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Nitroimidazoles: Part XV—1-Methyl-5-nitro-2-oxy (mercapto)imidazoles, 1-Methyl-5-nitroimidazole-2-methanol (carboxaldehyde & glyoxalic ester) Derivatives & 1-Substitutedalkyl 2-Methyl-5 & 4-nitroimidazoles†‡

V P ARYA, K NAGARAJAN* & S J SHENOY
CIBA-GEIGY Research Centre, Goregaon East, Bombay 400 063

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V P ARYA, K NAGARAJAN* & S J SHENOY
CIBA-GEIGY Research Centre, Goregaon East, Bombay 400 063

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Treatment of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**2**) with *p*-hydroxybenzaldehyde gives the aldehyde (**3a**) which is derivatised further to **3b-d**. Displacement reactions on **2** with other phenols affords **4a-c**. 1-Methyl-2-mercaptoimidazole (**5a**) is condensed with reactive halides to form sulphides **5b-e** which are nitrated further to lead to nitroimidazoles **6a-d** among which **6a** and **6d** undergo oxidation to form sulphone (**7a**) and sulphoxide (**8**) respectively; some nitroimidazolyl sulphides (**6e-h**) are also prepared from **2** by displacement with thiophenol salts. **6f** is further oxidised to **7b**. 1-Methyl-5-nitroimidazole-2-methanol (**9a**) is converted into sulphate esters (**9b** and **9c**), chloride (**9d**), urethanes (**10a-e**) and amines (**11a-c**). 1-Methyl-5-nitroimidazole-2-aldehyde (**12a**) is characterised as the hydrazones (**12b-f**) and the vinyl derivatives (**13a-f**) and (**14**). Reactions of 1-methyl-5-nitroimidazole (**15**) with ethoxalyl and oxalyl chlorides yield **16a** and **19** respectively. **16a** is further reacted with aminoguanidine to yield **18**. Metronidazole (**22a**) is transformed into the urethane (**22b**) and via the chloride (**22c**) into the bases (**22d-g**). Ornidazole (**23a**) likewise affords the amines (**23b** and **c**) while the isomer **24a** yields **24b-g**. Alkylation of the sodium salts of 4-nitro and 4-nitro-2-methylimidazole with 3-chloro-4-hydroxysulpholane (**25**) provides the 4-nitro derivatives (**26a**) and (**26b**). Reaction of 2-bromo-1-indanol with 2-methyl-4-nitroimidazole does not provide **28**, but **30**, for which a mechanism is proposed.

The major part of work on nitroimidazoles which has been reported in our earlier papers and which resulted in the discovery and development of the potent antiprotozoal agent, 1-methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone (**1**)[1] (Code No. C 10213-Go) has been concerned with the construction of nitroimidazoles with a functionalised N atom at position-2. In connection with various allied studies including structure-activity relationship deductions, we had occasion to prepare a large number of diverse nitroimidazoles belonging to the groups mentioned in the title. We describe below their synthesis under appropriate headings.

