Nucleophilic Substitutions in Some Derivatives of 4- and 5-Nitroimidazoles

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Hydrogen, as well as the halogen atom, at the 4 or 5 position in some 5- and 4-nitroimidazoles were displaced by various nucleophiles such as the amino, cyano, hydroxy, and alkoxy groups. The greater reactivity of the departing group in the 4 position, which was regularly observed, is ascribed to the double activating effect of the azo and nitro groups. Cyanide ion in alcoholic solution reacted peculiarly with both 4- and 5-nitroimidazoles giving *o*-cyanoazoxyimidazoles as the only products. In some of the nucleophilic displacements at the 4 position of 5-nitroimidazoles the formation of intermediate Σ-complexes was observed.

A. Introduction.

Nucleophilic substitution reactions in many aromatic and heteroaromatic compounds have been well investigated and numerous review papers dealing with these reactions from the preparative (2) or theoretical (3) point of view have been published. However, this type of reaction in the imidazole ring has been less explored. The reactivity of the imidazole ring toward nucleophiles is much lower than that of benzenoid compounds or six membered nitrogen heterocyclic compounds. This lower reactivity is due to the high separation of charge of the resonance structures of the imidazole ring in which the negative charge is shared by the carbon atoms (4). On nitration the entering nitro group occupies the 4 (or 5) position of the imidazole ring (5) and activates the ring toward nucleophilic substitution through its electron withdrawing effect. Nitro- and azo-activation plays a major role in nucleophilic heteroaromatic substitution and the principle properties associated with these groups have been discussed in detail (3c). It has been shown that the relative position of the activating group in the isomeric nitroimidazoles results in quite different behaviour toward some nucleophilic agents. For example, as shown by earlier literature, a chlorine atom in the 5 position of some 4-nitroimidazoles is readily exchanged by a cyano (6), a sulfonic acid (7) or an amino group (8). It has also been noted (9,10) that the 1-methyl-4-chloro-5-nitro isomer reacts in an abnormal way with cyanide ion in the presence of potassium iodide in dimethylformamide giving the 4-nitro-5-cyano isomer only. This second finding is briefly discussed in part C of this paper. We have performed hydrogen exchange in the 4- and 5-positions of some 5- and 4-nitroimidazoles as well as displacement of the bromine atom in 4- and 5-bromo-5-(or 4)-nitroimidazoles with some typical nucleophilic agents.

B. Substitution in 4- and 5-Nitroimidazoles.

Direct substitution (hydrogen exchange) in the compounds I and IV (Scheme I) revealed some interesting information regarding the relative reactivity of the 4 and 5 positions on the ring and the products obtained (11). Amination with hydroxylamine was possible when the nitro group was in either the 4 or 5 position giving rise to compounds V and II, respectively. The fact that substitution had occurred in the ring was substantiated by the nmr spectra in which no peaks for aromatic protons could be observed. The 4 position was shown to have the higher reactivity by the fact that a lower optimal reaction temperature was required for amination in the 4 position than for the 5 position (see experimental). However, in both cases, optimal reaction temperature was much lower than earlier reported for amination of some other heterocyclic compounds (12a,b) or nitrobenzenes (12c).

Cyanide ion reacted with compounds I and IV in an abnormal way giving rise to the *o*-cyanoazoxy compounds, III and VI. It is proposed that the hydride ion as a leaving group participated in the reduction of the nitro group which in turn formed the azoxy compound in the alkaline alcoholic solution. The azoxy group along with the entering cyano group, prevented the typical cine substitution (2a) from taking place. A similar reaction of *p*-methoxynitrobenzene was observed (13) when the photo-

