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A series of nitroimidazoles were subjected to hydroxymethylations under a variety of conditions. Hydroxymethylation of 1-(2-hydroxyethyl), 1-(2-acetoxyethyl), and 1-(2-chloroethyl) substituted 5-nitroimidazoles with paraformaldehyde in dimethyl sulfoxide yielded the respective 2-hydroxymethyl analogs (**5-7**). However, attempts to hydroxymethylate 1-(2-hydroxyethyl), 1-(2-acetoxyethyl), 1-(2-cyanoethyl) substituted 4-nitroimidazoles and 1-(2-hydroxyethyl)-2-nitroimidazole were unsuccessful. Treatment of 1-(2-acetoxyethyl)-5-nitro-2-imidazolecarbaldehyde(**10**) with hydroxylamine-*O*-sulfonic acid afforded a mixture of corresponding 2-carbonitrile (**12**) and 2-(*N*-hydroxy)carboximidamide (**13**). Hydrolysis of **10** with ethanolic hydrochloric acid yielded 8-ethoxy-5,6-dihydro-3-nitro-8*H*-imidazo[2,1-*c*][1,4]oxazine (**11**) which, on subsequent reaction with hydroxylamine-*O*-sulfonic acid, afforded 1-(2-hydroxyethyl)-5-nitroimidazole-2-(*N*-hydroxy)carboximidamide (**15**). Reaction of 4(5)-nitroimidazole with chloropropionitrile produced a mixture of the isomeric 1-(2-cyanoethyl) substituted 4- and 5-nitroimidazoles. Treatment of 2,4(5)-dinitroimidazole with chloropropionitrile afforded a mixture of 4(5)-chloro-5(4)-nitroimidazole and 1-(2-cyanoethyl)-4-nitro-5-chloroimidazole. Reaction of nitroimidazoles with acrylonitrile in the presence of Triton B yielded the corresponding 1-(2-cyanoethyl) substituted derivatives.

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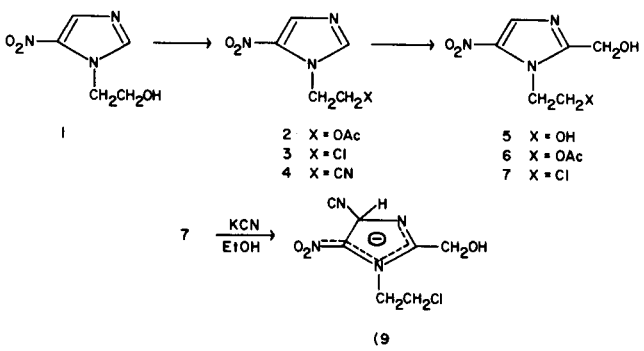
Nitroaromatic compounds are known to differentially sensitize hypoxic tumor cells to the lethal effects of ionizing radiation (2). Of these, the nitroimidazoles are particularly promising as radiosensitizers in view of their favorable pharmacological properties, *i.e.*, low toxicity, free distribution in tissues, and relatively long metabolic half-life (3). 1-(2-Hydroxy-3-methoxypropyl)-2-nitroimidazole (Ro-07-0582, misonidazole) is a considerably more effective radiosensitizer than 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) and this has been attributed to a higher electron affinity of the 2-nitro derivative (4). During the synthesis of a series of nitroimidazoles possessing potential for electronic, hydrophobic or hydrophilic interactions, we have investigated extensively the hydroxymethylation and cyanoethylation reactions of 2-, 4- or 5-substituted nitroimidazoles.

Results and Discussion.

Grindley and Pyman (5) reported the condensation of 1-methyl-5-nitroimidazole with aqueous formaldehyde but failed to isolate the product. However, we succeeded in hydroxymethylating the 2-position of this compound with 40% aqueous formaldehyde to the extent of 30% by heating at 140° for 6 hours; the product was separated from the starting material by preparative tlc using 1:1 ethyl acetate/hexane as eluant. Simiarly, hydroxymethylation of 1-(2-hydroxethyl)-5-nitroimidazole (**1**), obtained by alkylation of 4(5)-nitroimidazole with chloroethanol (6), was also attempted (Scheme I). Upon heating **1** with 40% aqueous formaldehyde (125°, 21 hours), hydroxymethylation at the 2-position occurred to the extent of 20% as analyzed by nmr; however, the separation of the product from **1** proved very difficult. When **1** was reacted with paraformaldehyde in DMSO (130°, 24 hours) (7), only 50% of **1** was converted to its hydroxymethyl analog (**5**). However, we were able to obtain exclusively **5** by further retreatment of the reaction mixture with paraformaldehyde in DMSO (130°, 24 hours). Similarly, the acetoxy analog (**2**), prepared by treating **1** with acetic anhydride, was hydroxymethylated with 40% aqueous formaldehyde (130°, 5 hours) to the extent of 35% and with paraformaldehyde in DMSO (130°, 24 hours) to the extent of 80%.

