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Nitroimidazoles: Part XI—Some Halonitro- & Dinitroimidazoles†‡

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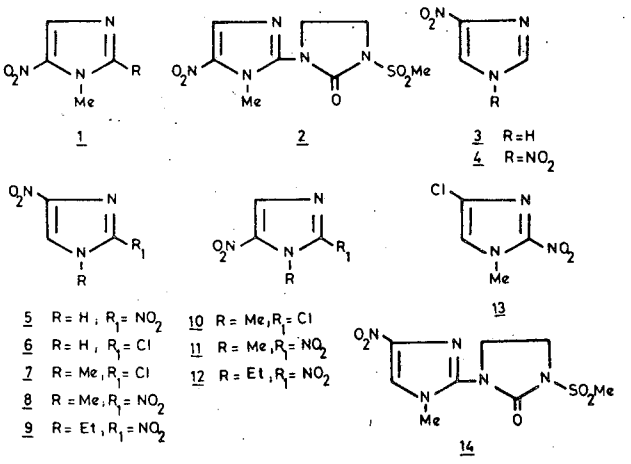
Methylation of 2-chloro-4-nitroimidazole (**6**), obtained from imidazole in four steps, either with dimethyl sulphate or with diazomethane affords a mixture of 2-chloro-1-methyl-5-nitroimidazole (**10**) and the 4-nitro-isomer (**7**). The corresponding dinitro compounds **11** and **8** are formed in the methylation of 2,4-dinitroimidazole (**5**), **8** being converted to **7** by the action of $POCl_3$. Reaction of **10** with the sodium salt of N-methanesulphonyl-2-imidazolidinone provides the potent amoebicide, 1-methylsulphonyl-3-(1-methyl-5-nitroimidazol-2-yl)-2-imidazolidinone (**2**). The isomer **14** is synthesised from **7** in low yield. Ethylation of **5** leads to preponderant N-alkylation, providing a mixture of 1-ethyl dinitroimidazoles (**9**) and (**12**), but a small amount of N,C-diethyl derivative **15** is also obtained. The formation of **15** from **5** is rationalised. The diiodination product of imidazole is shown to be 4,5-diiodoimidazole (**19**), nitric acid transforming it to 4-iodo-5-nitroimidazole (**20**). Methylation of **20** affords a mixture of isomeric 1-methyliodonitro derivatives (**21**) and (**22**). The structures of **21** and **22** are established by ^{13}C NMR data as well as by conversion into morpholine derivatives **26** and **24** respectively which also arise from 1-methylchloronitroimidazoles (**25**) and (**23**). A mechanism is proposed for the reported conversion of **5** into 4-chloro-5-nitroimidazole (**32**) in boiling 2-chloroethanol.

In an earlier communication[1] of this series, we reported the synthesis of 1-methylsulphonyl-3-(1-methyl-5-nitroimidazol-2-yl)-2-imidazolidinone (**2**), a potent antiprotozoal agent currently undergoing clinical trials, by a displacement reaction on the sulphone (**1**, $R=SO_2CH_3$). We considered it worthwhile to evaluate the potentials of other leaving groups in **1**, such as chlorine or iodine atom in this sequence. We present in this paper, the results of these endeavours which incidentally also lead to some corrections and elaborations of existing literature.

Reaction of 4-nitroimidazole (**3**)[2] with acetic anhydride and fuming nitric acid yielded 1,4-dinitroimidazole (**4**) in 65% yield, which underwent a thermal 1,5-sigmatropic shift of the nitro group at position-1 to afford 2,4-dinitroimidazole (**5**) in 85% yield[3]. Treatment of **5** with phosphorus oxychloride in DMF gave 2-chloro-4(5)-nitroimidazole (**6**), which on methylation with dimethyl sulphate in the presence of a phase transfer catalyst or with diazomethane furnished a mixture of 2-chloro-1-methyl-4-nitroimidazole (**7**) and the 5-nitro-isomer (**10**)[4] which were separated by column chromatography. Reaction of **10** with the sodium salt of N-methanesulphonylethyleneurea[1] afforded **2** in 65% yield, confirming the orientation of chlorine atom in **10** and thus in **6**. In contrast **7** underwent a similar transformation to **14** only in marginal yield; nor was the chlorine atom in **7** displaced by morpholine. Structures **7** and **10** were also supported by ^{13}C NMR spectral studies which are reported elsewhere[5].



