Synthesis of 1-Alkyl-2-nitroimidazole-5-carboxaldehydes

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We report the preparation of 1-methyl- and 1-ethyl-2-nitroimidazole-5-carboxaldehydes (Ia,b). For Ia three different routes of synthesis are described, which appear of general value for preparing 1-alkyl substituted 2-nitroimidazole-5-carboxaldehydes.

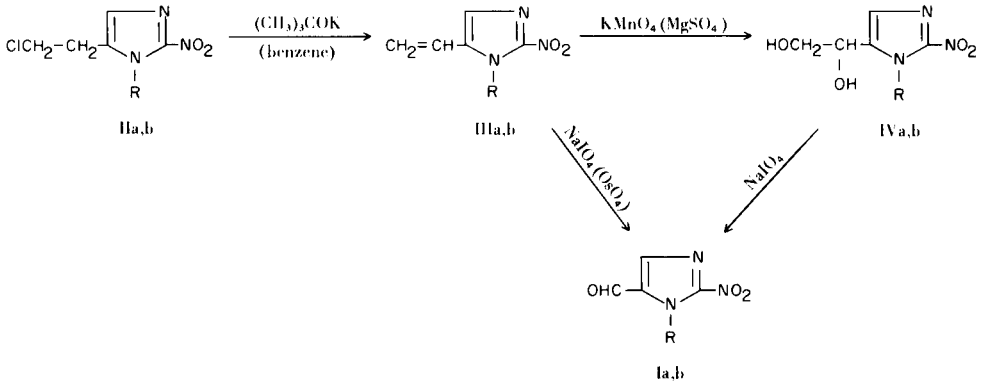
In connection with previous research (1) concerning the 2-nitroimidazoles we have developed the synthesis of 1-substituted 2-nitroimidazole-5-carboxaldehydes with the aim of obtaining intermediates suitable for the preparation of derivatives possessing antimicrobial activity. We have been encouraged in this work by the existence of several nitroheterocyclic aldehyde derivatives possessing interesting antibacterial and antifungal activity, particularly the well-known derivatives of the 2-nitrothiophene- and of the 2-nitrofuran-5-carboxaldehyde and the more recently described derivatives of the 1-methyl-5-nitroimidazole-2-carboxaldehyde (2, 3, 4).

Several possible routes for the synthesis of the desired compounds were unsuccessfully tried. Since negative results have been reported (5) for the direct introduction in the 2-nitroimidazole ring of the hydroxymethyl or aldehyde group, we tried the oxidation of the methyl group in position 5 of the 1,5-dimethyl-2-nitroimidazole either with cerium ammonium nitrate or selenium dioxide but the formation of the desired product could not be demonstrated.

Attempts were made to prepare the 1-methyl-2-amino-5-hydroxymethylimidazole which could be a good intermediate for the preparation of the corresponding 2-nitroimidazole to be subsequently oxidized to the aldehyde. For this reason 2-methylamino-3-hydroxypropionaldehyde diethyl acetal was synthesized but this product failed to condense with cyanamide to give the imidazole ring in contrast with its higher homolog which readily undergoes this reaction (1). We have also prepared 1-methyl-2-amino-5-carbethoxyimidazole (VI) but attempts to reduce the carbethoxy function to hydroxymethyl failed.

The 1-methyl-2-nitroimidazole-5-carboxaldehyde (Ia) was first synthesized by the route outlined in Scheme I. Treatment of the 1-methyl-2-nitro-5-(2-chloroethyl)imidazole (IIa) (1) with potassium *t*-butoxide led to the corresponding 1-methyl-2-nitro-5-vinylimidazole (IIIa). This compound could not be submitted to ozonization due to instability of the 2-nitroimidazole ring to this reagent but the oxidation with potassium permanganate gave the diol IVa, an intermediate suitable for cleavage with sodium periodate. This reaction led to the 1-methyl-

