RESEARCH ON IMIDAZO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES

X.* NITRATION OF 2,9-DISUBSTITUTED IMIDAZOLE[1,2-*a*] BENZIMIDAZOLES

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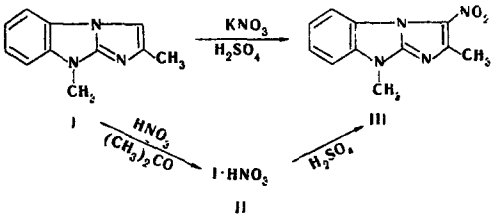
Depending on the nature of the substituent in the 2 position of the heteroring, imidazo[1,2-*a*] benzimidazole derivatives undergo either mononitration in the 3 position or form dinitro derivatives. In the latter case, one nitro group enters the phenyl group in the 2 position, and the other enters the benzimidazole fragment of the molecule.

It has been shown that 3-bromo-9-methyl-2-phenylimidazole[1,2-*a*]benzimidazole readily exchanges a bromine atom for a nitro group in dimethylformamide (DMFA) [2]. This reaction cannot be extended to 3-bromo-2-methyl-substituted imidiazo[1,2-*a*]benzimidazoles, inasmuch as the bromine atom in them has low lability. We therefore studied the possibility of direct nitration of imidazo[1,2-*a*]benzimidazole.

A nitro group cannot be introduced into the ring by the action of fuming nitric acid on 2,9-dimethylimidazo[1,2-*a*]benzimidazole (I) in acetic acid: only the nitrate (II) of the starting base is formed. The nitrate can also be obtained by the action of nitric acid (sp. gr. 1.32) on a solution of imidazo[1,2-*a*]benzimidazole in an organic solvent (acetone, dioxane). Mononitro compound III is formed in good yield when salt II is added to concentrated sulfuric acid at −5 to −10° C. An identical product was also obtained by nitration of I with an equivalent amount of potassium nitrate in concentrated sulfuric acid.



Asymmetrical (ν_{as} 1526 cm^{-1}) and symmetrical (ν_{s} 1345 cm^{-1}) stretching vibrations of the NO_2 group appear distinctly in the IR spectrum of mononitro compound III in the region characteristic for aromatic nitro groups [3]. On the basis of the transformations of the amine [4] obtained by reduction of III, the 3-nitro structure was assigned to the synthesized nitro compound.

The action of an equivalent amount of potassium nitrate on a solution of 9-methyl-2-phenylimidazo[1, 2-*a*]benzimidazole (IV) in concentrated sulfuric acid even under very mild conditions (from −10 to −12°) gives a mixture of a dinitro derivative (V, 47% yield) and unchanged starting compounds. When the amount of nitrating agent is increased to 2 equivalents the yield of dinitro derivative V is raised to 90%. It seemed that a mononitro product should have been formed when the nitrate of the starting base was added to sulfuric acid, but in this case a mixture of a dinitro derivative of the imidazo[1,2-*a*]benzimidazole and starting IV was obtained. Inasmuch as the mononitration of 2-(p-nitrophenyl) derivative VIa gives the same dinitro com-compound, it might be supposed that one of the nitro groups enters the para position of the phenyl ring.

*See [1] for communication IX.

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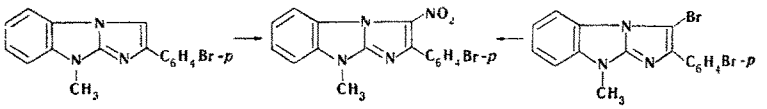
This is in agreement with the nitration of arylimidazoles, which also proceeds primarily in the para position of the aryl group [5]. Results of this sort are also characteristic for many polycyclic systems containing an imidazole or pyrrole-condensed ring that contains a phenyl substituent [6-9]. It has been shown [6, 10] that the imidazole ring in such systems becomes a π-surplus ring; therefore, if the para position in the phenyl ring is substituted, the nitro group enters the imidazole ring in the position adjacent to the bridge nitrogen atom. The single instance of entry of a nitro group in the meta position of the phenyl ring when the para position was occupied was observed for imidazo[2, 1-b][1,3,4]thidiazole [6].

