-methyl-4,5-dinitroimidazole, and gave no depression of the melting point in admixture with it.

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