Scheme I



Treatment of **1** with thionyl chloride produced the chloroethyl compound (**3**) (8), which upon reaction with potassium cyanide in aqueous ethanol, did not yield the corresponding nitrile (**4**) by displacement of chlorine. Tlc fractionation and analysis by ir, nmr, and ms of the complex mixture indicated either the attack of the

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cyanide ion on the imidazole ring or formation of a hydrogen cyanide addition complex. Similar anionic addition products have been observed by interaction of various nucleophilic reagents and polynitroaromatic compounds (9). However, no further attempts were made to resolve these cyano substituted 1-(2-chloroethyl)-5-nitroimidazoles. Alkylation of 4(5)-nitroimidazole with chloropropionitrile resulted in the formation of the nitrile (**4**) and the isomeric 1-(2-cyanoethyl)-4-nitroimidazole (**19**) in poor yield. Treatment of **3** with paraformaldehyde in DMSO afforded the hydroxymethyl analog (**7**), which upon treatment with potassium cyanide in aqueous ethanol, also did not result in the formation of 1-(2-cyanoethyl)-2-hydroxymethyl-5-nitroimidazole (**8**). The reaction mixture contained a product which was purified by tlc fractionation and exhibited the presence of nitrile group in ir (2200 cm^{-1}). Mass spectrum analysis (M^+ m/e, 232) indicated the product probably to be an anionic species as σ complex (**9**). The major fragment peak at 205 was probably due to the loss of HCN.

In an effort to introduce the nitrile function at the 2-position of the imidazole ring, **6** was oxidized with lead tetracetate to give the carboxaldehyde (**10**) (characterized as its thiosemicarbazone), which on subsequent treatment with hydroxylamine-*O*-sulfonic acid (10) afforded a mixture of the nitrile (**12**) and the carboxamidoxime (**13**) (Scheme II). Hydrolysis of **12** and **13** with dilute ethanolic hydrochloric acid gave the corresponding hydroxyethyl analogs **14** and **15**, respectively. Treatment of **13** with acetyl chloride in the presence of triethylamine gave the *N*-acetoxycarboximidamide (**16**) (11). Hydrolysis of **10** with dilute ethanolic hydrochloric acid produced the ketal (**11**) (12) whose structure was assigned on the basis of ir (absence of aldehyde, ester, or hydroxy function), nmr (methine proton singlet at 5.65 ppm), and its ms m/e (M^+ 213). Treatment of **11** with hydroxylamine-*O*-sulfonic acid gave the carboxamidoxime (**15**) as a minor product; **11** was also recovered unchanged.

In an attempt to synthesize the 4-nitro isomers of this series, alkylation of 4(5)-nitroimidazole with chloroethanol in the presence of sodium methoxide in DMF was carried out to yield 4-nitro-1-(2-hydroxyethyl)imidazole (**17**) (13) as the major product along with a small amount of **1**. The acetoxy analog (**18**) was prepared by treating **17** with acetic anhydride. Hydroxymethylation of **17** or **18** under various conditions was unsuccessful; the starting materials were recovered unchanged. 1-Methyl-4-nitroimidazole is also known not to condense with aqueous formaldehyde (5). Furthermore, 1-methyl-5-chloroimidazole has been reported to condense with aqueous formaldehyde whereas 1-methyl-4-chloroimidazole did not react under similar conditions (5). Treatment of **17** with thionyl chloride followed by potassium cyanide in aqueous ethanol, as in the case of **1**, also did not yield the corresponding nitrile (**19**). However, **19** was obtained in about 80% yield from 4(5)-nitroimidazole by heating with acrylonitrile in the presence of Triton B (13). In a similar manner, reaction of 2-nitroimidazole with acrylonitrile in the presence of Triton B resulted in the formation of the corresponding nitrile (**20**). Hydroxymethylation of the nitrile, **19**, was also unsuccessful; the product (m.p. > 300°) appeared to be a dimer from its mass spectrum (the molecular ion peak was at 284 apparently resulting from the loss of a nitro group and a major fragment at 166 which could arise from fragmentation of the dimer into the monomer).