We obtained p-nitrobenzoic acid by oxidation of the dinitro compounds that we obtained with potassium permanganate. Consequently, the second nitro group enters the heterocyclic ring. However, 9-methyl-3-nitro-2-(p-nitrophenyl)imidazo[1,2-*a*]-benzimidazole (VIIIa), which was obtained by alternative synthesis [by replacement of the bromine in 3-bromo-2-(p-nitrophenyl) derivative VIIa] proved to be different from the product of direct dinitration. The para position of the phenyl ring is probably nitrated initially. The resulting p-nitrophenyl grouping by means of its electron-acceptor effect deactivates the 3 position of the imidazole ring, and the second nitro group therefore enters the benzimidazole fragment of the molecule, especially since benzimidazole itself and its derivatives are usually nitrated under rather mild conditions [11, 12]. The position of the second nitro group cannot be more accurately established.

The unsuccessful attempt to isolate a mononitro compound in the nitration of 2-phenyl derivative IV indicates the greater ease of entry of the second nitro group into the molecule than in the case of the first nitro group. This effect on the course of the reaction is characteristic only for the nitrophenyl group. If there is a bromine atom present as a para substituent in the phenyl ring, IX undergoes mononitration in the 3 position of the cyclic system. The structure of this mononitro derivative was proved by alternative synthesis:



IX VIIIe VIIe

The nitration of 6,7-dimethyl-2-phenyl-9-ethylimidazo[1,2-*a*]benzimidazole, even at −10 to −15°, is accompanied by side redox processes. 3-Nitro (VIIId), 2-(p-nitrophenyl) (Xd), and 3-nitroso derivatives, the structures of which were proved by alternative syntheses, and a number of other compounds of unknown structure were isolated from the reaction mixture.

EXPERIMENTAL

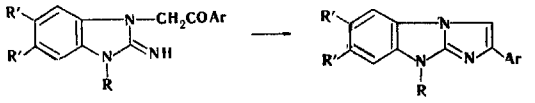
2,9-Dimethylimidazo[1,2-*a*]benzimidazole Nitrate (II). A 0.3-g sample of nitric acid (sp. gr. 1.32, 20% excess) was added with stirring to a solution of 0.92 g (5 mmole) of I in 10 ml of acetone. After 1h, the precipitated nitrate was removed by filtration and washed with ether to give 1 g (81%) of snow-white plates with mp 254° (from alcohol). Found: C 53.2; H 5.1; N 22.4%. $C_{11}H_{11}N_3 \cdot HNO_3$. Calculated: C 53.2; H 4.9; N 22.6%.

9-Methyl-2-phenylimidazo[1,2-*a*]benzimidazole Nitrate. This compound was obtained as snow-white needles with mp 213° (dec., aqueous alcohol) in 98% yield by the action of nitric acid on a solution of IV in acetic acid. Found: C 62.2; H 4.7; N 18.2%. $C_{16}H_{13}N_3 \cdot HNO_3$. Calculated: C 61.9; H 4.6; N 18.1%.

3-Nitro-2,9-dimethylimidazo[1,2-*a*]benzimidazole (III). A) A 0.8-g sample of salt II was added in small portions with vigorous stirring to a cooled (to −5 to −10°) concentrated H_2SO_4 (sp. gr. 1.82, 8 ml), and the mixture was held at this temperature for 1 h, after which it was poured over ice. The aqueous mixture was carefully made alkaline with concentrated ammonium hydroxide. The resulting precipitate was removed by filtration and dried in a desiccator. It was then treated with dry chloroform, the chloroform solution was filtered to remove inorganic salts, and the filtrate was chromatographed with a column filled with aluminum oxide to give 0.65 g (88%) of bright-yellow needles with mp 248° (from DMFA). Found: N 24.3%. $C_{11}H_{10}N_4O_2$. Calculated: N 24.3%

B) A solution of 0.3 g (3 mmole) of potassium nitrate in 5 ml of acid was added dropwise with stirring to a cooled (to −8 to −10°) solution obtained by careful dissolving of 0.55 g (3 mmole) of 2,9-dimethylimidazo[1,2-*a*]benzimidazole in 10 ml of concentrated H_2SO_4, after which the resulting solution was held at a low temperature for 1 h. It was then worked up as in experiment A to give 0.52 g (70%) of product. Sometimes III crystallized from aqueous alcohol with one molecule of water to give a product with mp 221°. Found: C 53.5; H 4.7; N 22.8%. $C_{11}H_{10}N_4O_2 \cdot H_2O$. Calculated: C 53.2; H 4.9; H 22.6%.