SCHEME I

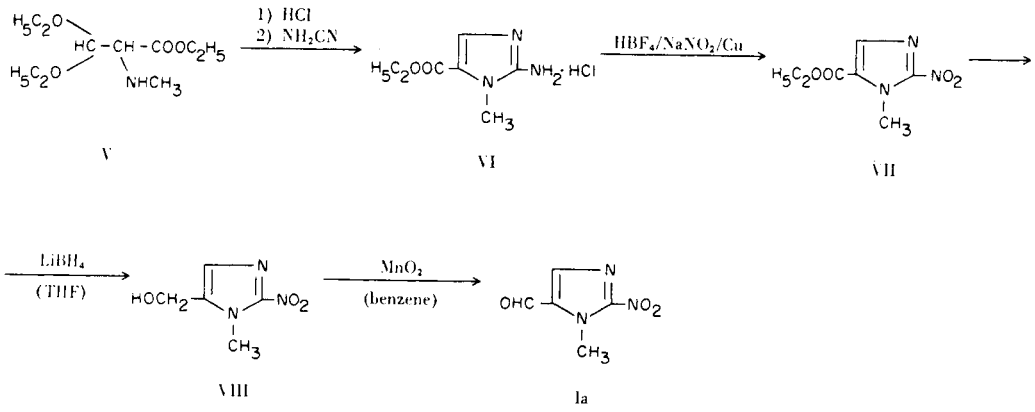


IIa,b IIIa,b IVa,b

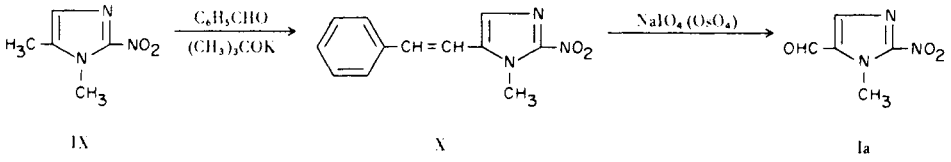
Ia,b

a, R = CH_3
b, R = C_2H_5
IVb = Isolated as crude material

SCHEME II



SCHEME III



2-nitroimidazole-5-carboxaldehyde (Ia) with excellent yields. Alternatively the 5-vinyl derivative IIIa could be directly oxidized with sodium periodate in the presence of osmium tetroxide to the aldehyde Ia with a 63.4% yield, an improvement over the two-step oxidation (39.8%).

The pure aldehyde Ia is a crystalline stable product, light yellow colored, which melts at 114-115°. The ir spectrum (chloroform) which exhibits absorption at 1680 cm^{-1} (ν C=O), 1530 cm^{-1} (ν asym. NO_2), 1350 cm^{-1} (ν sym. NO_2), and the pmr spectrum (deuteriochloroform) which shows bands at δ 4.36 (singlet, CH_3), 7.80 (singlet, ring H) and 9.95 (singlet, CHO) are consistent with the structure assigned. Further characterization is provided by the 2,4-dinitrophenylhydrazone, prepared by standard methods.

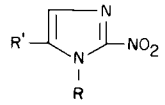
Scheme II outlines the sequence of reactions involved in an alternative route of synthesis, starting from the 1-methyl-2-nitro-5-carbethoxyimidazole (VII), which was prepared from the 1-methyl-2-amino-5-carbethoxyimidazole hydrochloride (VI) by diazotization in fluoboric acid followed by the reaction of the diazonium salt with nitrous acid in the presence of copper, as previously reported (1) for other 2-nitroimidazoles. Compound VII was converted by reduction with lithium borohydride to the 5-hydroxymethyl derivative (VIII) which by subsequent oxidation with manganese dioxide in benzene gave the aldehyde Ia in a 40.5% yield.

Finally, a further approach utilized as a precursor the 1,5-dimethyl-2-nitroimidazole (IX) (1) (Scheme III). This was condensed with an excess of benzaldehyde in the presence of potassium *t*-butoxide to give the *trans*-1-methyl-2-nitro-5-(2-phenylvinyl)imidazole (X). The *trans* configuration of the vinyl hydrogens was supported by pmr spectrum (deuteriochloroform/DMSO-d_6) which shows bands at δ 6.98 (d, 1H, = CH-C-N) and δ 7.31 [d, 1H, =CH-(C_6H_5)] with the characteristic $J_{CH=CH}$ = 17 Hz. The last step involves the oxidative cleavage with sodium periodate-osmium tetroxide of the alkene bond.