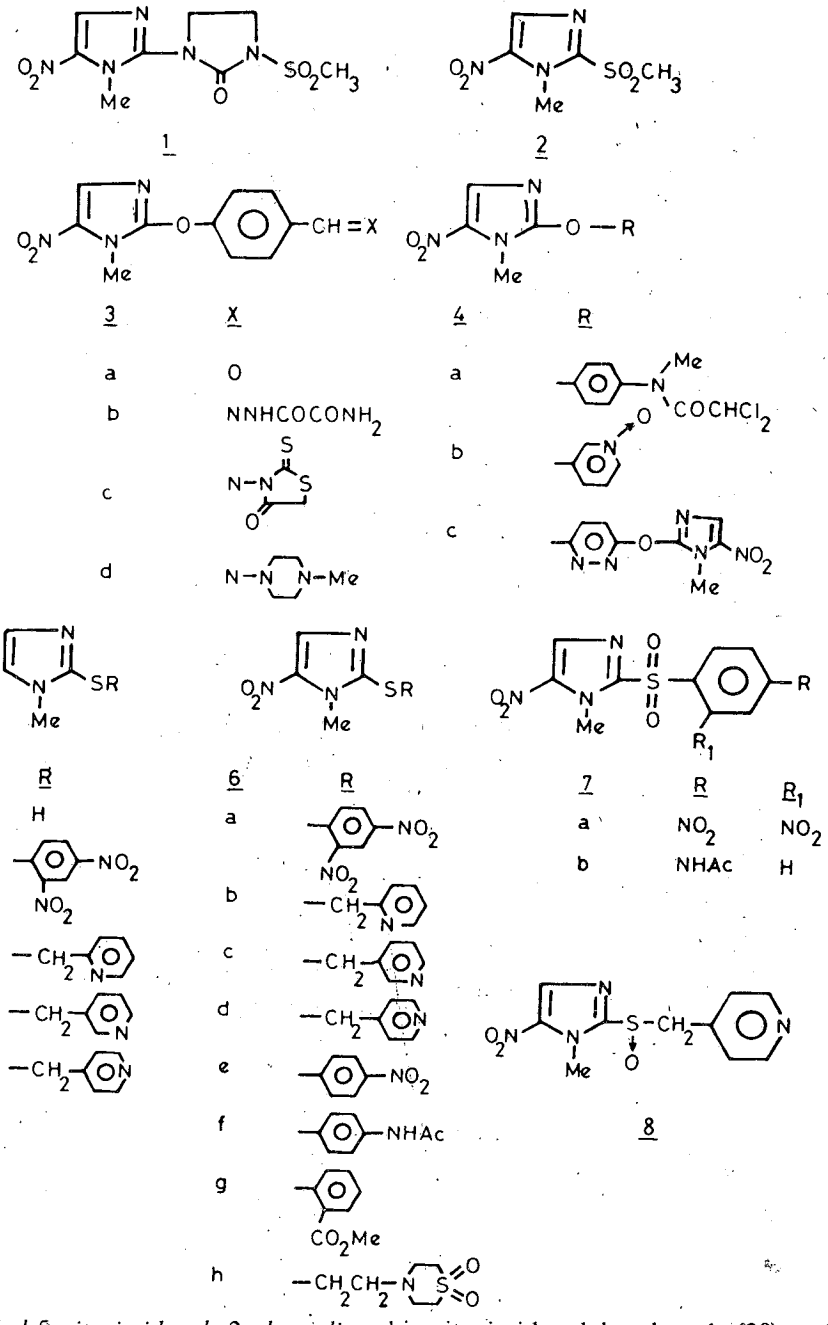
1-Methyl-2-oxy(mercapto)-5-nitroimidazoles—Reaction of the sulphone (**2**)[1] with the sodium salt of *p*-hydroxybenzaldehyde afforded **3a** which was further derivatised at the C=O terminal as hydrazones (**3b-d**). **2** and the sodium salt of the well-known amoebicide diloxanide[2] gave **4a** in satisfactory yield. **4b** was similarly obtained using 3-hydroxypyridine-N-oxide. 3,6-Dihydroxypyridazine underwent two-fold condensation to yield **4c**. A byproduct often obtained in these reactions was identified as 1-methyl-2-methylsulphonyl-5-(1-methyl-5-nitro-2-imidazolyl-oxy) imidazole which we had been encountered earlier[1].

The 2-mercapto derivatives **5b-5e** were prepared by the reaction of commercially available 1-methyl-2-mercaptoimidazole (**5a**) with a reactive halide. Nitration of the intermediates **5c** and **5d** gave the corresponding **6b** and **6c**. During such a nitration, **5b** was transformed into the sulphone (**7a**) and **5e** to the sulphoxide (**8**). The sodium salts of *p*-nitro- and *p*-acetamido-thiophenols, methylthiosalicylate and 4-(2-mercaptoethyl)thiamorpholine-1,1-dioxide displaced the sulphone group from **2** to afford **6e-h** respectively. Deliberate oxidation of **6f** gave **7b**.

Derivatives of 1-methyl-5-nitroimidazole-2-methanol (**9a**)—**9a**[3] was transformed into the sulphonates (**9b**) and (**9c**) and the urethanes (**10a-e**) by reaction with appropriate sulphonyl chlorides and isocyanates. These urethanes are analogues of the antibacterial, rhonidazole[4]. **9a** was also converted into the corresponding chloride **9d**[5] which was used for alkylating 4-aminopyridine while **9c** was reacted with 1-diethylcarbamoylpiperazine and 3-azabicyclo[3.2.2] nonane to afford **11a-c** respectively.