Methylation of **5** with methyl iodide in the presence of a phase transfer catalyst afforded the 2,4-dinitro-isomer (**8**) in 30% yield. Two minor products obtained were identified as **7** and the corresponding iodo compound. These were evidently formed from either **5** or **8**, by reaction with chloride ion (from catalyst) and iodide ion respectively. Reaction with diazomethane however afforded both **8** and the 2,5-dinitro-isomer (**11**)[6]. The structures **8** and **11** were established by spectral, especially ^{13}C NMR data[5].

Treatment of **8** with phosphorus oxychloride in DMF has been reported to afford 4-chloro-1-methyl-2-nitroimidazole (**13**)[4]. In our hands, the only isolable and unambiguously identified product was 2-chloro-1-methyl-4-nitroimidazole (**7**). We did not obtain any useful results from a similar reaction of **11** with phosphorus oxychloride.

Ethylation of **5** with diazoethane yielded the expected isomeric N-ethylimidazoles (**9**) and (**12**).

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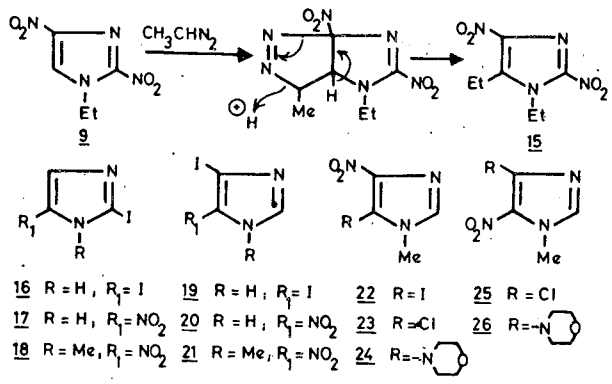

Chart 1

These were distinguished by the fact that the former was a solid and the latter, an oil in keeping with our general observation that 4-nitroimidazoles are higher melting than their 5-nitro counterparts[5]. Another useful factor was the lower chemical shift of the N-CH_2 in **12** (4.98 ppm) compared to that in **9** (4.80 ppm). A very minor but interesting byproduct was tentatively identified as 1,5-diethyl-2,4-dinitroimidazole (**15**) from mass and PMR spectral data. The observed chemical shift (4.85 ppm) for the N-CH_2 protons in the PMR spectrum of the product appeared more consistent with **15** than with the isomeric 1,4-diethyl-2,5-dinitroimidazole structure. The formation of the unexpected product can be envisaged as shown in Chart 1. It has been our finding[7,8] that only those nitroimidazoles undergo reactions with diazomethane, which carry acyl or sulphonylamino groups at position-2. We believe that **9** is an exception (to a marginal degree) due to the presence of two electron depleting groups in the molecule, situated rightly (at positions-2 and -4), to render position-5 exceedingly vulnerable to nucleophilic attack by diazoethane, a structural feature not manifested by the isomer **12** to the same extent. A similar product may have been also formed in the reaction of **5** with diazomethane but escaped detection.

Condensation of **5** with triethyl orthoformate in the presence of a catalytic amount of trifluoroacetic acid again gave a mixture of the N-ethylated derivatives **9** and **12** in the ratio of 8:1. Unlike 4-nitroimidazoles, 2,4-dinitroimidazole seems to prefer to form 1-substituted-2,4-dinitroimidazoles even under neutral or acidic alkylating conditions.