We have also prepared the 1-ethyl-2-nitroimidazole-5-carboxaldehyde (Ib) by the sequence of reactions indicated in Scheme I. The starting material 1-ethyl-2-nitro-5-(2-chloroethyl)imidazole (IIb) was not previously known. It was synthesized starting from γ-bromobutyrolactone which was converted into the α-ethylamino-γ-butyrolactone (XI) which submitted to Akabori reduction and treated with cyanamide gave the 1-ethyl-2-amino-5-(2-hydroxyethyl)imidazole (XII). Conversion of the latter into the 1-ethyl-2-nitro-5-(2-chloroethyl)imidazole (IIb) was achieved in two steps according to the method described for the 1-methyl substituted compound (1).

The routes of synthesis described appear of general value for preparing 1-alkyl substituted 2-nitroimidazole-5-carboxaldehydes. It is difficult to assess which of them is the most convenient for laboratory scale preparations since in all cases the last steps in the series of reactions proceed smoothly with good yields, whereas in all cases the starting compounds indicated in the schemes are not commercially available and have to be prepared in several steps.

TABLE I



Compound	R	R′	Yield %	M.p., °C	Tlc (a) Rf	Recryst. solvent	Molecular formula	Elemental Analysis					
								Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	CH_3	CHO	95.7 (b)	114-115	0.54	Ethyl acetate	$C_5H_5N_3O_3$ (c)	38.72	3.25	27.09	38.65	3.30	27.21
IIIa	CH_3	$CH=CH_2$	62.7	106-108	0.60	Ethyl ether	$C_6H_7N_3O_2$ (c)	47.06	4.60	27.44	46.75	4.70	27.12
IVa	CH_3	$CH(OH)-CH_2OH$	41.6	120-121	0.18	Methyl ethyl ketone	$C_6H_9N_3O_4$	38.51	4.85	22.45	38.80	5.00	22.70
X	CH_3	$CH=CH-C_6H_5$	16.2	178-180	0.67	Methyl ethyl ketone	$C_{12}H_{11}N_3O_2$ (c)	62.87	4.84	18.33	62.79	4.96	18.45
VII	CH_3	$COOC_2H_5$	27.3	65-66	0.63	Hexane	$C_7H_9N_3O_4$	42.21	4.55	21.10	42.05	4.79	20.90
VIII	CH_3	CH_2OH	33.0	142-144	0.31	Acetone	$C_5H_7N_3O_3$	38.22	4.49	26.74	38.22	4.60	26.68
Ib	C_2H_5	CHO	29.0	38-40	0.67	Ethyl ether	$C_6H_7N_3O_3$	42.61	4.17	24.84	42.46	4.32	24.93
IIb	C_2H_5	CH_2-CH_2Cl	9.4	36-37	0.62	— (d)	$C_7H_{10}ClN_3O_2$ (e)	41.28	4.95	20.63	41.25	5.12	20.71
IIIb	C_2H_5	$CH=CH_2$	82.8	45-47	0.65	— (d)	$C_7H_9N_3O_2$	50.30	5.43	25.14	50.37	5.45	25.00

(a) Performed on the same plate. (b) From 1-methyl-2-nitro-5-(1,2-dihydroxyethyl)imidazole (IVa). (c) Molecular weight confirmed by the M^+ peak in the mass spectrum. (d) Analysis without recrystallization. (e) Determination of Cl: Calcd. %: 17.40. Found: 17.46.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 157 spectrophotometer as nujol mulls. Uv spectra were recorded with a Unicam S.P. 800 spectrophotometer. Pmr spectra were obtained on a Varian A-60 (60 MHz) spectrometer in the solvent indicated. Chemical shifts are reported as δ relative to TMS (δ = 0.00 ppm).