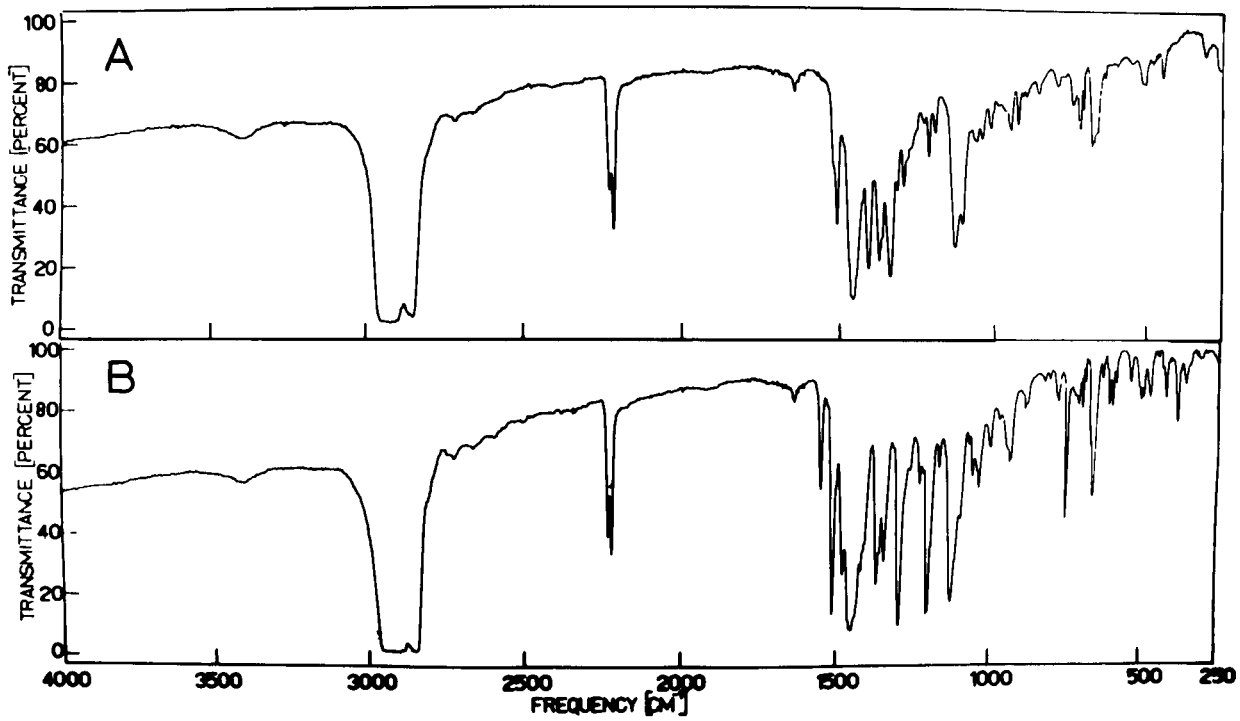


Figure 1. Infrared spectra of the compounds IIIa and VIb.

activated substrate reacted with cyanide ion giving 3,3′-dicyano-4,4′-dimethoxyazoxybenzene as one of the isolable products. *o*-Cyanoazoxyimidazoles were formed even when a halogen atom of low reactivity was present in the substituent at the 1 position as in the compounds IIIa and VIa which indicates the higher reactivity of the reaction sites 4 and 5 in the imidazole ring. However, rapid exchange of activated halogen for the nitrile group with subsequent rearrangement was recently described for 2-chloromethylimidazole (14). In this reaction the nitrile group occupies the 5 position of the imidazole ring. Infrared, ultraviolet and nmr spectra confirmed the structures discussed above. Infrared spectra of the compounds III and VI (Fig. 1) show the characteristic doublet of cyano groups at about 2220 cm^{-1} (15a). Both cyano groups in the 4 and 4′ positions have characteristic frequencies about 10 cm^{-1} lower than the same groups in the 5 and 5′ positions. Ultraviolet spectra exhibited a rather simple feature; the first maximum belongs to the B-band of the imidazole ring (4), the second one, along with the inflexion at 260-270 mμ, belongs to the azoxy-group between the aromatic rings (15b) (Table I).

TABLE I

Characteristic Data from UV-VIS Spectra of the *o*-Cyanoazoxyimidazoles (a).

Compound	λ max (mμ), (ε)	λ inflex (mμ)
III	208, (5630); 406, (5450)	260
IIIa	212, (6200); 362, (4980)	265
VI	214, (6320); 411, (4880)	262
VIa	216, (6270); 388, (4960)	268

(a) Measured in 96% ethanol.

Nmr spectra showed no peaks for the protons in the imidazole ring. Furthermore, a clear difference between the chemical shifts for the methyl group protons in the same position on the rings appeared because of the assymetric structure of the azoxy group. 2,2′-Methyl

groups in the compounds III and VI showed singlet peaks at 2.48, 2.52 ppm and 2.56, 2.60 ppm, respectively. 1,1'-Methyl groups in the same compound gave rise to singlet peaks at 3.81, 3.87 ppm and 3.96, 4.05 ppm, respectively (tetramethylsilane as internal standard; determined on solutions in DMF-d_7).

The most unusual behaviour was exhibited by the isomeric 4- and 5-nitro compounds in their reaction with hydroxy and alkoxy ions. When the 5-nitro isomers were heated in strong base an intense red colour appeared; whereas after prolonged heating, ammonia was evolved from the solution and the substance decomposed. Since this behaviour was regularly observed with 5-nitro isomers having different groups attached in the 1 position, we made use of it for the preliminary determination of the position of the nitro group in some compounds recently prepared (16a). The behaviour of 5-nitroimidazoles resembles that of activated aromatic polynitro compounds which interact with a variety of bases giving brightly coloured solutions (3b), the colour being ascribed to the various intermediates which could be formed. With compounds I and IV we were not able to give evidence of the formation of Σ-complexes of the 5-nitro isomer. In the case of compound I it was possible to follow by nmr the decrease of the intensity of a singlet peak of the proton in the ring (H_4) at 8.12 ppm (see Table II). However, shifting of the H_4 signal to the higher field because of the formation of the tetrahedral carbon (3b) was not observed. Some recent findings (19e) indicate taht the Σ-complex is a highly unstable species and can not be indicated by nmr under the experimental conditions used.

