IMIDAZOLE DERIVATIVES

VIII. NITRATION OF 4(5)-(4-ALKOXYPHENYL)IMIDAZOLES

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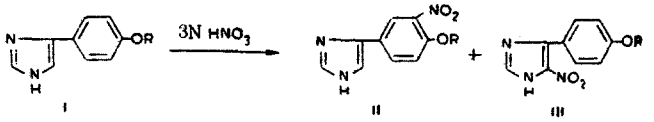
It is shown that 4(5)-(4-alkoxyphenyl)-5(4)-nitroimidazoles are obtained when 4(5)-(4-alkoxyphenyl)imidazoles are refluxed with 3-4 N nitric acid. The use of concentrated nitric acid (d_4^{20} 1.42, 1.46) leads to di- and trinitro-substituted phenylimidazoles. The mass spectra of the nitro derivatives were studied, and the principles of the fragmentation were ascertained.

According to the data in [1], the nitration of 4(5)-phenylimidazole leads to a mixture of o- and p-nitrophenylimidazoles. The nitration of 4(5)-(4-chlorophenyl)imidazole proceeds simultaneously in the phenyl and imidazole rings to give primarily 4(5)-(4-chlorophenyl)-5(4)-nitroimidazole [2].

In the present research we investigated the reaction of 4(5)-(4-alkoxyphenyl)imidazoles (I) with nitric acid at various concentrations in order to obtain nitroimidazoles, which are of interest for the synthesis of pharmacologically active derivatives.

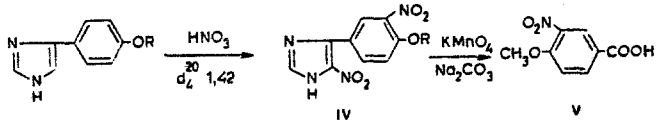
Nitro-substituted imidazoles II and III were isolated by the action on I of boiling 3 N nitric acid.



I II III

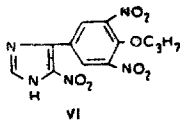
The principal reaction product is III (55-60% yield). The nitration of the benzene ring of I under these conditions also gives II in 17-18% yield. The use of 4 N nitric acid raises the yield of II and III. The ease of formation of III is explained by the effect of the alkoxy group, which leads to an increase in the nucleophilicity of the $C_{4(5)}$ atom.

Dinitro-substituted derivative IV is obtained in the nitration of I with nitric acid with d_4^{20} 1.42. The position of the nitro groups was proved by oxidation of IV (R = CH_3) with potassium permanganate to known acid V [3].



IV V

More concentrated nitric acid (d_4^{20} 1.46) leads to trinitro-substituted phenylimidazole VI.



VI

Nitrates (VII) of 4(5)-(4-alkoxyphenyl)imidazoles were synthesized by refluxing the bases in 0.1 N nitric acid. We were unable to obtain nitroimidazoles by reaction of VII with sulfuric acid under the conditions in [2].

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TABLE 1. Mass Spectra

Compound	R	Mass of the ions (peak intensity in percent of the intensity of the maximum peak)
I	CH_3	174 (100), 159 (70), 131 (55), 119 (9), 104 (8), 77 (20)
II	C_2H_5	233 (87), 205 (100), 204 (6), 159 (54), 133 (8), 132 (14), 131 (16), 130 (10), 103 (17), 77 (6), 76 (20)
III	C_2H_5	233 (100), 205 (30), 203 (6), 175 (4), 174 (8), 160 (8), 159 (4), 148 (12), 147 (22), 136 (15), 133 (8), 132 (18), 131 (8), 124 (10), 120 (24), 119 (58), 105 (24), 103 (6), 91 (8)

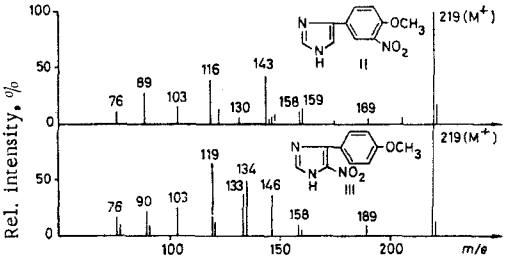
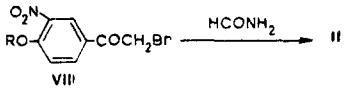


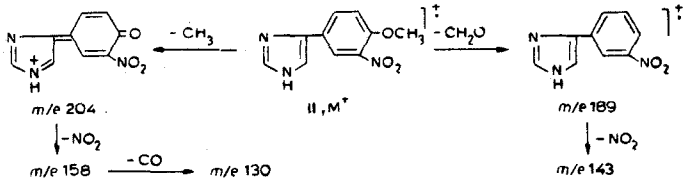
Fig. 1. Mass spectra of II and III.