Thin-layer chromatograms (tlc) were run on silica-gel plates HF/UV_{254} to a distance of 10.0 cm (developed with a 1:9 mixture of methanol and chloroform). The spots were detected by visual examination under uv light.

1-Methyl-2-nitro-5-vinylimidazole (IIIa).

To a solution of 18.9 g. (0.1 mole) of 1-methyl-2-nitro-5-(2-chloroethyl)imidazole (IIa) (1) in 2.8 l. of anhydrous benzene cooled at 5-10° was added 16.8 g. (0.15 mole) of potassium *t*-butoxide. The reaction mixture was then stirred for 2 hours at the same temperature, filtered and evaporated *in vacuo* to dryness. By washing the oily residue with ether, a crystalline product was collected and dried *in vacuo* at 40°, yield 9.6 g., m.p. 104-106°. A sample was crystallized for analysis; ir 1530 (ν asym. NO_2), 1360 (ν sym. NO_2), 980 and 925 (γ CH, vinyl), 840 cm^{-1} (γ CH and C-N); pmr (DMSO-d_6) δ 4.00 (s, 3H, CH_3), 5.50-7.15 (m, 3H, $CH=CH_2$), 7.50 (s, 1H, ring H).

1-Methyl-2-nitro-5-(1,2-dihydroxyethyl)imidazole (IVa).

A solution of 5.46 g. (34.5 mmoles) of potassium permanganate and 8.85 g. (35.9 mmoles) of magnesium sulphate hetpahydrate in 750 ml. of water was added with stirring to a solution of 6.2 g. (40.5 mmoles) of IIIa in 570 ml. of ethanol cooled at -10°. The reaction mixture was filtered through celite and evaporated *in vacuo* to give a residue which was crystallized from methyl ethyl ketone yielding 3.15 g. of product, m.p. 118-120°. A sample was recrystallized for analysis; ir 3300 and 3100 (ν OH), 1540 (ν asym. NO_2), 1360 (ν sym. NO_2), 1070 (ν C-O), 840 cm^{-1} (γ CH and C-N); pmr (DMSO-d_6) δ 3.70 (d, 2H, CH_2), 3.98 (s, 3H, CH_3), 4.70 [t, 1H, CH-(OH)], 4.50-6.00 (broad s, 2H, OH), 7.11 (s, 1H, ring H).

1-Methyl-2-nitroimidazole-5-carboxaldehyde (Ia).

(a) From 1-methyl-2-nitro-5-(1,2-dihydroxyethyl)imidazole (IVa).

A solution of 3.6 g. (16.8 mmoles) of sodium periodate in 85 ml. of water was added at room temperature to a stirred solution of 3.15 g. (16.8 mmoles) of IVa in 200 ml. of methanol. By cooling a precipitate was formed which was filtered off and washed with methanol. Evaporation *in vacuo* to dryness of the solution and washing gave a residue which was extracted several times with ethyl acetate. The extracts were concentrated to a small volume. After standing at 4° a crystalline product was collected, 2.5 g. (95.7%), m.p. 113-114°. A portion was recrystallized from ethyl acetate to give an analytical sample; ir (chloroform) 2900-2680 (ν CH), 1680 (ν C=O), 1530 (ν asym. NO_2), 1350 (ν sym. NO_2), 840 cm^{-1} (γ CH and C-N); uv λ max (methanol) 318 nm (log ε 3.92); pmr (deuteriochloroform) δ 4.36 (s, 3H, CH_3), 7.80 (s, 1H, ring H), 9.95 (s, 1H, CHO).

The 2,4-dinitrophenylhydrazone melted at 276-279°; Rf (relative to Ia): 1.08; uv λ max (methanol) 408 nm (log ε 4.48).

Anal. Calcd. for $C_{11}H_9N_7O_6$: C, 39.41; H, 2.70; N, 29.24. Found: C, 39.36; H, 2.71; N, 29.34.

Molecular weight confirmed by the M^+ peak in the mass spectrum.

(b) From 1-Methyl-2-nitro-5-vinylimidazole (IIIa).