TABLE II

Relation between Inteisity of H_4 and H_5 Signals of the Compounds I and IV and Heating Time (40° in 5% sodium hydroxide)(a).

Compound I		Compound IV	
Time (sec.)	Integr. area of H_4	Time (sec.)	Integr. area of H_5
0	5.5	0	5.4
20	3.9	20	5.4
50	2.4	50	5.3
180	0.2	180	5.2

a. Position of H_4 and H_5 peaks in deuterium oxide was 8.12 ppm according to DSS internal and 8.17 ppm in deuteriochloroform according to TMS.

C. Substitution in 4-(or 5)Nitro-5-(or 4) bromoimidazoles.

Nucleophilic displacement of the bromine atom in compounds VII and XII was performed with alkoxy groups and with substituted amino and cyano groups. The positions of the substituents in compounds VII and XII were confirmed by uv and nmr spectra. The uv spectrum of compound VII exhibited a characteristic bathochromic shift (20) of the K-band (λ max (ethanol), 317 mμ, ε, 8,290) in relation to the 4-nitroisomer XII (λ max (ethanol), 309 mμ, ε, 7,020). The nmr spectra confirmed the assigned structures by revealing different chemical shifts for the signals of the N-C*H*$_3$ protons (singlet, 3.93 δ for VII; singlet, 3.74 δ for XII - in DMF-d_7). Shifting of the N-C*H*$_3$ signal of the compound VII to the lower field is caused by the stronger electron-deshielding effect of the nitro group when it is in the 5 position (16b). The alkoxy group displaced halogen in the 4 position only, which has an expected higher reactivity due to a double activating effect (*vide supra*). An intense blue-green colour which appeared during the reaction was ascribed to the formation of the intermediate complex,VIIa. Similar complex formation has been previously observed (17) in the reaction of 2-halo-3-nitropyridines indicating close similarity between the two reaction sites. 4-Alkoxy compounds reacted further with alkoxy ions giving green and blue coloured reaction solutions. Ultraviolet spectra indicated that the highly unstable Meisenheimer's complexes (18) are formed in the solution (see Fig. 2. and 3).

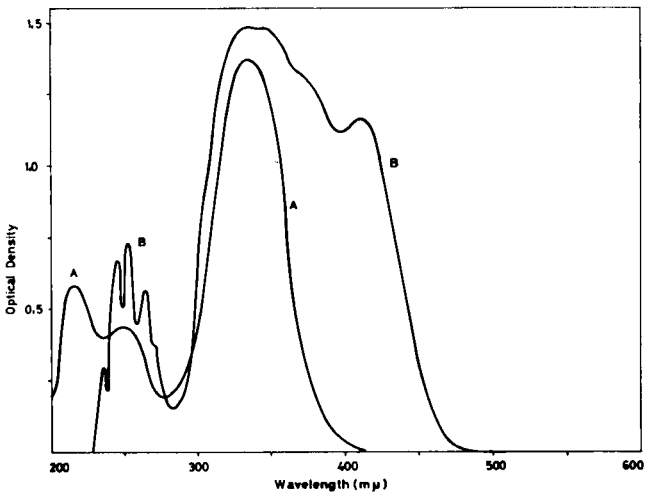


Figure 2. Absorption spectra of 1,2-dimethyl-4-methoxy-5-nitroimidazole, VIII, in methanol at 20° using a pair of 1.00 cm. matched cells. A, VIII, 5 x 10^{-5} *M*. B, VIII, 5 x 10^{-5} *M*; $NaOCH_3$, 0.25 *M*.

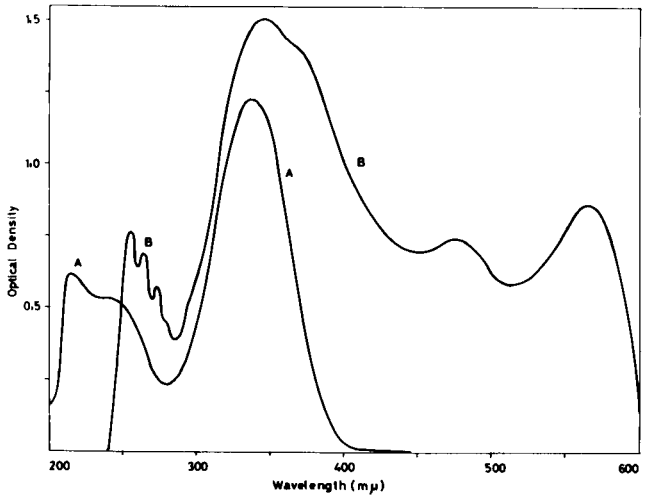
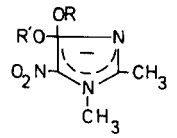


Figure 3. Absorption spectra of 1,2-dimethyl-4-ethoxy-5-nitroimidazole, IX, in ethanol at 20° using a pair of 1.00 cm. matched cells. A, IX, 5×10^{-5} *M*. B, IX, 5×10^{-3} *M*; $NaOC_2H_5$, 0.25 *M*.



a RO = R'O = CH_3O
b RO = R'O = C_2H_5O

This instability was reflected in the high concentration of the compounds VIII and IX and alcoholates needed in order to obtain the complexes in the solution (19e). Under these conditions probably an equilibrium state was established which can be concluded from the superposition of the bands of the spectra in the region of 400-450 mμ causing high optical density in the whole region. Furthermore, on standing or by shorter heating, the alcoholate solution became more reddish coloured and partial recovery of the starting ethers indicated decomposition of the substance.