We were interested in testing iodine as a leaving group in **1** for the synthesis of **2**. 2-Iodo-1-methyl-5-nitroimidazole (**18**) has been reported in the literature and used for the synthesis of a variety of compounds[9,10]. The preparative route involves diiodination of imidazole to **16**[11], treatment of **16** with nitric acid to form **17** and subsequent methylation. The approach appeared to be potentially useful, but a suspicion has been raised in the literature based on PMR spectral data that the diiodoimidazole claimed to be **16** may be in fact 4,5-diiodoimidazole (**19**)[12]. Our investigations summarised below conclusively established that iodination of imidazole in fact afforded **19** and that its subsequent nitration product must be formulated as **20****. Methylation with dimethyl sulphate alone gave **21** as the major and **22** as the minor products, while in the presence of alkali, the reverse was the case. Structural assignments were made readily from ^{13}C NMR data. Both **21** and **22** had no substituent at position-2, as evidenced by doublets at δ 143.7 ppm ($^1J_{CH}$ = 216.7 Hz) and 139.8 ppm ($^1J_{CH}$ = 218.6 Hz) respectively. The observed one-bond C, H coupling fits in with C-2 only; $^1J_{CH}$ of C-4 or C-5 of imidazole is around 200 Hz[5]. Further, in both the cases, the iodine-bearing carbon atom was recognised readily by its upfield position[13] (**21**, δ C-4 90.8 ppm; **22**, δ C-5 81.55 ppm). Consistent with the structural assignments, the former exhibited only a doublet structure, ($^3J_{CH}$ = 11.8 Hz) and the latter a quintet structure ($^3J_{CH}$ = 3 Hz) (one C-5 H-2 and three C-5 CH_3 couplings). Conclusive confirmation was obtained readily by conversion of **21** and **22** into the morpholino derivatives **26** and **24** respectively which were unambiguously synthesised from the known chloromethyl nitroimidazoles **25** and **23** of established structures[14]. Both **24** and **26** were different from 1-methyl-2-morpholino-5-nitroimidazole[15] as expected.

While the classical synthesis of **23** and **25**[14] emanates from 5-chloro-1-methylimidazole synthesised from N,N'-dimethyloxamide by a Wallach reaction[16], the fortuitous formation of 4-chloro-5-nitroimidazole (**32**) reported by Italian workers[17] in the reaction of 2,4-dinitroimidazole (**5**) with 2-chloroethanol offers a new route to these compounds. This unexplained reaction, we believe, probably takes place as shown in Chart 2 invoking the preponderant formation of 1-alkyl-2,4-dinitroimidazoles from **5** (*vide supra*) and the better leaving properties of the nitro group at position-2 in **5**. An intramolecular S_{N^2} displacement reaction by the hydroxyethyl group in the primary alkylation product **27** would lead to the formation of **29**, wherein the isoxazoline ring can be ruptured by chloride ion, with loss of ethylene oxide, leading finally to **32**[δ]. However, in view of the fact that the melting points of the pairs **10**, **25** and **7**, **23** are close to one another, it is still possible that the reaction product of **5** with 2-

**This work was completed in August 1980, and an account of the results presented in the Symposium on Medicinal Chemistry and Natural Products held by the Institute of Science, Bombay, November 13-15, 1980. Recent publications[18] have arrived at the same conclusion.

δTwo other publications[19,20] report repetition of this work, taking structure **32** for granted for the product.

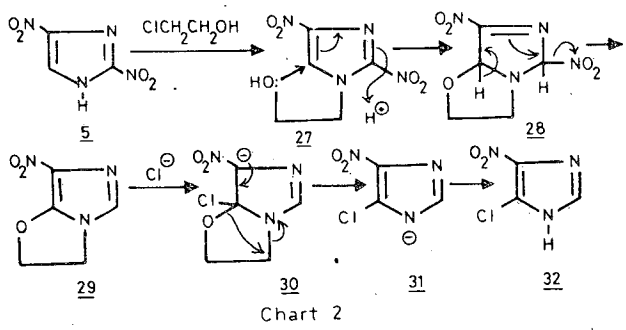

Chart 2

chloroethanol is in fact only **6**, and we propose to investigate this further.