TABLE 1. 2-Imino-1-alkyl-3-nitrophenacylbenzimidazolines and Their Cyclization Products

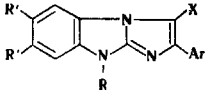


X a-r

VI a-r

Compound	R	R′	Ar	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Br	N	C	H	Br	N	
Xa·HBr	CH_3	H	$C_6H_4NO_2$-*p*	290 (dec., 50% methanol)	$C_{16}H_{14}N_4O_3 \cdot HBr$	49,3	4,1	20,1	14,3	49,1	3,9	20,4	14,3	80
Xa	CH_3	H	$C_6H_4NO_2$-*p*	126—127 (aqueous methanol	$C_{16}H_{14}N_4O_3 \cdot {}^1/_2H_2O$	60,2	4,9			60,2	4,7			
Xb·HBr	CH_3	H	$C_6H_4NO_2$-*m*	296 (dec., aqueous alcohol)	$C_{16}H_{14}N_4O_3 \cdot HBr$	49,4	3,8	20,2	14,5	49,1	3,9	20,4	14,3	87
Xb	CH_3	H	$C_6H_4NO_2$-*m*	213—214 (dec., ethanol)	$C_{16}H_{14}N_4O_3$	61,9	4,9		18,3	61,9	4,6		18,1	
Xc·HBr	CH_3	H	$C_6H_4NO_2$-*o*	247 (dec., 90% ethanol)	$C_{16}H_{14}N_4O_3 \cdot HBr$	48,9	4,0	20,4	14,1	49,1	3,9	20,4	14,3	90
Xc	CH_3	H	$C_6H_4NO_2$-*o*	138 (dec. aqueous alcohol)	$C_{16}H_{14}N_4O_3$	61,8	4,8		18,2	61,9	4,6		18,1	
Xd·HBr	C_2H_5	CH_3	$C_6H_4NO_2$-*p*	278 (aqueous methanol)	$C_{19}H_{20}N_4O_3 \cdot HBr$	52,9	5,0	18,4	13,0	52,7	4,9	18,4	12,9	75
Xd	C_2H_5	CH_3	$C_6H_4NO_2$-*p*	175 (aqueous alcohol)	$C_{19}H_{20}N_4O_3$	64,9	6,0		15,7	64,8	5,7		15,9	
VIa	CH_3	H	$C_6H_4NO_2$-*p*	192 (ethanol)	$C_{16}H_{12}N_4O_2$	65,5	4,3		19,3	65,7	4,1		19,2	82
VIb	CH_3	H	$C_6H_4NO_2$-*m*	225 (alcohol – DMFA)	$C_{16}H_{12}N_4O_2$	65,7	4,2		19,1	65,7	4,1		19,2	70
VIc	CH_3	H	$C_6H_4NO_2$-*o*	118 (methanol)	$C_{16}H_{12}N_4O_2$	65,5	4,0		19,3	65,7	4,1		19,2	52
VId	C_2H_5	CH_3	$C_6H_4NO_2$-*p*	163 (ethanol)	$C_{19}H_{18}N_4O_2$	68,4	5,5		16,9	68,2	5,4		16,8	68