Ultraviolet spectra showed that the benzenoid B-band of the imidazole ring at 210-215 mμ (4) was completely destroyed in the complexes formed and that the second maximum belonging to the K-band of nitroimidazole, usually found at 312-320 mμ (20a,b), was shifted to 337-338 mμ in the compounds VIII and IX due to conjugation with the neighbouring alkoxy groups. Using the procedures described (19e, 21b) we attempted to isolate the nitro-dialkoxy-imidazole complexes in the crystalline form, but even in a nitrogen atmosphere only a brownish-red syruplike mass could be obtained. The lower stability of the nitroimidazole complexes in relation to the complexes of the same type observed (and in some examples isolated) in dinitro and trinitrobenzenes (19a,b) as well as in dinitronaphthalenes (21) could be ascribed to their lower resonance stabilization (19e, 21b).

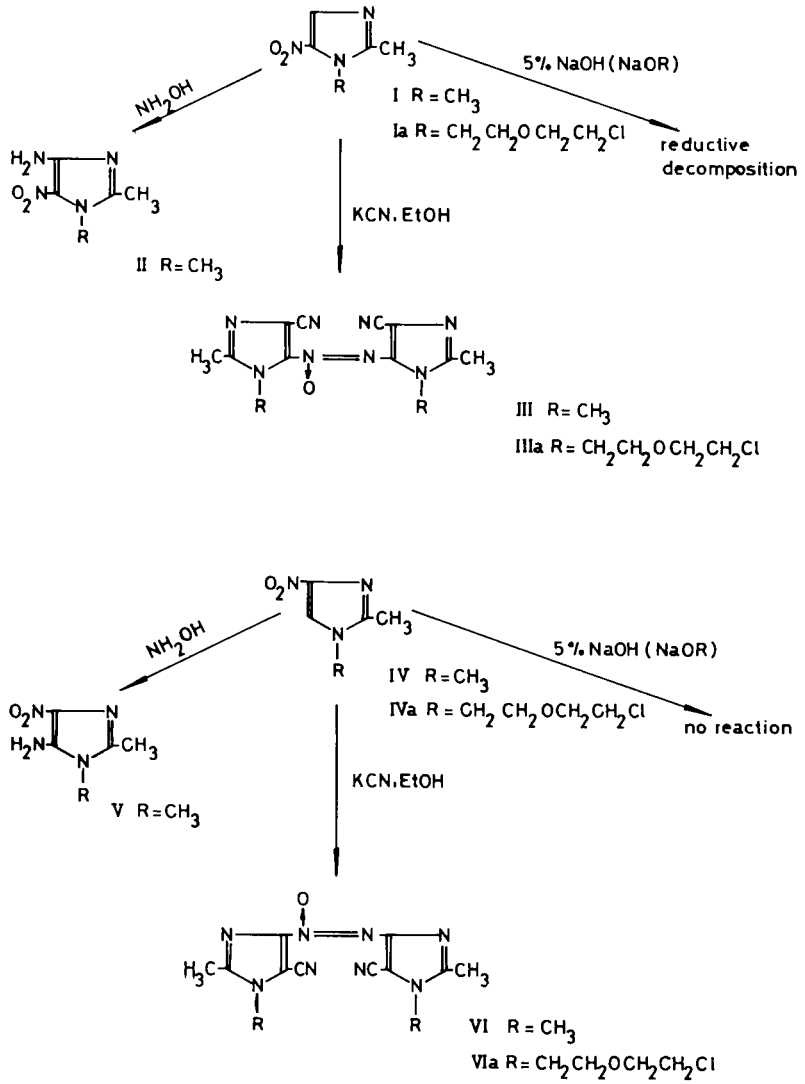
Ammonolysis of the halogen atom in the 4 and 5 positions repeatedly revealed the greater reactivity of the halogen in the 4 position (see experimental). Of the amines used, greater reactivity was exhibited by piperidine than by 2-hydroxyethylamine probably because of the greater basicity of the former. Accordingly, in an earlier work (8c) a series of 1-substituted 4-nitro-5-morpholino, pyrrolidino and piperidino derivatives have been obtained in fairly good yields. Cyanide ion reacted with the 4-nitro-5-bromo isomer (XII) giving the 4-nitro-5-cyano compound (XIII) but did not react with the 5-nitro isomer (VII). Compound XIII exhibited high instability in the presence of the cyanide ion in different media (ethanol, dimethylsulfoxide, acetone) and only decomposition resins could be obtained along with unreacted substance. The different behaviour of the 5-nitro-4-bromo isomer (VII) toward cyanide ion in relation to the 4-nitro-5-bromo isomer (XII), as well as to the 5-nitro compounds I and Ia could not be explained at the time. However, these findings are fairly in accordance with the earlier observed unusual behaviour of 1-methyl-4-chloro-5-nitroimidazole toward cyanide ion in dimethylformamide solution (9,10). The unexpected transmethylation of this compound into the 4-nitro-5-cyano isomer, could be hardly understood without some mechanistic details. It is our finding that this isomerization did not proceed in the absence of potassium iodide. The high reaction temperature (150°) and the presence of potassium iodide which was needed for this reaction (9) indicated that it proceeded as a high-temperature decomposition reaction of 1,3-dimethyl-4(5)-nitroimidazolium iodide into the 4-nitro isomer, the more stable of the two possible isomers (23,24).