A solution of 2 g. (9.3 mmoles) of sodium periodate in 5 ml. of water was added to a stirred solution of 0.67 g. (4.3 mmoles) of IIIa in 20 ml. of dimethoxyethane. After adding 0.025 g. of osmium tetroxide the mixture was stirred at room temperature for 8 hours. The solution was evaporated to dryness *in vacuo* at 40° and the residue was extracted with ethyl acetate. After filtering, the solution was concentrated to a small volume and allowed to crystallize overnight at 4°. The yield was 0.43 g. (63.4%).

(c) From 1-Methyl-2-nitro-5-hydroxymethylimidazole (VIII).

To a solution of 0.15 g. of VIII in 20 ml. of benzene was added 0.33 g. of manganese dioxide. After stirring 2 hours at reflux, the mixture was filtered. Evaporation *in vacuo* to dryness gave a residue which was crystallized from ethyl acetate yielding 0.06 g. (40.5%) of Ia.

(d) From *Trans*-1-Methyl-2-nitro-5-(2-phenylvinyl)imidazole (X).

A solution of 1.6 g. (7.5 mmoles) of sodium periodate in 40 ml. of water was added to a solution of 0.8 g. (3.5 mmoles) of X in 300 ml. of methanol at room temperature followed by 0.02 g. of osmium tetroxide. The mixture was stirred for 10 hours and then additional 0.01 g. of osmium tetroxide was added. Stirring was continued for 8 hours more. The mixture was filtered and solvents were evaporated *in vacuo* at 40° to dryness. By treating the residue as described in (b), 0.325 g. (60%) of Ia were obtained.

The products obtained as described in (b), (c), and (d) were identical through mixed m.p., tlc, ir and pmr spectra with Ia obtained as described in (a).

Trans-1-Methyl-2-nitro-5-(2-phenylvinyl)imidazole (X).

A mixture of 7.2 g. (51 mmoles) of 1,5-dimethyl-2-nitroimidazole (IX) (1), 41.2 ml. (0.4 mole) of freshly distilled benzaldehyde and 7.9 g. (70 mmoles) of potassium *t*-butoxide in 300 ml. of methanol was stirred at room temperature under nitrogen for 20 minutes, then heated to reflux for 30 minutes. The solvent was evaporated *in vacuo* and the residue was dissolved in ether and filtered. By concentration an oily residue was obtained which was chromatographed on 700 g. of silica-gel 0.2-0.5 mm in chloroform. Fractions of 1 l. were collected eluting with chloroform. Fractions 4 ÷ 11 were collected and the solvent was evaporated obtaining an oily residue. By standing, a crystalline product was formed which was filtered and washed with a little methyl ethyl ketone (1.6 g., m.p. 175-178°).

The mother liquor was evaporated. From the residue a mixture of benzaldehyde and benzyl alcohol was bulb to bulb distilled off at 75-80°/0.5 mm. The residue was treated with methyl ethyl ketone as above obtaining an additional crop of product (0.32 g., m.p. 175-176°). An analytical sample was recrystallized, m.p. 178-180°; ir 1520 (ν asym. NO_2), 1360 (ν sym. NO_2), 965 (γ CH trans), 830 (γ CH and C-N), 770 and 705 cm^{-1} (γ CH phenyl); pmr (deuteriochloroform/DMSO-d_6 3:2), δ 4.09 (s, 3H, CH_3), 6.98 (d, $J_{CH=CH}$ = 17 Hz, 1H, =CH-C-N), 7.31 [d, 1H, $=CH-(C_6H_5)$], 7.25-7.75 (m, 5H, arom. H), 7.47 (s, 1H, ring H).

1-Methyl-2-amino-5-carbethoxyimidazole Hydrochloride (VI).