A possible explanation of the failure, to hydroxymethylate the 4-nitro isomers, may be due to delocalization of electrons at the 2-position by resonance with the 4-nitro group. Although the nitro group in the 5-position similarly would not be expected to assist the electrophilic attack, an increased electron density resulting due to resonance stabilization with *N*-alkylated derivatives makes the 2-position susceptible to such reactions.

Scheme II

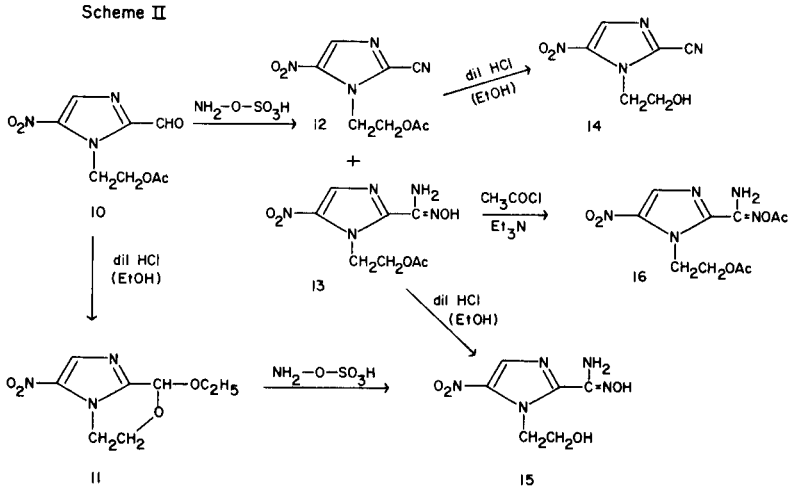


Table I

Proton Chemical Shifts and Mass Spectral Fragments for Nitroimidazole Derivatives

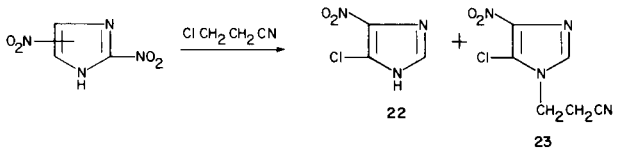
Compound	Proton Bands, Ppm						Mass Spectrum		Recrystallization
	C_2	C_4/C_5	$N\text{-}CH_2$	$CH_2\text{-}X$	$C\text{-}CH_2O$	$COCH_3$	M^+ (m/e)	M.p. °C	Solvent
1 (a)	7.63 bs	7.92 bs	3.94 t	4.52 t			157	96-97	Ethanol
2 (a)	7.57 bs	7.96 bs	4.42 m	4.66 m		2.02 s	199; ($M\text{-}NO_2$), 153	57-58	Ethanol
3 (a)	7.70 bs	8.03 bs	4.72 t	3.90 t			175	Oil	
4 (a)	7.79 bs	8.06 bs	4.68 t	3.02 t			166; ($M\text{-}NO_2$), 120	51-52.5	Ethyl Acetate/Hexane
5 (b)		7.93 s	3.65 t	4.46 t	4.57 s		187; (M-OH), 170	117-119	Ethanol
6 (a)		7.87 s	4.44 m	4.74 m	4.72 s	2.00 s	229; (M-OH), 212	88-90	Benzene/Hexane
7 (a)		7.96 s	4.80 t	3.92 t	4.85 s		205; (M-OH), 188; ($M\text{-}NO_2$), 159	89-90	Chloroform/Hexane
10 (a,c)		8.07 s	4.40 t	5.18 t		1.93 s	($M\text{-}CH_3CO$), 184	Oil	
11 (a,d)		7.90 s	3.82 m	4.27 m	5.65 s		213; ($M\text{-}C_2H_5O$), 168	115-116	Ethanol
12 (a)		8.07 s	4.48 t	4.88 t		2.07 s	(M-HCN), 197; $M\text{-}(NO_2 + CH_3COO)$, 119	Oil	
13 (e)		8.08 s	4.45 t	5.22 t		1.97 s	257; (M-OH), 240	116-117	Benzene
14 (a)		8.09 s	4.00 t	4.77 t			182	102-103.5	Benzene
15 (e)		8.05 s	3.94 t	4.98 t			215; (M-OH), 198	178-180	Methanol/Benzene
16 (a)		8.02 s	4.49 t	5.37		1.97 s 2.25 s	299; ($M\text{-}CH_2CO$), 257	134-136	Benzene
17 (b)	7.82 s	8.34 s	3.75 t	4.16 t			157; (M-O), 141	117-118	Ethyl Acetate
18 (a)	7.53 bs	7.88 bs	4.38 bs	4.38 bs		2.10 s	199; (M-O), 183; ($M\text{-}CH_2CO$), 157	93-95	Ethanol
19 (b)	7.95 bs	8.47 bs	4.41 t	3.17 t			166; (M-O), 150; ($M\text{-}NO_2$), 120	110-111	Methanol
20 (b)		7.21 bs 7.70 bs	4.68 t	3.16 t			166; (M-O), 150; ($M\text{-}NO_2$), 120	112-113.5	Methanol
21 (b)		7.12 bs 7.54 bs	4.45 t	4.96 t			157	110-111	Chloroform
22 (b,f)	8.30 s						147	218-220	Ethyl Acetate
23 (e)	7.95 s		4.42 t				200; ($M\text{-}NO_2$), 154	96-97	Chloroform/Ethyl Ether