Experimental Procedure

1,4-*Dinitroimidazole* (**4**)—To a suspension of 4-nitroimidazole (88.7 g) in glacial acetic acid (178 ml) cooled to 0° was added fuming nitric acid ($d=1.52$; 48 ml) dropwise with stirring, keeping the temperature at or below 5° over a period of 30 min. The mixture was cooled to 0°, acetic anhydride (150 ml) added dropwise with stirring at 0°, stirred at 0° for 2 hr and at room temperature overnight. The solid gradually went into solution, which was then poured onto crushed ice and neutralised at or below 5° with saturated aq. potassium bicarbonate. The precipitate was filtered, washed with water, dried at room temperature *in vacuo*, dissolved in ether and filtered from a little insoluble matter. Concentration of ether yielded **4** (80 g), m.p. 90°; PMR (90 MHz, $DMSOd_6+CDCl_3$); δ 8.53 (1H, *d*, $J=1.5$ Hz, C-5H), 8.76 (1H, *d*, $J=1.5$ Hz, C-2H) (Found: C, 23.1; H, 1.57; N, 35.8. $C_3H_2N_4O_4$ requires C, 22.8; H, 1.3; N, 35.5%).

2,4-*Dinitroimidazole* (**5**)—A mixture of **4** (23 g) and chlorobenzene (460 ml) was heated with stirring at 120-25° for 50 hr on an oil-bath, cooled, the solid filtered and washed with cold chlorobenzene and hexane to yield **5** (21 g), m.p. 264-67°. (Found: C, 23.4; H, 1.5; N, 35.8. $C_3H_2N_4O_4$ requires C, 22.8; H, 1.3; N, 35.5%).

2-*Chloro*-4-*nitroimidazole* (**6**)—To a suspension of **5** (14 g) in DMF (45 ml) was added dropwise with stirring phosphorus oxychloride (14 ml), the mixture heated at 85° for 6 hr and left at room temperature overnight. The solvent was removed *in vacuo* and the residue flushed with xylene and treated with ice. The solid was filtered, washed with ice cold water and dried to yield **6** (11 g), m.p. 201-4°. A small sample was crystallised from methylene chloride-ether, m.p. 202-5° PMR (90 MHz, DMSO-d_6): δ 8.48 (1H, *s*, C-5H); M^+ 147††. (Found: C, 24.5; H, 1.7; N, 28.1. $C_3H_2ClN_3O_2$ requires C, 24.4; H, 1.4; N, 28.5%).

2-*Chloro*-1-*methyl*-4-*nitroimidazole* (**7**) *and* 2-*chloro*-1-*methyl*-5-*nitroimidazole* (**10**)—(a) To a suspension of **6** (2.2 g) in toluene (75 ml) was added benzyl trimethylammonium chloride (0.3 g) and dimethyl sulphate (1.8 ml). The mixture was heated with stirring under nitrogen at 120-25° (oil-bath temperature) for 8 hr, cooled in ice and dil. ammonium hydroxide added to *p*H 8. It was then saturated with sodium chloride and extracted with methylene chloride. The oil obtained by the removal of solvent was chromatographed over silica gel (50 g). Elution with toluene yielded an oil which solidified on cooling and was crystallised from methylene chloride-ether-hexane to yield **10** (0.75 g), m.p. 83°; PMR (90 MHz, $CDCl_3$): δ 4.0 (3H, *s*, N-CH_3), 7.9 (1H, *s*, C-4 H); M^+ 161 (Found: C, 30.0; H, 2.7; N, 26.3. $C_4H_4ClN_3O_2$ requires C, 29.7; H, 2.5; N, 26.0%).

Elution with methylene chloride-toluene (1:1) yielded a solid which crystallised from methylene chloride-ether-hexane to give **7** (0.15 g), m.p. 156-58°, PMR (90 MHz, $CDCl_3$): δ 3.77 (3H, *s*, N-CH_3), 7.78 (1H, *s*, C-5H); (Found: C, 29.5; H, 2.9; N, 26.0. $C_4H_4ClN_3O_2$ requires C, 29.7; H, 2.5; N, 26.0%).

(b) To a solution of **6** (4 g) in methanol (50 ml) cooled in ice was added excess of an ethereal solution of diazomethane (prepared from 30 g nitrosomethyl urea) in ether. The solution was left at room temperature overnight and the solvent removed under reduced pressure. The residue was chromatographed over silica gel (50 g) as above to yield **10** (1.5 g), m.p. 81-83° and **7** (1 g), m.p. 156-58°, identical (m.p. and m.m.p.) with the samples prepared earlier.