Derivatives of 1-methyl-5-nitroimidazole-2-carboxaldehyde (**12a**)—**12a**[5] was condensed with various hydrazides to form the derivatives (**12b-f**) and with compounds containing active methyl groups to form the vinyl derivatives (**13a-f**). Acetic anhydride used for the condensation caused acetylation of free NH groups. **14** resulted from the reaction of 1-acetyl-3-methylhydantoin with **12a**.

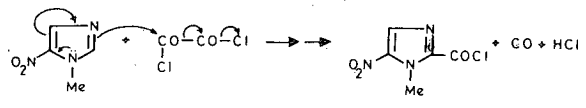
†Contribution No. 652 from CIBA-GEIGY Research Centre.
‡Part XIV: *Indian J Chem*, **21B** (1982) 1030.

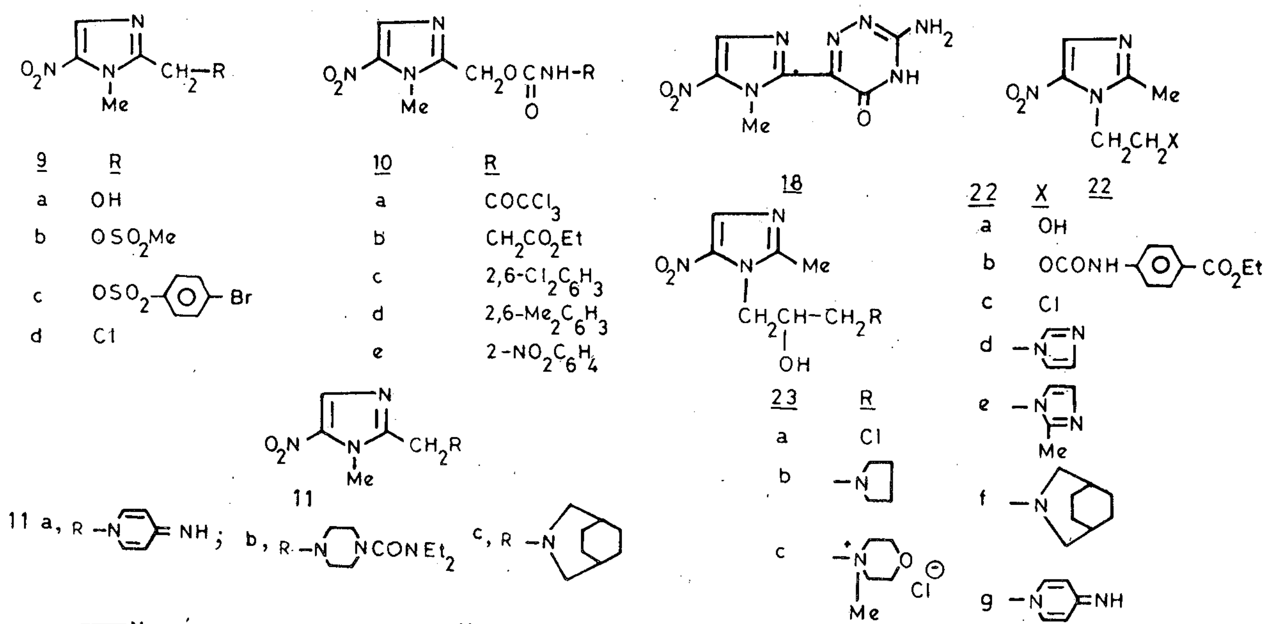


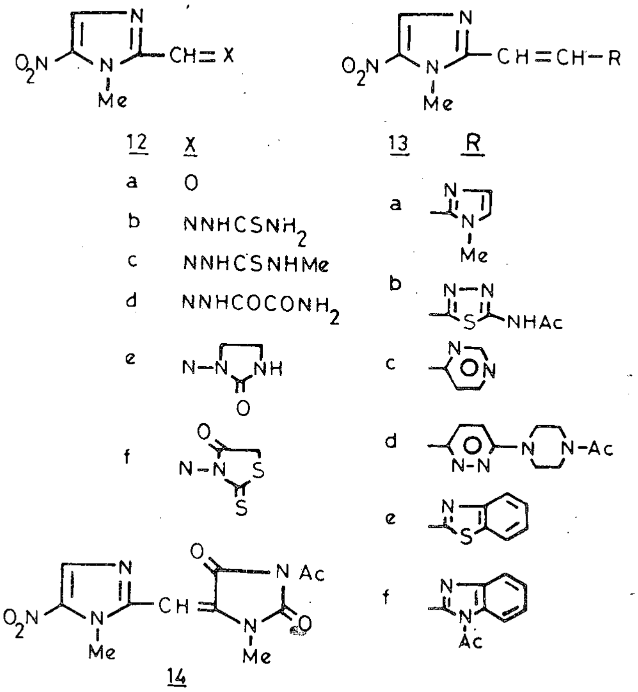
Derivatives of 1-*methyl-5-nitroimidazole-2-glyoxalic acid*—Treatment of 1-methyl-5-nitroimidazole (**15**) with ethoxalyl chloride gave the expected ester **16a**. Two other minor products were also isolated. One was identified as the formic acid salt of **15**, and the other, as the bis-nitroimidazole (**17a**) on the basis of analysis and spectral data (see Experimental). **17a** arises obviously by condensation of **16a** with a second molecule of **15** (Scheme 1). The genesis of formic acid in this experiment is not clear. **16a** was further transformed to the triazine (**18**) with aminoguanidine.