A solution of 10 g. (45 mmoles) of *N*-methyl-β,β-diethoxyalanine ethyl ester (6) in 137 ml. of 10% hydrochloric acid was heated at 60° for three hours. After cooling to -30° the *p*H was brought to 4.5 with 10% sodium hydroxide solution and 5.2 g. (0.12 mole) of cyanamide was added. The resulting mixture was stirred at 60° for two hours maintaining the *p*H at 4.5 by addition of 10% hydrochloric acid, decolorized and then evaporated *in vacuo*

to dryness. The residue was triturated with ethyl ether to remove unreacted cyanamide and extracted several times with anhydrous ethanol containing 5% hydrogen chloride. The extracts were concentrated to a small volume under reduced pressure and ethyl ether was added. A syrupy product separates which was dissolved in 2-propanol. After cooling the crystals were collected. A second crop was obtained from the mother liquor. The product was dried at 50° *in vacuo*, 5.8 g. (61.7%), m.p. 200-205°. An analytical sample was recrystallized from 2-propanol, m.p. 209-211°; ir 3200-2400 (ν NH^+_2, NH^+_3), 1675 (ν C=O), 1600 and 1580 (NH^+_2, NH^+_3), 1260 and 1120 (ν C-O), 840 cm^{-1} (γ CH and C-N); pmr (DMSO-d_6) δ 1.29 [t, J = 7 Hz, 3H, $CH_3(CH_2)$], 3.69 (s, 3H, CH_3-N), 4.32 (q, 2H, CH_2), 7.74 (s, 1H, ring H), 7.90-9.90 (two broad s, 3H, mobile H).

Anal. Calcd. for $C_7H_{12}ClN_3O_2$: C, 40.90; H, 5.88; Cl^-, 17.25; N, 20.45. Found: C, 40.70; H, 6.01; Cl^-, 17.15; N, 20.25.

1-Methyl-2-nitro-5-carbethoxyimidazole (VII).

A solution of 2.5 g. (36 mmoles) of sodium nitrite in 8 ml. of water was added dropwise at -20° to a stirred mixture of 6.8 g. (33 mmoles) of VI, 20 ml. of water, and 28 ml. of 40% fluoboric acid. The stirring was continued for fifty minutes at -15°. The solution was poured into a well-stirred mixture of 23 g. of sodium nitrite, 7 g. of copper powder, and 630 ml. of water. After two hours the copper was filtered off and the solution, brought to *p*H 2 with 10% hydrochloric acid, was extracted with ethyl acetate. The combined extracts were concentrated to 300 ml. and washed with a sodium bicarbonate solution which was reextracted with ethyl acetate. The combined organic phases on concentration gave an oily residue which was extracted several times with hexane. After concentration and standing at 4°, 1.8 g. of light yellow crystals, m.p. 60°, were obtained; ir 1715 (ν C=O), 1550 (ν asym. NO_2), 1370 (ν sym. NO_2), 840 cm^{-1} (γ CH and C-N); pmr (deuteriochloroform) δ 1.43 [t, J = 7 Hz, 3H, $CH_3(CH_2)$], 4.42 (s, 3H, CH_3-N), 4.47 (q, 2H, CH_2), 7.80 (s, 1H, ring H).

1-Methyl-2-nitro-5-hydroxymethylimidazole (VIII).

To a suspension of 0.024 g. of lithium borohydride in 30 ml. of anhydrous tetrahydrofuran, 0.2 g. (1 mmole) of VII was gradually added under stirring at room temperature. Stirring was continued for a total of twenty hours and further 0.020 g. of lithium borohydride was added. The reaction was checked by tlc. After cooling, the excess of lithium borohydride was decomposed with 10% hydrochloric acid. The mixture was filtered and the solution was evaporated to dryness *in vacuo*. The residue was extracted with acetone. After evaporation an oily product was obtained which was dissolved in a few milliliters of chloroform and absorbed in a column containing 7 g. of silica-gel 0.02-0.05 mm. Fractions of three ml. were collected eluting with chloroform (fractions 1 to 25); chloroform containing 1% (v/v) of methanol (fractions 26-59); chloroform containing 2% (v/v) of methanol (fractions 60-79); chloroform containing 3% (v/v) of methanol (fractions 80-97).