Compounds II were also synthesized by cyclization of 4-alkoxy-3-nitrophenacyl bromides VIII with formamide.



The starting 4-alkoxy-3-nitroacetophenones (IX) were obtained by nitration of 4-alkoxyacetophenones (X) with a mixture of nitric and sulfuric acids.

In order to use the mass spectrometric method for the identification of the nitro isomers we studied the principles of the fragmentation of I-III. The mass spectrum of I (R = CH_3) is quite simple (Table 1). The primary ions formed from the molecular ion are associated with successive elimination of a methyl group and a CO molecule. The fragmentation of the heteroring is almost identical to the fragmentation of imidazole [4].



The introduction of a nitro group in the alkoxyphenylimidazole molecules leads to differences in the mass spectra of isomeric II and III (Fig. 1, Table 1).

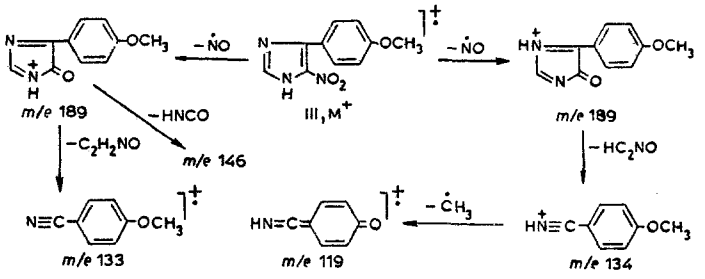
Elimination of a formaldehyde molecule (ion with m/e 189) with subsequent detachment of a nitro group is characteristic for isomers II (R = CH_3). The resulting ion with m/e 143 subsequently successively loses two HCN molecules. An NO_2 group is also split out from the $(M - CH_3)^+$ ion to give an ion with m/e 158, which in the first step of its fragmentation successively eliminates a CO molecule and two HCN molecules.

The dissociative ionization of III (R = CH_3) differs markedly from the fragmentation of isomer II (Fig. 1). Detachment of NO from the molecular ion is characteristic for III (R = CH_3). The $(M - NO)^+$ ion with m/e 189 undergoes fragmentation to give ions with masses 146, 134, 133, and 119 in conformity with the following scheme:

TABLE 2. Characteristics of the Compounds Obtained

R	R_1	R_2	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %	Dec. temp. of the hydrochloride, °C	R_f*
				C	H	N		C	H	N			
CH_3	NO_2	H	231—232	54,9	4,1	19,0	$C_{10}H_9N_3O_3$	54,8	4,1	19,2	46	247—248	0.46
C_2H_5	NO_2	H	194—195	56,5	5,0	18,2	$C_{11}H_{11}N_3O_3$	56,6	4,7	18,0	44	239—240	0,48
C_3H_7	NO_2	H	172—173	58,4	5,5	17,2	$C_{12}H_{13}N_3O_3$	58,3	5,3	17,0	35	219—220	0,51
C_4H_9	NO_2	H	169—170	60,0	5,7	16,6	$C_{13}H_{15}N_3O_3$	59,8	5,8	16,1	33	227—228	0,53
CH_3	NO_2	NO_2	269—270	45,6	3,3	21,4	$C_{10}H_8N_4O_5$	45,5	3,1	21,2	83	—	0,80
C_2H_5	NO_2	NO_2	246—247	47,7	3,5	20,3	$C_{11}H_{10}N_4O_5$	47,5	3,6	20,1	95	—	0.83
CH_3	H	NO_2	312—313	55,0	4,1	19,0	$C_{10}H_9N_3O_3$	54.8	4,1	19,2	57	—	0.77
C_2H_5	H	NO_2	305—306	56,8	5,0	17,9	$C_{11}H_{11}N_3O_3$	56,6	4,7	18,0	56	—	0.81
C_3H_7	H	NO_2	275—276	58,2	5,4	17,2	$C_{12}H_{13}N_3O_3$	58,3	5,3	17,0	60	—	0,83

*Thin-layer chromatography in an absolute acetone–absolute ethanol system (2 : 1).