Oxalyl chloride and **15** gave the expected diketone **19** as the major product. Two byproducts were again encountered in this reaction. One was identified as the bis-nitroimidazolylmethanol (**20**) arising probably from the precursor **17b** (R = H). **17b** in turn could have been formed from **16b** (R = H), which might have been generated from the corresponding chloride, a primary product of reaction of **15** with oxalyl chloride. The second byproduct corresponded to the ester (**21**) which was perhaps formed during chromatography by the interaction of a susceptible intermediate** with methanol (Scheme 1).

**e.g. 1-methyl-5-nitroimidazole-2-carboxylic acid chloride is formed as follows:







1-*Substituted alkyl-2-methyl-5-nitroimidazoles*—Reaction of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (**22a**) (metronidazole) with ethyl *p*-isocyanobenzoate gave the urethane (**22b**). Metronidazole was also converted into the chloride **22c** which was reacted without purification with appropriate bases to afford aminoethyl derivatives (**22d-g**).

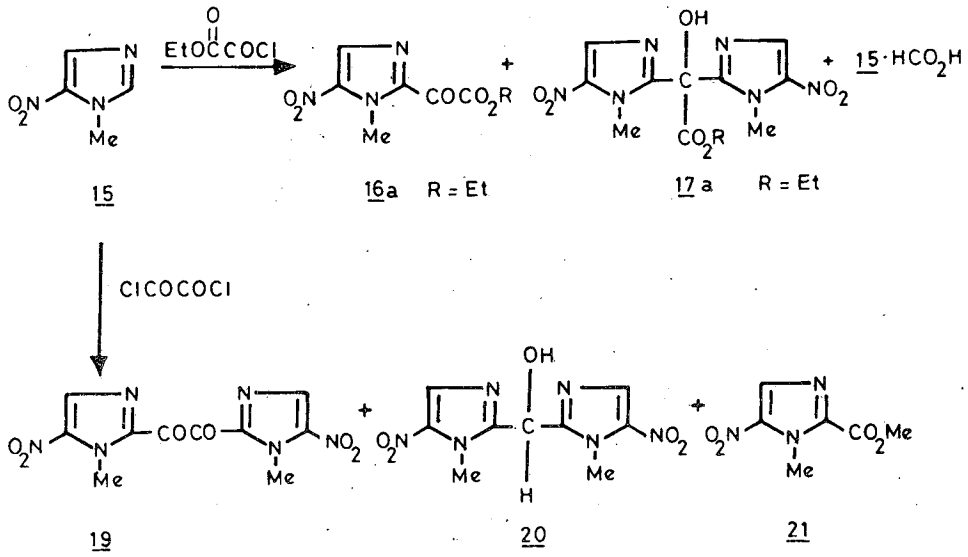
Substitution of the chlorine atom in ornidazole (**23a**) by pyrrolidine and N-methylmorpholine yielded **23b** and **23c** respectively.