Since the 4 position shows higher reactivity toward various nucleophiles one can assume it has lower reactivity in electrophilic substitution reactions. This was confirmed by bromination reactions of both the 4 and 5 positions. The 4-nitro isomers IVa and XVII were brominated in chloroform-acetic acid solution whereas the 5-nitro isomers (Ia, XVI) failed to react under the same conditions (see Scheme III).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were run on the Perkin-Elmer Model 137 Spectrophotometer in nujol mull, with the exception of the spectra of III and VI which were scanned on the Perkin-Elmer Model 521 Grating Infrared Spectrophotometer. Ultraviolet spectra were obtained on the Unicam SP 800 instrument; nmr spectra were recorded on a Varian Associates A-60

SCHEME I



Spectrometer with automatic temperature control. The solvents (deuteriochloroform, dimethylformamide-d_7 and deuterium oxide) were used as indicated in the text. Tetramethylsilane (TMS; δ = 0.00 ppm) was used as an internal standard except when deuterium oxide was the solvent in which case the sodium salt of 2,2-dimethyl-2-silapentane-5-sulphonic acid (DDS) was used as an internal standard.

The compounds I and IV were prepared according to the procedure described earlier (25) from 2-methyl-4(5)-nitroimidazole and dimethylsulphate. The compounds Ia and IVa are described in reference 16a, the compounds XVI and XVII in reference 25, and the starting substance for the compounds VII and XII in reference 26.

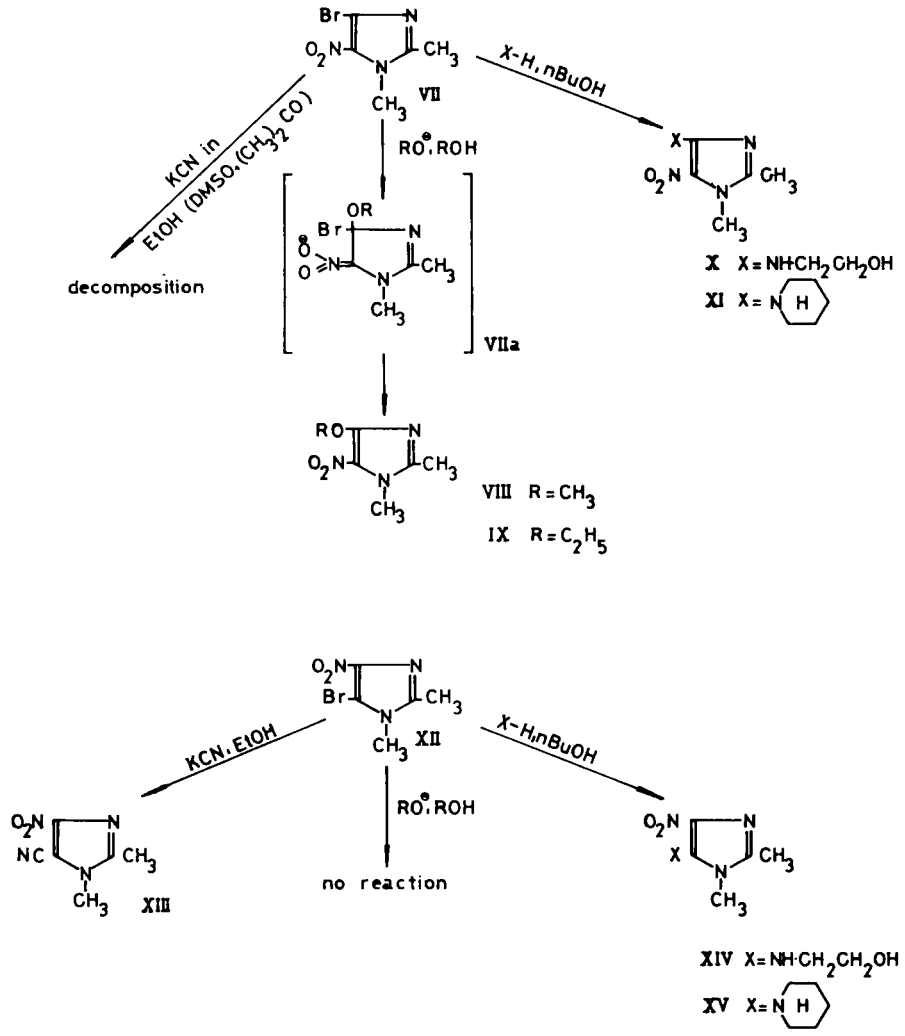
1,2-Dimethyl-4-amino-5-nitroimidazole (II).