(a) Chloroform-d solvent. (b) D_6-DMSO solvent. (c) The chemical shift due to the proton of CHO was at 9.86 s. (d) The chemical shifts due to $O\text{-}C_2H_5$ were at 4.29 q, 1.30 t. (e) Deuteriomethanol solvent. (f) The chemical shift due to NH was at 7.55 bs.

Attempted hydroxymethylations of 4(5)-nitroimidazole, 2-nitroimidazole or 1-(2-hydroxyethyl)-2-nitroimidazole (**21**) were unsuccessful.

Reaction of 2,4(5)-dinitroimidazole with chloropropionitrile was attempted in an effort to introduce the cyanoethyl group at the 1-position. However, the only products isolated were 4(5)-chloro-5(4)-nitroimidazole (**22**) and 1-(2-cyanoethyl)-5-chloro-4-nitroimidazole (**23**) (Scheme III). Compound **23** was also independently synthesized

Scheme III



from reaction of **22** with acrylonitrile in the presence of Triton B. In another attempt to obtain the 1-(2-cyanoethyl) derivative of 2,4(5)-dinitroimidazole, its sodium salt was reacted with chloropropionitrile in dimethylformamide; however, the starting material was recovered unchanged.

Table I summarizes the nmr and mass spectral data of the nitroimidazoles reported herein. The 4- and 5-nitro isomers could be differentiated by the downfield shift of the methylene protons closer to the imidazole ring, caused by the electron-withdrawing effect of the nitro group, an effect which is higher for the 5-nitro than for the 4-nitro isomers (14).

EXPERIMENTAL

Infrared spectra were obtained using a Beckman Ir-10 spectrophotometer. Nmr spectra were recorded with a Varian A-60 spectrophotometer with tetramethylsilane as the internal reference. Mass spectra (70 eV) were run on a Hitachi Perkin-Elmer RMU-6E spectrometer. The elemental analyses were performed by Integral Microanalytical Laboratories, Raleigh, North Carolina. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Thin-layer chromatograms were run on silica gel PF-254 plates (E. Merck AG, Darmstadt, Germany) to a distance of 14 cm. Separation of products was achieved by preparative thin-layer chromatography; approximately 100-125 mg. of samples were streaked on silica gel plates (2 mm thick). The spots or streaks were detected by visual examination under uv light. Evaporation of solvent was done under reduced pressure using a rotary evaporator. Hydroxymethylations were carried out in a 25 ml. Parr Reflon lined digestion bomb.

Reaction of 4(5)-Nitroimidazole with Chloropropionitrile.