1-*Substituted alkyl-2-methyl-4-nitroimidazoles*—Similar reactions of the isomer **24a**[6] with various bases gave **24b-g**.

Treatment of 4-nitroimidazole and 2-methyl-4-nitroimidazole with the sulpholane (**25**) under basic conditions led to the products **26a** and **26b**. These were formulated as the 4-nitro derivatives rather than the 5-nitro isomers, because of the alkaline reaction conditions. Further in the PMR spectra in DMSO-d_6, the imidazole protons appeared at very low fields (8.65 ppm in **26a** and 8.60 ppm in **26b**) indicating the correctness of the structural assignment[8]. The products are given *trans* geometry in view of expected participation of the $-$OH group in the reaction (epoxide formation; see Chart 1).

Alkylation of the sodium salt of 2-methyl-4-nitroimidazole with 2-bromo-1-indanol (**27**) led to an unexpected result. The PMR spectrum of the product in DMSO-d_6 displayed signals at δ 2.55 (3H, *s*, 2′ $-$Me), 2.75 (1H, $d \times d$, $J = 17$, 6.5 Hz, C$-$3H), 3.35 (1H, $d \times d$, $J = 17$, 6.5 Hz, C$-$3H), 4.58 (1H, *quintet*, $J = 6.5$ Hz, changing to a quartet, $J = 6.5$ Hz, on treatment with D_2O, C$-$2H), 5.6 (1H, *d*, $J = 6.5$ Hz, C$-$1H), 5.80 (1H, *d*, $J = 6.5$ Hz, disappearing with D_2O, OH), 7.1 (1H, *m*, C$-$7H), 7.30 (3H, *m*, at C-4, C-5, C-6) and 7.83 (1H, *s*, C-5′H). The conversion of the quintet at 4.58 ppm to a quartet upon deuteration of the OH at 5.80 identifies it as the α-proton. The multiplicity of this signal as well as the doublet nature of the second methine proton at 5.60 ppm rule out the expected structure **28** in favour of **30**. The assignments of various proton signals are consistent with this proposal. The formation of **30** from **27** must be mediated by the formation of the epoxide **29** and its subsequent opening by attack at the benzylic carbon atom.

However, another source of structural ambiguity had to be considered. The alkaline conditions of the