Compound I (3.2 g., 0.0227 mole) and 9.8 g. (0.142 mole) of hydroxylamine hydrochloride were dissolved in 200 ml. of absolute ethanol. The solution was cooled to 5-8° and then 19.5 g. (0.35 mole) of potassium hydroxide in 50 ml. of methanol were added dropwise during 1 hour. The resulting yellow suspension was stirred for 1 hour and then neutralized (concentrated hydrochloric acid) to *p*H 7-8. The precipitate which separated was collected by filtration, washed with water and dried to furnish 2.3 g. of II as a yellow powder, m.p. 248-255°. Evaporation of the filtrate gave a second crop (0.3 g.) of crude II (total yield, 75%). Recrystallization from dimethylformamide gave pure II, m.p. 260-263° dec. Infrared cm^{-1}, ν max (NH_2) 3460 (broad), 3120, 1650.

Anal. Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.14; N, 35.89. Found: C, 38.25; H, 5.25; N, 35.47.

1,2-Dimethyl-4-nitro-5-aminoimidazole (V).

SCHEME II



From 3.2 g. (0.0227 mole) of IV was obtained 1.75 g. (51%) of crude V, m.p. 284-289°, by the same method as was described for II, but maintaining the reaction temperature of 20-25°. The pure substance (from dimethylformamide) melted at 289-291° dec. Infrared cm^{-1}, ν max (NH_2) 3410 (broad), 3280, 1650.

Anal. Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.14; N, 35.89. Found: C, 38.18; H, 5.36; N, 36.07.

1,1′,2,2′-Tetramethyl-4,4′-dicyanoazoxy-(5)-imidazole (III).

Compound I (1.41 g., 0.01 mole) and potassium cyanide (0.78 g., 0.012 mole) were heated in 25 ml. of 96% ethanol at reflux temperature for 2 hours. On chilling, 0.65 g. of crude III separated in the form of purple plates, m.p. >360°. On evaporation of the filtrate a second crop (0.12 g.) was obtained (yield 54.2%). A pure sample (from dimethylformamide) melted above 360°.

Anal. Calcd. for $C_{12}H_{12}N_8O$: C, 50.70; H, 4.25; N, 39.42. Found: C, 50.76; H, 4.28; N, 39.05.

1,1′,2,2′-Tetramethyl-5,5′-dicyanoazoxy-(4)-imidazole (VI).

Compound VI was obtained from 1.41 g. (0.01 mole) of IV and 0.78 g. (0.012 mole) of potassium cyanide by the same procedure as described for III giving yellow plates, m.p. >360°, yield 0.86 g. (60.6%).

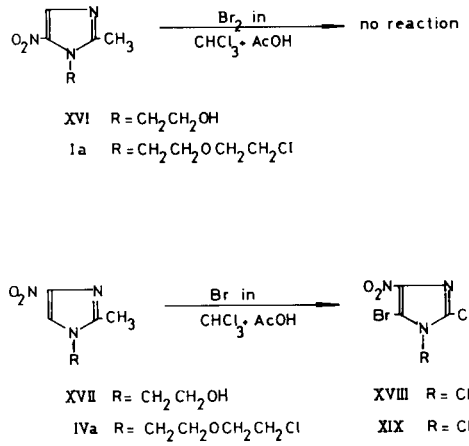
Anal. Calcd. for $C_{12}H_{12}N_8O$: C, 50.70; H, 4.25; N, 39.42. Found: C, 50.59; H, 4.56; N, 39.28.

1,1′-Di(2′-chloroethoxyethyl)-2,2′-dimethyl-4,4′-dicyanoazoxy-(5)-imidazole (IIIa).

Compound Ia (16a) (1.67 g., 0.005 mole) and potassium cyanide (0.48 g., 0.0075 mole) in 35 ml. of 96% ethanol were heated on a steam bath for 3 hours. The solvent was removed, the solid residue was slurried in 10 ml. of water, and the insoluble IIIa was collected and dried giving 0.48 g. (41%) of crude product. Recrystallization from ethanol gave yellow plates which melted at 157-158°. Infrared cm^{-1}, ν max (CN), 2225, 2235.

Anal. Calcd. for $C_{18}H_{22}Cl_2N_8O_3$: C, 46.06; H, 4.73; N,

SCHEME III



XVI R = CH_2CH_2OH
Ia R = $CH_2CH_2OCH_2CH_2Cl$

XVII R = CH_2CH_2OH
IVa R = $CH_2CH_2OCH_2CH_2Cl$

XVIII R = CH_2CH_2OH
XIX R = $CH_2CH_2OCH_2CH_2Cl$

23.87. Found: C, 46.16; H, 4.51; N, 23.59.

1,1′-Di-(2′-chloroethoxyethyl)-2,2′-dimethyl-5,5′-dicyanoazoxy-(4)-imidazole (VIa).