A suspension of 4(5)-nitroimidazole (2.0 g., 17.7 mmoles) in chloropropionitrile (10.0 g.) was heated at 150-160° for 20 hours. The reaction mixture turned dark during heating. The excess of chloropropionitrile was then distilled under reduced pressure; the residue was taken up in water, neutralized with sodium carbonate solution (*p*H 8), extracted with chloroform (6 x 25 ml.) and dried over anhydrous sodium sulfate. Removal of solvent after filtration produced a light brown oil (269 mg.), which was subjected to tlc using 1:5 methanol:ethyl acetate as eluant. Resulting fractions were extracted with chloroform and methanol. Spectral analysis (ir, nmr) indicated the upper fraction as the 5-nitro isomer (**4**) and the lower fraction as the 4-nitro isomer (**19**). Compound **4** was obtained as pale yellow oil, which was crystallized (ethyl acetate/hexane) in colorless needles (98 mg., 3.34%), m.p. 51-52.5° [lit. (15) m.p. 55-58°]; ir (potassium bromide): 2240 (CN), 1510 and 1350 cm^{-1} (NO_2). Compound **19** was obtained as crystalline material, which was recrystallized (methanol) (48 mg., 1.63%), m.p. 110-111° [lit. (12) m.p. 112°]; ir (potassium bromide): 2240 (CN), 1540, 1320 cm^{-1} (NO_2).

Hydroxymethylation of 1-(2-Chloroethyl)-5-nitroimidazole (**3**).

A solution of **3** (0.6 g., 3.4 mmoles) in dimethyl sulfoxide (5 ml.) was added to 0.5 g. paraformaldehyde in the digestion bomb and heated at 130° for 19 hours. The solution was then evaporated *in vacuo* (60-80°/0.5 mm) leaving a viscous dark brown syrup, which was chromatographed by thin-layer, developing with ethyl acetate. The major fraction was extracted with chloroform and methanol. Light brown syrup was obtained after removal of the solvent (418 mg.) which was crystallized (chloroform/hexane) to give **7** (316 mg., 44.96%), m.p. 89-90°; ir (potassium bromide): 3240 (OH), 1525 and 1350 cm^{-1} (NO_2).

Anal. Calcd. for $C_6H_8ClN_3O_3$: C, 35.04; H, 3.89; N, 20.44. Found: C, 35.03; H, 3.81; N, 20.31.

1-(2-Acetoxyethyl)-5-nitro-2-imidazolecarbaldehyde Thiosemicarbazone (**24**).

Compound **10** (0.5 g., 2.2 mmoles) and thiosemicarbazide (0.25 g., 2.75 mmoles) were added to 50% ethanol (60 ml.) containing concentrated hydrochloric acid (1 ml.) and heated on the steam-bath for 30 minutes. Ethanol was removed under reduced pressure. The crude product was dissolved in water (50 ml.), filtered, neutralized with sodium carbonate, repeatedly extracted with chloroform (6 x 25 ml.), and dried over anhydrous sodium sulfate. The residue from chloroform extract was recrystallized (absolute ethanol) to give **24** as yellow crystals (0.21 g., 31.78%), m.p. 161-163°; ms: m/e 300 (M^+), and nmr in deuteriochloroform were also consistent with the assigned structure.

Anal. Calcd. for $C_9H_{12}N_6O_4S$: C, 36.00; H, 4.00; N, 28.00. Found: C, 36.42; H, 4.21; N, 28.01.

Reaction of 1-(2-Acetoxyethyl)-5-nitro-2-imidazolecarbaldehyde (**10**) with Hydroxylamine-*O*-sulfonic Acid.

A solution of hydroxylamine-*O*-sulfonic acid (375 mg., 3.32 mmoles) in water (5 ml.) was added dropwise to a stirred suspension of **10** (0.5 g., 2.2 mmoles) in water (10 ml.) over a 10 minute period. The mixture was stirred for 1 hour at room temperature and then the temperature of the water-bath was raised to 65° during 1 hour and was heated for an additional 0.5 hour. The pale yellow solution was then cooled, neutralized with sodium carbonate solution, repeatedly extracted with chloroform (6 x 25 ml.) and dried over anhydrous sodium sulfate. Preparative tlc (silica gel, ethyl acetate) of the residue, obtained after removing chloroform, gave a mixture of **12** and **13** in the ratio of 45:55 as analyzed by nmr. This mixture was separated into its components by rechromatography on silica gel using 1:2 hexane/-ethyl acetate. Compound **12** was obtained as an oil (45 mg., 9.12%) [lit. (16) m.p. 55-57°]; ir (film): 2236 (CN), 1736 (CH_3COO), 1530 and 1365 cm^{-1} (NO_2). Compound **13** was obtained as yellow crystalline solid which was recrystallized (benzene) (51 mg., 9.01%), m.p. 116-117° [lit. (11) m.p. 116-

118°]; ir (potassium bromide): 3425 and 3335 (C-NH_2), 1730 (CH_3COO), 1633 (C=N), 1528 and 1352 cm^{-1} (NO_2).