Fractions 72 to 89 contained the desired compound (checked by tlc). By evaporation to dryness 0.052 g. of pure product m.p. 140° was obtained. An analytical sample was recrystallized from acetone; ir 3250 (ν OH), 1550 (ν asym. NO_2), 1360 (ν sym. NO_2), 1040 (ν C-O), 840 cm^{-1} (γ CH and C-N); pmr (DMSO-d_6) δ 3.93 (s, 3H, CH_3-N), 4.55 (s, 2H, CH_2), 4.57 (broad s, 1H, OH), 7.14 (s, 1H, ring H).

α-Ethylamino-γ-butrolactone Hydrochloride (XI).

A suspension of 120 g. of α-ethylamino-γ-hydroxybutyric acid (7) in 1.5 l. of ethanol was saturated with hydrogen chloride keeping the temperature at 20-30° (6 hours). The reaction mixture was concentrated *in vacuo* at 50° to a small volume. After addition of 200 ml. of ethanol the solid was filtered, washed with ethanol and dried *in vacuo* at 50°. The compound (103.5 g., 76.6%) melted at 158-162° and was sufficiently pure for the next step. A sample was crystallized from ethanol, m.p. 163-164°; ir 2800-2200 (ν NH^+_2), 1750 cm^{-1} (ν C=O).

Anal. Calcd. for $C_6H_{12}ClNO_2$: C, 43.60; H, 7.32; Cl^-, 21.36; N, 8.36. Found: C, 43.51; H, 7.30; Cl^-, 21.40; N, 8.46.

1-Ethyl-2-amino-5-(2-hydroxyethyl)imidazole Hydrochloride (XII).

It was prepared essentially according to the procedure described (1) for the 1-methyl analog. Starting from 89.3 g. of XI, 44.6 g. (43%) of XII, m.p. 103-105°, were obtained. A sample recrystallized from 2-propanol melted at 105-107°; ir 3250-3100 (ν OH and NH), 2700-2400 (ν NH^+_2, NH^+_3), 1660 cm^{-1} (ν C=N); pmr (DMSO-d_6) δ 1.17 (t, J = 7 Hz, 3H, CH_3), 2.66 [doublet of triplets, 2H, J = 6 Hz; J all. = ~0.5 Hz, CH_2-C=], 3.66 [t, 2H, CH_2(OH)], 4.01 [q, 2H, $CH_2(CH_3)$], 4.55-5.55 (broad s, 1H, OH), 6.73 (t, 1H, ring H), 7.80 (broad s, 2H, mobile H), 10.3-13 (broad s, 1H, mobile H).

Anal. Calcd. for $C_7H_{14}ClN_3O$: C, 43.86; H, 7.36; Cl^-, 18.50; N, 21.92. Found: C, 43.98; H, 7.46; Cl^-, 18.32; N, 21.81.

The *picrate* after recrystallization from ethanol melted at 157-158°.

1-Ethyl-2-amino-5-(2-chloroethyl)imidazole Hydrochloride (XIII).

It was prepared according to the general directions described (1) for the 1-methyl analog. Starting from 5.4 g. of XII, 3.5 g. (59%) of XIII, m.p. 166-168°, were obtained. Crystallization from 2-propanol gave an analytical sample, m.p. 170°; ir 3100 (ν NH), 2700-2400 (ν NH^+_2), 1650 cm^{-1} (ν C=N); pmr (DMSO-d_6) δ 1.20 [t, J = 7 Hz, 3H, CH_3], 3.05 [doublet of triplets, J = 7 Hz, J all. = ~0.5 Hz, 2H, CH_2-C=], 3.91 (t, 2H, CH_2Cl), 4.04 [q, 2H, $CH_2(CH_3)$], 6.90 (t, 1H, ring H), 7.98 (broad s, 2H, mobile H), 10.9-13.6 (broad s, 1H, mobile H).

Anal. Calcd. for $C_7H_{13}Cl_2N_3$: C, 40.02; H, 6.24; Cl, 33.75; N, 20.00. Found: C, 40.22; H, 6.35; Cl, 33.55; N, 20.13.

1-Ethyl-2-nitro-5-(2-chloroethyl)imidazole (IIb).