VIa was obtained in the same way as IIIa using 1.67 g. (0.005 mole) of IVa (13) and 0.48 g. (0.0075 mole) of potassium cyanide giving 0.68 g. (58%) of crude product, m.p. 170-173°. This was recrystallized from dimethylformamide-ethanol (2:1) to furnish yellow plates with m.p. 177-178°. Infrared cm^{-1}, ν max (CN) 2215, 2228.

Anal. Calcd. for $C_{18}H_{22}Cl_2N_8O_3$: C, 46.06; H, 4.73; N, 23.87. Found: C, 45.87; H, 4.59; N, 23.97.

1,2-Dimethyl-4-bromo-5-nitroimidazole (VII).

A mixture of 4.12 g. (0.02 mole) of 2-methyl-4(5)-nitro-5(4)-bromoimidazole (26) and 2.5 g. (0.02 mole) of dimethylsulphate was kept at 30-40° for 0.5 hour. After cooling it was neutralized (5% sodium hydroxide) and a mixture consisting of unreacted starting material and crude VII was removed by filtration. After fractionation in 10% sodium hydroxide the undissolved VII was collected by filtration and dried to furnish 1.2 g. (54%), m.p. 95-105°. Upon acidification of the filtrate, 2 g. of unreacted substance was recovered. The crude VII was recrystallized from ethanol-water (1:1) to give the pure compound which melted at 108-109°. Infrared cm^{-1}, ν max (NO_2), 1540, 1375.

Anal. Calcd. for $C_5H_6BrN_3O_2$: C, 27.30; H, 2.75; N, 19.10. Found: C, 27.50; H, 2.85; N, 18.98.

1,2-Dimethyl-4-nitro-5-bromoimidazole (XII).

2-Methyl-4(5)-nitro-5(4)-bromoimidazole (10.3 g. 0.05 mole) (26) was dissolved in 35 ml. of 15% sodium hydroxide and 7.5 ml. of dimethylsulphate was added in two portions. The first portion (4.0 ml.) was added at 25° and then the mixture was heated at 60° (steam bath) for 20 minutes. After cooling, the second portion (3.5 ml.) of dimethylsulphate was added and the mixture was heated at 60° for 1 hour. The crude solid which separated was removed by filtration and slurried in 5% sodium hydroxide to dissolve unreacted material. The undissolved residue was slurried once more in 10% hydrochloric acid to dissolve traces of the isomer VII. The residue was collected and dried to furnish 3.5 g. of crude XII, m.p. 154-160°. After recrystallization from ethanol-water (2:1) the pure compound melted at 161-162°. Infrared cm^{-1}, ν max (NO_2) 1540, 1370.

Anal. Calcd. for $C_5H_6BrN_3O_2$: C, 27.30; H, 2.75; N, 19.10. Found: C, 27.07; H, 2.43; N, 18.91.

1,2-Dimethyl-4-methoxy-5-nitroimidazole (VIII).

Compound VII (2.2 g., 0.01 mole) was heated on a steam bath in a methanolic solution of sodium methoxide (from 0.92 g. 0.04 mole, of sodium in 60 ml. of methanol) for 0.5 hour. After neutralization with concentrated hydrochloric acid, the methanol was removed by evaporation and the residue was slurried in water. Undissolved VIII was filtered off and dried to furnish 1.1 g. (62%), m.p. 123-126°. On recrystallization from water the m.p. rose to 127-128°. Infrared cm^{-1}, ν max (ArOR) 1025, 1186; (NO_2) 1545, 1375.

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.31; N, 24.55. Found: C, 42.09; H, 5.60; N, 24.69.

1,2-Dimethyl-4-ethoxy-5-nitroimidazole (IX).

Compound VII (2.2 g., 0.01 mole) was dissolved in 30 ml. of absolute ethanol and the solution was heated on the steam bath to 40°. A second solution composed ot 0.92 g. (0.04 mole) of sodium in 40 ml. of ethanol was added dropwise over a period of 20 minutes. After further heating for 20 minutes the solution was cooled and neutralized (concentrated hydrochloric acid). The same treatment of the reaction mixture as described for VIII gave 1.0 g. (58%) of crude IX, m.p. 92-97°. The recrystallized compound melted at 97-98°. Infrared cm^{-1}, ν max (ArOR), 1030, 1180.

Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.18; H, 5.94; N, 22.46.

1,2-Dimethyl-4(2′-hydroxyethyl)amino-5-nitroimidazole (X).