Anal. Calcd. for $C_8H_{11}N_5O_5$ (**13**): C, 37.35; H, 4.28; N, 27.24. Found: C, 37.19; H, 4.26; N, 27.39.

1-(2-Hydroxyethyl)-5-nitroimidazole-2-carbonitrile (**14**).

A solution of **12** (40 mg., 0.18 mmole) in ethanol (10 ml.) containing 6*N* hydrochloric acid (1 ml.) was heated at 90° for 10 minutes, cooled, and the solvent evaporated under reduced pressure. The residue was diluted with water (20 ml.), neutralized with sodium carbonate solution, extracted with chloroform (4 x 25 ml.), dried over anhydrous sodium sulfate, and the solvent evaporated *in vacuo* to yield **14** which was crystallized (benzene), (23 mg., 70.77%), m.p. 102-103° [lit. (16) m.p. 99.5-101°]; ir (potassium bromide): 3365 (OH), 2225 (CN), 1520 and 1350 cm^{-1} (NO_2).

1-(2-Hydroxyethyl)-5-nitroimidazole-2-(*N*-hydroxy)carboximidamide (**15**).

A solution of **13** (25 mg., 0.116 mmole) in ethanol (10 ml.) containing 6*N* hydrochloric acid (1 ml.) was heated at 90° for 20 minutes, cooled, and the solvent removed *in vacuo*; the residue diluted with water (10 ml.), neutralized with sodium carbonate solution and washed with chloroform (3 x 10 ml.). The chloroform washings were discarded. The aqueous solution was evaporated *in vacuo* to dryness and the residue extracted with boiling absolute ethanol (6 x 15 ml.). The solvent was removed *in vacuo*, and the residue, after preparative tlc (silica gel, ethyl acetate), was recrystallized (methanol/benzene) to give **15** (16 mg., 76.52%), m.p. 178-180°; ir (potassium bromide): 3415 and 3300 (NH_2), 1630 (C=N), 1522 and 1348, cm^{-1} (NO_2).

Anal. Calcd. for $C_6H_9N_5O_4$: C, 33.49; H, 4.18; N, 32.56. Found: C, 33.73; H, 4.04; N, 32.40.

1-(2-Acetoxyethyl)-5-nitroimidazole-2(*N*-acetoxy)carboximidamide (**16**).

A solution of **13** (20 mg., 0.08 mmole) in chloroform (20 ml.) was treated with acetyl chloride (20 mg., 0.25 mmole) followed by triethylamine (30 mg., 0.3 mmole). The mixture was stirred for 30 minutes. The solvent was then removed *in vacuo*, the residue dissolved in water (10 ml.), neutralized with sodium carbonate solution and repeatedly extracted with chloroform (6 x 15 ml.). The residue obtained after removing chloroform was purified by tlc (silica gel, ethyl acetate) to yield **16** (16 mg., 68.76%), which which was crystallized (benzene), m.p. 134-136°.

Anal. Calcd. for $C_{10}H_{13}N_5O_6$: C, 40.13; H, 4.35; N, 23.41. Found: C, 39.82; H, 4.47; N, 23.44.

Hydrolysis of 1-(2-Acetoxyethyl)-5-nitro-2-imidazolecarbaldehyde (**10**).

A solution of **10** (100 mg., 0.461 mmole) in ethanol (25 ml.) containing 6*N* hydrochloric acid (1 ml.) was heated at 90° for 2 hours, cooled and neutralized with sodium carbonate solution. The mixture was evaporated to dryness *in vacuo* and the residue extracted with boiling absolute ethanol (6 x 15 ml.). The solvent was evaporated *in vacuo* and the residue purified by tlc on silica gel, eluted with 1:5 methanol/ethyl acetate and then recrystallized (ethanol) to give **11**, m.p. 115-116° (61 mg., 65.01%).

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.16; N, 19.72. Found: C, 44.91; H, 5.13; N, 19.42.