The principal pathways in the fragmentation of the molecular ions are confirmed by the shifts of the corresponding ion peaks in the spectra of methoxy and ethoxy derivatives II and III.

In the case of the ethoxy analogs an ethylene molecule is eliminated initially. The subsequent fragmentation of the $(M - C_2H_4)^+$ ions follows the basic principles established for methoxy derivatives II and III.

The differences in the mass spectra of the isomers make it possible to use the mass spectrometric method for the identification of the examined isomeric pairs.

EXPERIMENTAL

The mass spectra of the compounds were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 30 V and 20-30°C below the melting points of the compounds. The PMR spectra of solutions of the compounds in dimethyl sulfoxide (DMSO) were recorded with a Varian T-60 spectrometer (60 MHz) with tetramethylsilane as the internal standard.

Nitration of I with Nitric Acid. A) A mixture of 0.01 mole of I [5] and 50 ml of 3 N nitric acid was refluxed for 15-20 min, after which it was cooled, 100 ml of water was added, and the resulting precipitate was removed by filtration and refluxed in 50 ml of dilute hydrochloric acid. The precipitated III was washed with methanol and recrystallized from dimethylformamide (DMF) (Table 2). The hydrochloric acid filtrate was neutralized with ammonium hydroxide, and the precipitated II was recrystallized from ethanol (Table 2).

B) A mixture of 1.9 g (0.01 mole) of I ($R = C_2H_5$) and 50 ml of 4 N nitric acid was refluxed for 15 min, and the mixture was then treated as in the previous experiment. Workup gave 0.5 g (21.4%) of II ($R = C_2H_5$) and 1.5 g (64.3%) of III. PMR spectrum of III ($R = CH_3$): protons of the benzene ring (an AB spin system) 7.44 (4H, q), imidazole proton 7.92 (1H, s), and NH group 13.34 ppm (1H, broad hump).

4(5)-(4-Alkoxy-3-nitrophenyl)-5(4)-nitroimidazoles (IV). A mixture of 0.02 mole of I and 30 mole of nitric acid (d_4^{20} 1.42) was heated on a water bath for 1 h, after which it was cooled, 100 ml of water was added, and the resulting precipitate was removed by filtration and recrystallized from ethanol (Table 2). PMR spectrum of IV ($R = CH_3$): benzene ring protons 7.8 (2H, q), isolated benzene proton 7.9 (1H, s), imidazole proton 8.2 ppm (1H, s).

Oxidation of 4(5)-(4-Methoxy-3-nitrophenyl)-5(4)-nitroimidazole. A mixture of 0.8 g (0.003 mole) of IV ($R = CH_3$), 1 g of sodium bicarbonate, and 50 ml of water was heated with stirring on a water bath for 20-30 min, after which 5 g of finely ground potassium permanganate was added in the course of 15 min. The mixture

was then heated with stirring on a water bath for 6 h, after which the pricipitated manganese dioxide was removed by suction filtration, the filtrate was acidified with hydrochloric acid, and the precipitate was removed by filtration. The yield of 4-methoxy-3-nitrobenzoic acid (V), with mp 189-190°C (from ethanol), was 0.4 g (69.5%).

4(5)-(4-Propoxy-3,5-dinitrophenyl)-5(4)-nitroimidazole (VI). A mixture of 3 g (0.014 mole) of I (R = C_3H_7) and 30 ml of nitric acid (d_4^{20} 1.46) was heated on a water bath for 30 min, after which it was cooled, 100 ml of water was added, and the precipitate was removed by filtration and recrystallized from ethanol to give 3.4 g (72.0%) of a product with mp 221-222°C. Found: C 42.9; H 3.6; N 21.1%; M 337 (mass spectrometrically). $C_{12}H_{11}N_5O_7$. Calculated: C 42.7; H 3.3; N 20.7%. The product had R_f 0.88 [TLC, Silufol, acetone–ethanol (2 : 1)].