1-*Methylsulphonyl*-3-(1-*methyl*-5-*nitro-imidazol*-2-*yl*)-2-*imidazolidinone* (**2**)—To sodium hydride (50%, 0.3 g) in DMF (10 ml) cooled in ice was added dropwise under nitrogen, a solution of 1-methanesulphonyl-imidazolidinone (0.9 g) in DMF (15 ml) during 5 min. The mixture was stirred at room temperature for 30 min, cooled in ice and treated with a solution of **10** (0.8 g) in DMF (10 ml). It was stirred at room temperature for 1 hr and at 55° for 3 hr and left overnight at room temperature. Acetic acid (0.2 ml) was added, the solvent removed *in vacuo*, the residue flushed with xylene and treated with ice and hexane (10 ml). The solid was filtered off, washed with water and hexane and crystallised from acetone-methanol to yield **2** (0.9 g), m.p. 186-88°; M^+ 289, identical (TLC, m.p. and m.m.p.) with an authentic sample prepared earlier[1].

1-*Methyl*-2,4-*dinitroimidazole* (**8**) *and* 1-*methyl*-2,5-*dinitroimidazole* (**11**)—(a) To a suspension of **5** (4.1 g) in THF (50 ml) was added excess of an ethereal solution of diazomethane at 0° and the mixture left overnight at 0°. The solvent was removed *in vacuo* and the residue chromatographed over silica gel (200 g). Elution with toluene gave an oil which solidified slowly and crystallised from ether to yield **11** (1 g), m.p. 81-83°; M^+ 172; ^{1}PMR (60 MHz, $CDCl_3$): δ 4.45 (3 H, *s*,

††mass units given for ^{35}Cl isotope for all chlorine containing compounds.

N-CH_3), 8.05 (1H, *s*, C-4H) (Found: C, 28.3; H, 2.5; N, 32.8. $C_4H_4N_4O_4$ requires C, 27.9; H, 2.3; N, 32.6%).

Elution with methylene chloride-toluene (1:1) yielded a solid which crystallised from methylene chloride-ether to give **8** (1.2 g), m.p. 144-46°; M^+ 172; ^{1}PMR (60 MHz, DMSO-d_6): δ 4.07 (3H, *s*, N-CH_3), 8.73 (1H, *s*, C-5H) (Found: C, 28.3; H, 2.6; N, 32.4. $C_4H_4N_4O_4$ requires C, 27.9; H, 2.3; N, 32.6%).

(b) A mixture of **5** (2 g), methyl iodide (3 g) and benzyl trimethylammonium chloride (0.5 g) in dioxan (50 ml) was heated in a glass sealed tube at 100° for 24 hr. The solvent was removed under reduced pressure and the residue treated with dry ether and filtered. Concentration of the ether filtrate yielded a solid which recrystallised from methylene chloride-ether to give **8** (0.5 g), m.p. 144-46°; M^+ 172, identical (m.p., m.m.p. and TLC) with a sample of **8** prepared above.

The residue from mother-liquor showed in the mass spectrum peaks for chloro and iodo derivatives. Chromatographic separation on silica gel afforded **7**, m.p. and mixed m.p. 155-58° and the corresponding iodo derivative, m.p. 205-10°, which was still contaminated with **7**.

Treatment of **8** *with* $POCl_3$: *Formation of* **7**—To a solution of **8** (1.7 g) in DMF (5 ml) cooled in cold water was added dropwise with stirring phosphorus oxychloride (2 ml). After the addition was over, the mixture was heated at 85° for 6 hr and left overnight at room temperature. The solvent was removed under reduced pressure, the residue flushed with xylene, treated with ice, the solid extracted with methylene chloride and crystallised from methylene chloride-ether to yield **7** (1.2 g), m.p. 151-54°; M^+ 161 (Found: C, 29.9; H, 2.8; N, 26.3. $C_4H_4ClN_3O_2$ requires C, 29.7; H, 2.5; N, 26.0%). It was identical (m.p., m.m.p., IR, NMR, MS) with an authentic sample.