Scheme 1

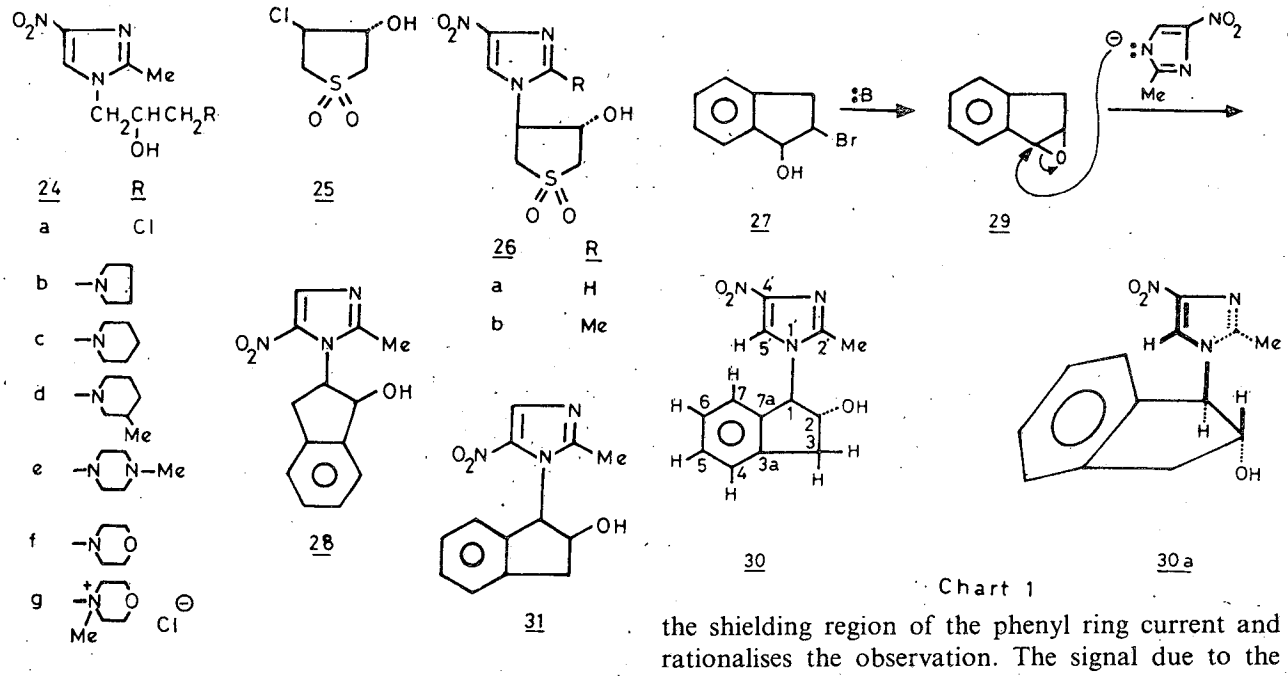


Chart 1

above reaction would almost certainly produce a 4-nitroimidazole derivative[8]. But in the DMSO-d_6 spectrum, the nitroimidazole proton appeared at δ 7.83 which was at a higher field compared to that expected for C-5H in similar molecules ($\geq$8.2), and seemed to correspond to values found for C-4H in 5-nitroimidazoles. Thus it became obligatory to consider structure **31** for the product. The PMR spectrum was rerun in $CDCl_3$ and the imidazole proton appeared at δ 7.43 giving rise to a $\Delta\delta$ (DMSO-d_6-$CDCl_3$) of 0.40 ppm[8], which is definitely supportive of structure **30** and rules out **31**. It is obvious that in the PMR spectrum (in both the solvents), C-5H is being shielded considerably (~0.5 ppm). Depiction of the stereo-structure of **30** as **30a** places the imidazole proton in the shielding region of the phenyl ring current and rationalises the observation. The signal due to the methyl protons has a normal chemical shift as required. The *trans*-geometry is dictated by the mechanism postulated. The study emphasises the potential pitfalls in the use of chemical shifts alone in structure assignments of nitroimidazoles and the significance of $\Delta\delta$ values in such exercises[8].

^{13}C NMR data were additionally invoked in support of structure (**30**). The compound exhibited signals at 146.0 (*m*, C-2′), 140.1, 138.0 (*m*, C-3a, C-7a), 129.0, 127.4, 125.3, 123.9 (C-4, C-5, C-6, C-7)[§], 119.1 (*d* × *d*, $^1J_{CH}$ = 200.5 Hz, $^3J_{CH}$ = 4.6 Hz, C-5; C-5′ signal was easily recognised by virtue of its large $^1J_{CH}$), 79.3

[§]All signals were large doublets ($^1J_{CH}$ ~ 165 Hz), split further into broadened doublets (J 4-8 Hz). Individual assignments were not attempted.

(broad *d*, C-1), 68.8 (broad *d*, C-2), 38.5 (*t*, C-3) and 13.2 (*q*, CH_3). The chemical shift of the proton-bearing imidazole carbon atom and the multiplicity of its signal clearly conform to the requirements of structure **30a**[8]. **31** is ruled out since δ for its C-4 would be expected to be around 131 ppm and only a single one bond coupling would be observed.

Experimental Procedure

4-(1-Methyl-5-nitro-2-imidazolyloxy)benzaldehyde (**3a**)—To a suspension of NaH (50%, 4.8 g) in DMF (20 ml) was added dropwise under stirring and cooling (10-15°), a solution of *p*-hydroxybenzaldehyde (12.2 g) in DMF (30 ml). After the addition, the reaction mixture was stirred at room temperature for 1 hr after which a solution of **2** (20.5 g) in DMF (30 ml) was added and the mixture heated for 2 hr at 100°. The solvent was removed under reduced pressure, the residue treated with water (30 ml) and extracted with methylene chloride. The methylene chloride extract was evaporated *in vacuo* and the gummy residue filtered through silica gel column using chloroform-methanol (98:2) as a eluent to afford **3a** (Table 1).