Compound VII (1.1 g., 0.005 mole) and 1.52 g. (1.49 ml., 0.025 mole) of 2-hydroxyethylamine were dissolved in 10 ml. of 1-butanol and the stirred solution was kept at 110° for 2 hours. The solvent and the excess amine were removed *in vacuo* and the residue was crystallized upon addition of 3 ml. of water to furnish 0.65 g. (64%) of crude product, m.p. 106-114°. Recrystallization from ethanol-water (1:1) gave the pure compound which melted at 120-122°. Infrared cm^{-1}, ν max (NH) 3350, 1635.

Anal. Calcd. for $C_7H_{12}N_4O_3$: C, 42.00; H, 6.04; N, 27.99. Found: C, 41.74; H, 6.28; N, 27.65.

1,2-Dimethyl-4-nitro-5-(2′-hydroxyethyl)aminoimidazole (XIV).

Compound XIV was obtained from XII in the same way as X from VII, but was heated at the reflux temperature of 1-butanol for 3 hours. There was obtained 0.55 g. (54%) of crude XIX which melted at 168-174°. A pure sample was obtained upon recrystallization from ethanol-water (1:1), m.p. 176-177°. Infrared cm^{-1}, ν max (NH), 3350, 1620.

Anal. Calcd. for $C_7H_{12}N_4O_3$: C, 42.00; H, 6.04; N, 27.99. Found: C, 41.95; H, 6.42; N, 27.41.

1,2-Dimethyl-4-piperid-(1′)-yl-5-nitroimidazole (XI).

Compound VII (2.2 g., 0.01 mole) and 4.25 g. (4.92 ml., 0.05 mole) of piperidine were dissolved in 20 ml. of 1-butanol and the solution was heated under reflux for 2 hours followed by evaporation to dryness under reduced pressure. The residue crystallized upon addition of ether and upon cooling 1.85 g. (82%) of brownish-yellow crystals were obtained, m.p. 93-100°. The pure compound after recrystallization from ethanol-water (1:1) melted at 109-110°. Infrared cm^{-1}, ν max (ArN) 1370; (NO_2) 1590, 1395.

Anal. Calcd. for $C_{10}H_{16}N_4O_2$: C, 53.55; H, 7.20; N, 24.98. Found: C, 53.36; H, 7.44; N, 24.74.

1,2-Dimethyl-5-piperid-(1′)-yl-4-nitro-imidazole (XV).

Compound XII (2.2 g., 0.01 mole) and 4.25 g. (4.92 ml., 0.05 mole) of piperidine in 20 ml. of 1-butanol were heated under reflux for 5 hours. The same treatment of the reaction mixture as described for XI gave 1.05 g. (56.5%) of the crude XV which melted at 160-165°. On recrystallization (water) the m.p. rose to 167-168°. Infrared cm^{-1}, ν max (ArN) 1355; (NO_2) 1595, 1380.

Anal. Calcd. for $C_{10}H_{16}N_4O_2$: C, 53.55; H, 7.20; N, 24.98. Found: C, 53.78; H, 7.38; N, 24.77.

1-(2′-hydroxyethyl)-2-methyl-4-nitro-5-bromoimidazole (XVIII).

1-(2′-Hydroxyethyl)-2-methyl-4-nitroimidazole (1.72 g., 0.01 mole) (25), (XVII) was heated in 10 ml. of chloroform until dissolved and then 0.62 ml. (1.86 g., 0.105 mole) of bromine in 5 ml. of acetic acid was added. The solution was heated on a steam bath for 1 hour, then evaporated to dryness *in vacuo*. The oily residue was dissolved in 50 ml. of water and neutralized to pH 7.5. The crystals which separated were collected by suction, dried and extracted with benzene (4 x 10 ml.). Unreacted substance (0.4 g.) did not dissolve and the soluble crude XVII (0.9 g., 46%) which melted at 147-148° was obtained after evaporation of the solvent. Infrared cm^{-1}, ν max (OH) 3350 (broad); (NO_2), 1540, 1375.

Anal. Calcd. for $C_6H_8BrN_3O$: C, 28.81; H, 3.23; N, 16.80. Found: C, 28.93; H, 3.06; N, 16.79.

1-(2′-chloroethoxyethyl)-2-methyl-4-nitro-5-bromoimidazole (XIX).

Compound Ia (2.3 g., 0.01 mole) (16a) was dissolved in 15 ml. of chloroform, 0.80 ml. (2.5 g., 0.0155 mole) of bromine in 10 ml. of acetic acid were added and the mixture was heated on a steam bath for 2 hours. After evaporation of the solvent the residue was neutralized (5% sodium hydroxide) and recrystallized (water). The crystals obtained were dried and extracted with benzene (4 x 10 ml.). The undissolved residue was recrystallized (ethanol-water, 1:1) to furnish 1.2 g. (52%) of crude XIX, m.p. 66-70°. The pure substance melted at 73-74°. Infrared cm^{-1}, ν max (ROR) 1140; (NO_2) 1540, 1370.

Anal. Calcd. for $C_8H_{11}BrClN_3O_3$: C, 30.74; H, 3.55; N, 13.45. Found: C, 30.76; H, 3.72; N, 13.09.

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