1-*Methanesulphonyl*-3-(1-*methyl*-4-*nitro*-1*H*-*imidazol*-2-*yl*)-2-*imidazolidinone* (**14**)—To a suspension of sodium hydride (50%, 0.25 g) in DMF (5 ml) cooled to 0° was added dropwise a solution of 1-methanesulphonyl-2-imidazolidinone (0.8 g) in DMF (5 ml). The mixture was stirred at room temperature for 1 hr, cooled in ice and treated dropwise with a solution of **7** (0.8 g) in DMF (5 ml). The mixture was stirred at 0° for 1 hr, at room temperature for 30 min, the solvent removed under reduced pressure and the residue treated with ice. The gummy solid obtained was filtered off, washed with water and hexane and chromatographed over silica gel (50 g). Elution with methylene chloride yielded a solid which crystallised from acetone-methanol to give **14** (20 mg), m.p. 171-73°; identical (m.p., m.m.p. and TLC) with an authentic sample; M^+ 289 (Found: C, 32.4; H, 4.1; N, 24.2. $C_8H_{11}N_5O_5S$ requires C, 33.2; H, 3.8; N, 24.2%).

1-*Ethyl*-2,4-*dinitroimidazole* (**9**) *and* 1-*ethyl*-2,5-*dinitroimidazole* (**12**)—(a) To a suspension of **5** (5 g) in THF (50 ml) was added an excess of an ethereal solution of diazoethane (prepared from 25 g nitrosomethyl urea) at 0°. The solution was left at room temperature overnight, the solvent removed under reduced pressure and the residue chromatographed over silica gel (200 g). Elution with hexane yielded **15** as an oil (20 mg); M^+ 214; PMR (60 MHz, $CDCl_3$): δ 1.33 (3H, *t*, J=7.5 Hz, CH_3CH_2-C), 162 (3H, *t*, J =7.5 Hz, CH_3-CH_2-N), 3.05 (2H, *q*, J=7.5 Hz, $C-CH_2-CH_3$), 4.85 (2H, *q*, J=7.5 Hz, $N-CH_2-CH_3$).

Elution with toluene-hexane (1:1) yielded **12** again as an oil (0.9 g); M^+ 186; PMR (60 MHz, $CDCl_3$): δ 1.67 (3H, *t*, J=7.5 Hz, CH_3-CH_2), 4.98 (2H, *q*, J=7.5 Hz, CH_3-CH_2-), 8.08 (1H, *s*, C-4H). Further elution with toluene gave a solid, which crystallised from methylene chloride-ether to yield **9** (1.2 g), m.p. 84-86°; M^+ 186; PMR (60 MHz, $CDCl_3$): δ 1.7 (3H, *t*, J=7.5 Hz, CH_3-CH_2), 4.8 (2H, *q*, J=7.5 Hz, CH_2-CH_3), 8.37 (1H, *s*, C-5H) (Found: C, 32.6; H, 3.6; N, 30.2. $C_5H_6N_4O_4$ requires C, 32.3; H, 3.3; N, 30.1%).

(b) A mixture of **5** (3.2 g), triethyl orthoformate (50 ml) and trifluoroacetic acid (2 drops) was heated under reflux for 48 hr. The solvent was removed under reduced pressure, the residue flushed with xylene and chromatographed over silica gel (100 g). Elution with toluene-hexane (1:1) yielded **12** (300 mg), identical (TLC, PMR and MS) with a sample prepared by the previous method. Elution with toluene gave a solid which crystallised from methylene chloride-ether to yield **9** (2.6 g), m.p. 84-86°, identical (TLC, NMR, m.p. and m.m.p.) with the sample prepared earlier.

5-*Iodo*-1-*methyl*-4-*nitroimidazole* (**22**) and 4-iodo-1-methyl-5-nitroimidazole (**21**)—(a) The following experiment yielded **22** as the major and **21** as the minor product.

To a stirred solution of **19** (11.95 g) in 1*N* aq. sodium hydroxide (50 ml) was added dropwise at 60-70° (internal temperature) dimethyl sulphate (5.5 ml). After the addition, the reaction mixture was stirred at this temperature for 10-15 min, cooled to room temperature, the precipitate filtered, washed with water, dried and slurried with acetone (20 ml). The insoluble solid was filtered and recrystallised from DMF-water to yield **22** (8 g), m.p. 230-32°; M^+ 253; PMR (DMSO-d_6): δ 3.70 (N-Me, *s*), 8.10 (C-2H, *s*) (Found: C, 19.3; H, 1.9; N, 17.0. $C_4H_4IN_3O_2$ requires C, 19.0; H, 1.6; N, 16.6%).