Nitrates of 4(5)-(4-Alkoxyphenyl)imidazoles (VII). A mixture of 0.02 mole of I and 60 ml of 0.1 N nitric acid was refluxed until all the solid had dissolved, after which 0.3 g of activated charcoal was added, and the mixture was refluxed for another 3-5 min. It was then cooled, and the precipitate was removed by filtration to give 3 g (63.0%) of VII (R = CH_3) with mp 156-157°C (dec.). Found: C 50.3; H 4.9; N 17.8%. $C_{10}H_{11}N_3O_4$. Calculated: C 50.6; N 17.7%. Compound VII (R = C_2H_5) was obtained similarly. Yield 3.6 g (71.5%), mp 152-153°C (dec.). Found: C 53.0; H 5.0; N 16.7%. $C_{11}H_{13}N_3O_4$. Calculated: C 52.6; H 5.2; N 16.7%.

4(5)-(4-Alkoxy-3-nitrophenyl)imidazoles (II). A mixture of 0.15 mole of VIII and 200 ml of formamide was refluxed for 2 h, after which 3 N hydrochloric acid was added until the mixture was acidic with respect to Congo Red. Activated charcoal (3-4 g) was added, and the mixture was refluxed for 10 min. The hot solution was filtered, and the filtrate was cooled. The base was precipitated by the addition of ammonium hydroxide, and the mixture was allowed to stand overnight in a refrigerator. The precipitate was removed by filtration and recrystallized from ethanol (Table 2). PMR spectrum of II (R = CH_3): benzene ring protons 7.8 (2H, q), isolated benzene proton 7.76 (1H, s), imidazole proton attached to C_5 7.86 (1H, s), and imidazole proton attached to C_2 8.3 ppm (1H, d, weak coupling with the NH proton, $J \approx 2.5$ Hz).

4-Alkoxy-3-nitrophenacyl Bromides (VIII). A solution of 10.3 ml (0.2 mole) of bromine in 50 ml of acetic acid was added dropwise with stirring to a mixture of 0.2 mole of IX and 150 ml of acetic acid at a rate of 1 ml/min. Stirring was then continued for 2 h, and water was added. The precipitate was removed by filtration, recrystallized from ethanol, and dried in a vacuum desiccator. Compound VIII (R = C_3H_7), with mp 58-59°C, was obtained in 99.3% yield. Found: Br 27.0; N 4.9%. $C_{11}H_{12}BrNO_4$. Calculated: Br 26.4; N 4.6%. Compound VIII (R = C_4H_9), with mp 60-61°C, was obtained in 80.0% yield. Found: Br 25.4; N 4.3%. $C_{12}H_{14}BrNO_4$. Calculated: Br 25.3; N 4.4%.

4-Methoxy- and 4-ethoxy-3-nitrophenacyl bromides were similarly obtained [6, 7].

4-Alkoxy-3-nitroacetophenones (IX). An 8.6-ml sample of nitric acid (d_4^{20} 1.46) was added dropwise in the course of 2 h with cooling (−5 and −10°C) and stirring to a mixture of 0.2 mole of X and 80 ml of sulfuric acid, after which stirring was continued for another 2 h. The mixture was then poured into ice water, and the precipitate was removed by filtration and recrystallized from ethanol. Compound IX can be vacuum distilled. Compound IX (R = C_3H_7), with bp 155-157°C (1 mm), and mp 54-55°C, was obtained in 74.2% yield. Found: C 59.4; H 5.6; N 6.4%. $C_{11}H_{13}NO_4$. Calculated: C 59.2; H 5.9; N 6.3%. Compound IX (R = C_4H_9), with bp 169-171°C (1 mm) and mp 50-51°C, was obtained in 85.6% yield. Found: C 60.4; H 6.5; N 6.3%. $C_{12}H_{15}NO_4$. Calculated: C 60.7; H 6.4; N 5.9%.

4-Methoxy- and 4-ethoxy-3-nitroacetophenones were similarly obtained and are described in [8].

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