A solution of 10.4 g. (0.15 mole) of sodium nitrite in 50 ml. of water was added dropwise at -20° in 20 minutes to a stirred mixture of 28.1 g. (0.13 mole) of XIII, 94 ml. of water, and 124.5 ml. of 40% fluoboric acid. The solution was poured into a stirred mixture of 30 g. of copper powder, 98 g. of sodium nitrite, and 1450 ml. of water. After 2 hours the copper was filtered off and the solution, brought to *p*H 2.5-3.0 with 10% hydrochloric acid was extracted several times with ethyl acetate (six 100 ml. portions). The combined extracts were concentrated to 650 ml. and washed with 30 ml. of saturated sodium bicarbonate solution. The oily residue obtained by concentration was dissolved in a few milliliters of chloroform, absorbed in a column containing 400 g. of silica-gel 0.2-0.5 mm and eluted with chloroform. Fractions containing the product were collected and evaporated. The oily residue by treating with petrol ether gave 2.5 g. of IIb, m.p. 36-37°; ir 1525 (ν asym. NO_2), 1320 (ν sym. NO_2), 840 cm^{-1} (γ CH and C-N); pmr (deuteriochloroform) 1.45 (t, J = 7 Hz, 3H, CH_3), 3.13 (doublet of triplets J = 7 Hz, J all. = ~1Hz, 2H, CH_2-C=), 3.82 (t, 2H, CH_2Cl), 4.43 [q, 2H, $CH_2(CH_3)$], 7.08 (t, 1H, ring H).

1-Ethyl-2-nitro-5-vinylimidazole (IIIb).

This compound was prepared according to the method described for IIIa. Starting from 2.2 g. of IIb, 1.5 g. of IIIb, m.p. 45-47°,

were obtained; ir 1530 (ν asym. NO_2), 1370 (ν sym. NO_2), 980 (γ CH vinyl), 835 cm^{-1} (γ CH and C-N); (deuteriochloroform/DMSO-d_6 1:1) δ 1.43 (t, J = 7 Hz, 3H, CH_3), 4.53 [q, 2H, $CH_2(CH_3)$], 5.5-7.1 (m, 3H, $CH=CH_2$), 7.44 (s, 1H, ring H). 7.82 (s, 1H, ring H), 9.94 (s, 1H, CHO).

The 2,4-dinitrophenylhydrazone melted at 215-216°; uv λ max (methanol) 408 nm (log ϵ 4.49).

Anal. Calcd. for $C_{12}H_{11}N_7O_6$: C, 41.27; H, 3.17; N, 28.07. Found: C, 40.97; H, 3.08; N, 27.91.

1-Ethyl-2-nitroimidazole-5-carboxaldehyde (Ib).

A solution of 1.0 g. (6.3 mmoles) of potassium permanganate and 1.6 g. (6.5 mmoles) of magnesium sulphate heptahydrate in 140 ml. of water was added with stirring to a solution of 1 g. (6.0 mmoles) of IIIb in 70 ml. of ethanol cooled at -10°. By working as described for IIIa, 0.8 g. of crude 1-ethyl-2-nitro-5-(1,2-dihydroxyethyl)imidazole (IVb) was recovered. To a solution of the product in 70 ml. of methanol was added a solution of 0.9 g. (4.2 mmoles) of sodium periodate in 20 ml. of water at room temperature under stirring. The mixture was treated as reported for IVa. After evaporation of the ethyl acetate extracts an oily residue was obtained which was chromatographed on 10 g. of silica-gel 0.2-0.5 mm eluting with chloroform. Fractions of 20 ml. were collected and controlled by tlc. By evaporation 0.29 g. (29%) of Ib were obtained. An analytical sample was crystallized from ether; ir (chloroform) 2900-2680 (ν CH), 1685 (ν C=O), 1530 (ν asym. NO_2), 1320 (ν sym. NO_2), 8.40 cm^{-1} (γ CH and C-N); uv λ max (methanol) 318 nm (log ϵ 3.93); pmr (deuteriochloroform) δ 1.48 (t, J = 7 Hz, 3H, CH_3), 4.83 (q, 2H, CH_2),

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