The above acetone filtrate was evaporated *in vacuo* and the residue carefully chromatographed over silica gel (40 g). Elution with 2% methanolic chloroform gave a solid which recrystallised from 50% aq. ethanol to yield **21**, (0.6 g), m.p. 146-47°, identical (TLC, m.p. and

m.m.p.) with the major product **21** of method-b described below. Elution with 4% methanolic chloroform yielded 0.8 g of **22**.

(b) The following experiment yielded **21** as the major and **22** as the minor products.

A stirred mixture of **19** (23.9 g), dioxan (40 ml) and dimethyl sulphate (11 ml) was heated under reflux for 1 hr. After cooling, acetone (100 ml) was added and the reaction mixture stirred for 15-20 min, the precipitate filtered off treated with water (100 ml) and the insoluble solid filtered. The aqueous filtrate was neutralised with aq ammonium hydroxide solution under ice cooling, the precipitate filtered off, washed with water and recyrstallised from 50% aq. ethanol to yield **21** (11.3 g), m.p. 146-47°; M^+ 253; PMR (DMSO-d_6): δ 3.92 (N-Me, *s*), 8.00 (C-2H, *s*) (Found: C, 19.6; H, 1.9; N, 16.7. $C_4H_4IN_3O_2$ requires C, 19.0; H, 1.6; N, 16.6%).

TLC of both the above acetone filtrate and the water-insoluble solid showed the presence of **22** besides some **21**.

1-*Methyl*-5-*morpholino*-4-*nitroimidazole* (**24**)—A mixture of **22** (0.25 g) and morpholine (1 ml) was heated on a water-bath at 80° for 4 hr and left overnight at room temperature. The resulting gummy mass was triturated with water, the solid filtered and recrystallised from methylene chloride-ether to afford **24** (100 mg), m.p. 206-10°; M^+ 212; PMR (DMSO-d_6): δ 3.11 (4H, $N-CH_2$, *m*), 3.57 (3H, N−Me, *s*), 3.73 (4H, 2-CH_2, *m*), 7.62 (*C*-2*H*, *s*); PMR (90 MHz, $CDCl_3$): 3.18 (4H, $2N-CH_2$, *m*), 3.62 (1H, $N-CH_3$, *s*), 3.85 (4H, $2\times O-CH_2$, *m*), 7.29 (C-2H, *s*) (Found: C, 45.0; H, 5.9; N, 26.2. $C_8H_{12}N_4O_3$ requires C, 45.3; H, 5.7; N, 26.4%).

Compound **24** was identical (TLC, m.p. and m.m.p.) with an authentic sample obtained from the reaction of morpholine with the known 5-chloro-1-methyl-4-nitroimidazole (**23**).

1-*Methyl*-4-*morpholino*-5-*nitroimidazole* (**26**)—A mixture of **21** (0.25 g) and morpholine (1 ml) was heated on a water bath at 80° for 10 minutes. The reaction mixture was cooled and treated with ether (20 ml) and a few drops of water. The organic layer was evaporated *in vacuo* at room temperature, the residue triturated with ether, filtered and recrystallized from methylene chloride-hexane to yield **26** (100 mg), m.p. 118-20°; M^+ 212; PMR (DMSO-d_6): δ 3.41 (4H, $2N-CH_2$, *m*), 3.71 (4H, $2\times O-CH_2$, *m*), 3.84 (3H, $N-CH_3$, *s*), 7.85 (1H, *s*). PMR (90 MHz, $CDCl_3$); δ 3.53 (4H, $2N-CH_2$, *m*), 3.85 (4H, $2\times O-CH_2$, *m*), 3.94 (3H, $N-CH_3$, *s*); 7.27 (C-2H, *s*) (Found: C, 45.0; H, 5.9; N, 26.8. $C_8H_{12}N_4O_3$ requires C, 45.3; H, 5.7; N, 26.4%).

Compound **26** was identical (TLC, m.p. and m.m.p.) with an authentic sample obtained from the reaction of morpholine with the known 4-chloro-1-methyl-5-nitroimidazole (**25**).

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