TABLE 2. 3-Substituted Imidazo[1,2-*a*]benzimidazoles



VII, VIII

VII X = Br VIII X = NO_2

Compound	R	R′	Ar	mp °C (crystallization solvent)	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Br	N	C	H	Br	N	
VIIa·HBr	CH_3	H	$C_6H_4NO_2$-*p*	268 (DMFA)	$C_{16}H_{11}BrN_4O_2 \cdot HBr$	42,3	2,6	35,1	12,4	42,5	2,7	35,3	12,4	90
VIIa	CH_3	H	$C_6H_4NO_2$-*p*	256 (DMFA)	$C_{16}H_{11}BrN_4O_2$	52,0	3,3	21,7	15,4	51,8	3,0	21,5	15,1	
VIId·HBr	C_2H_5	CH_3	C_6H_5	(dec. without melting at 220°)	$C_{19}H_{18}BrN_3 \cdot HBr$	50,9	4,4	35,1	9,6	50,8	4,3	35,6	9,4	90
VIId	C_2H_5	CH_3	C_6H_5	158 (alcohol)	$C_{19}H_{18}BrN_3$	62,1	5,0	21,4	11,5	62,0	4,9	21,7	11,4	
VIIe	CH_3	H	C_6H_4Br-*p*	170 (alcohol–DMFA)	$C_{16}H_{11}Br_2N_3$	47,2	2,8	39,3	10,5	47,4	2,7	39,5	10,4	65
VIIIa	CH_3	H	$C_6H_4NO_2$-*p*	237 (alcohol–DMFA)	$C_{16}H_{11}N_5O_4$	57,1	3,5		21,0	57,0	3,3		20,8	75
VIIId	C_2H_5	CH_3	C_6H_5	234—235 (dec., DMFA)	$C_{19}H_{18}N_4O_2$	68,1	5,5		16,8	68,2	5,4		16,8	95
VIIIe	CH_3	H	C_6H_4Br-*p*	271—272 (DMFA)	$C_{16}H_{11}BrN_4O_2$	51,6	3,1	21,1	15,2	51,8	3,0	21,5	15,1	86,5

Nitro compound III had a very low basicity. It formed quaternary salts with difficulty, and the quaternary salts were extremely unstable; on treatment with dilute alkali in the cold they split out alkyl halide to give the starting nitro compound.

1-Alkyl-3-nitrophenacyl-2-iminobenzimidazolines (Xa-d). Reaction of 1-alkyl-2-aminobenzimidazoles with nitrophenacyl bromides in alcohol at room temperature gave 1-alkyl-3-nitrophenacyl-2-iminobenzimidazoline hydrobromides (X·HBr), treatment of which with 22% ammonium hydroxide or saturated sodium bicarbonate solution gave bases Xa-d (Table 1).

9-Alkyl-2-nitrophenylimidazo[1,2-*a*]benzimidazoles (VIa-d, Table 1). These compounds were obtained by cyclization of imines Xa-d by means of the following cyclizing agents (the reaction times are indicated in parentheses): concentrated HCl in the presence of a small amount of $POCl_3$ (8 h) for Xa, concentrated HCl (2 h) for Xb, and $POCl_3$ (12 h and 4 h, respectively) for Xc and Xd.

9-Alkyl-2-aryl-3-bromoimidazo[1,2-*a*]benzimidazoles (VIIa, d, e). Bromination of 9-alkyl-2-arylimidazo[1,2-*a*]benzimidazoles with an equivalent amount of bromine in dry chloroform by the method in [2] gave VII (Table 2).

2-(p-Bromophenyl)-9-methyl-3-nitroimidazo[1,2-*a*]benzimidazole (VIIIe). This compound was obtained by nitration of IX [2] with an equivalent amount of potassium nitrate in concentrated H_2SO_4 at −10 to −12° (86.5% yield) or by refluxing bromo derivative VIIe in DMFA with excess potassium nitrite (65% yield). The lemon-yellow needles obtained were insoluble in alcohol, water, chloroform, and acetone.

9-Methyl-3-nitro-2-(p-nitrophenyl)imidazo[1,2-*a*]benzimidazole (VIIIa). This compound was isolated as greenish-yellow needles by the exchange of the bromine atom in VIIa by a nitro group, as in the method described above.

Nitrophenyl-9-methyl-2-(p-nitrophenyl)imidazo[1,2-*a*]benzimidazole (V). This compound was obtained in 90% yield by nitration of IV with 2 equivalents of potassium nitrate in sulfuric acid at −5 to −10° or by nitration under the same conditions of 2-(p-nitrophenyl)-substituted VIa with an equivalent amount of potassium nitrate. The yield in the latter case was quantitative. The shiny dark-orange needles had mp 297-298° (dec., from DMFA) and were only slightly soluble in most organic solvents. Found: C 57.2; H 3.2; N 21.0%. $C_{16}H_{11}N_5O_4$. Calculated: C 57.0; H 3.3; N 20.8%.

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