Reaction of 8-Ethoxy-5,6-dihydro-3-nitro-8*H*-imidazo[2,1-*c*][1,4]-oxazine (**11**) with Hydroxylamine-*O*-sulfonic Acid.

A stirred suspension of **11** (300 mg., 1.409 mmoles) in water (10 ml.) was treated with a solution of hydroxylamine-*O*-sulfonic acid (200 mg., 1.77 mmoles) in water (5 ml.), utilizing the procedure described for the reaction of **10**. The chloroform extracts upon removal of the solvent *in vacuo* yielded unreacted **11** (140 mg.). The aqueous solution was evaporated *in vacuo* to dryness, and the residue was extracted with boiling absolute ethanol (6 x 15 ml.). The solvent was removed, and the residue was recrystallized (methanol/benzene) after preliminary purification by preparative tlc (silica gel, ethyl acetate) to give **15** (30 mg., 18.54%). This compound was identical to the one prepared from **13** as determined by ir and mixed melting point.

1-(2-Cyanoethyl)-2-nitroimidazole (**20**).

Triton B (0.4 ml., 40% in methanol) was added dropwise to a stirred suspension of 2-nitroimidazole (400 mg., 3.54 mmoles) in acrylonitrile (8 ml.) while cooling, and the resulting solution was refluxed for 6 hours. The excess acrylonitrile was distilled under reduced pressure, and the residue was extracted with boiling absolute ethanol (50 ml.). Removal of the solvent and purification by tlc (silica gel, ethyl acetate) gave a single component, which was recrystallized (methanol) to give **20** (248 mg., 42.4%) as pale yellow crystals, m.p. 112-113.5°; ir (potassium bromide): 2236 (CN), 1520 and 1340 cm^{-1} (NO_2).

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.37; H, 3.61; N, 33.73. Found: C, 43.33; H, 3.44; N, 33.48.

Reaction of 2,4(5)-Dinitroimidazole with Chloropropionitrile.

A solution of 2,4(5)-dinitroimidazole (1.0 g., 6.33 mmoles) (17) in chloropropionitrile (15.0 g.) was heated at 150° for 21 hours. The excess of chloropropionitrile was then distilled under reduced pressure, the crystalline residue was taken up in water, neutralized with sodium carbonate solution (*p*H 8), and the resulting orange solution was extracted with ethyl acetate (5 x 20 ml.) and dried over anhydrous sodium sulfate. The residue after removal of solvent was subjected to tlc using ethyl acetate as eluant. Resulting fractions were extracted with chloroform and methanol, and spectral analysis (ir, nmr) indicated the upper fraction as **23**; the lower fraction was confirmed as the sodium salt of 2,4(5)-dinitroimidazole (150 mg.), which on acidification (*p*H 2.0) yielded the 2,4(5)-dinitroimidazole. Compound **23** was obtained as a light brown oil which was recrystallized (ethyl ether/-chloroform) (122 mg., 9.61%), m.p. 96-97°; ir (potassium bromide): 2220 (CN), 1560, 1340 cm^{-1} (NO_2).

Anal. Calcd. for $C_6H_5ClN_4O_2$: C, 35.91; H, 2.49; N, 27.93. Found: C, 35.76; H, 2.43; N, 27.69.

The aqueous layer, after the ethyl acetate extraction, was acidified with dilute hydrochloric acid (*p*H 2) and extracted with ethyl acetate (6 x 25 ml.). The residue after removal of solvent was purified by tlc (silica gel, ethyl acetate). Resulting fractions were extracted with chloroform and methanol. Spectral analysis (nmr, ms) identified the upper fraction as **22** and the lower fraction as 2,4(5)-dinitroimidazole (190 mg.). Compound **22** was recrystallized from ethyl acetate (202 mg., 21.64%), m.p. 218-220° [lit. (17) m.p. 214-216°]; ir (potassium bromide): 1575, 1360 cm^{-1} (NO_2).

1-(2-Cyanoethyl)-5-chloro-4-nitroimidazole (**23**).

Triton B (0.15 ml., 40% in methanol) was added dropwise to a stirred suspension of **22** (150 mg., 1.02 mmoles) in acrylonitrile (8 ml.) while cooling and the resulting solution was refluxed for 8 hours. Work-up as in the case of **20** gave **23** (96 mg., 45.42%), as a single component.

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