N-[4-(1-Methyl-5-nitro-2-imidazolyloxy) benzylidene imino]oxamide (**3b**)—A mixture of **3a** (2.5 g) and N-aminooxamide (1.05 g) in ethanol (20 ml) was heated

Table 1—Nitroimidazoles

Compd.	Yield (%)	Solvent of crystallisation	m.p. °C	Mol. formula	Calc. (%)			Found (%)		
					C	H	N	C	H	N
3a	45	CH_2Cl_2-Et_2O	118	$C_{11}H_9N_3O_4$	53.44	3.67	17.00	53.38	3.58	17.34
3b	80	DMF-MeOH	299-300(d)	$C_{13}H_{12}N_6O_5$	46.99	3.64	25.30	46.53	3.99	24.80
3c	40	MeOH-CH_2Cl_2	215.7	$C_{14}H_{11}N_5O_4S_2$	44.57	2.94	18.56	44.84	3.07	18.67
3d	80	CH_2Cl_2-hexane	182-83	$C_{16}H_{20}N_6O_3$	55.80	5.85	24.41	55.82	6.16	24.18
4a	76	Benzene-hexane	150-51	$C_{13}H_{12}Cl_2N_4O_4$	43.47	3.37	15.60	44.80	4.00	15.50
4b	20	CH_3CN-Et_2O	182-83	$C_9H_8N_4O_4$	45.76	3.41	23.72	45.43	3.55	23.95
4c	18	CH_3CN-Et_2O	185-90	$C_{12}H_{10}N_8O_6$	39.78	2.78	30.93	39.36	3.30	30.93
6b	15	CH_2Cl_2-hexane	153	$C_{10}H_{10}N_4O_2S$	48.00	4.02	22.39	48.45	4.28	22.61
6c.HCl	45	MeOH-EtOAc	195-98	$C_{10}H_{10}N_4O_2S.HCl$	41.89	3.87	19.55	42.23	3.56	19.24
6e	15	CH_2Cl_2-Et_2O	106	$C_{10}H_8N_4O_4S$	42.86	2.88	20.00	43.13	3.22	20.04
6f	30	CH_2Cl_2-Et_2O	202	$C_{12}H_{12}N_4O_3S$	49.31	4.14	19.17	49.30	4.21	19.29
6g	60	CH_3CN	156-57	$C_{12}H_{11}N_3O_4S$	49.15	3.78	14.33	49.52	4.12	14.00
6h	12	-do-	155-56	$C_{10}H_{16}N_4O_4S_2$	37.50	5.04	17.50	37.80	5.12	17.73
7a	43	MeOH	195	$C_{10}H_7N_5O_8S$	33.62	1.98	19.61	33.75	2.60	20.17
7b	90	CH_2Cl_2-MeOH	252(d)	$C_{12}H_{12}N_4O_5S$	44.45	3.73	17.28	44.27	3.67	17.64
8.HCl	35	MeOH-EtOAc	213-15	$C_{10}H_{10}N_4O_3S.HCl$	39.68	3.66	18.44	39.91	4.09	18.01
9b	35	CH_2Cl_2-hexane	60	$C_6H_9N_3O_5S$	30.64	3.86	17.87	30.61	3.72	17.92
9c	35	-do-	213	$C_{11}H_{10}BrN_3O_5S$	35.12	2.68	11.17	35.48	2.47	10.83
10a	95	MeOH	195	$C_8H_7Cl_3N_4O_5$	27.81	2.04	16.22	28.51	2.35	16.57
10b	80	CH_2Cl_2-hexane	100	$C_{10}H_{14}N_4O_6$	41.96	4.93	19.58	41.90	5.22	19.88
10c	69	-do-	138	$C_{12}H_{10}Cl_2N_4O_4$	41.75	2.92	16.23	42.05	3.17	16.41
10d	55	-do-	108	$C_{14}H_{16}N_4O_4$	55.25	5.30	18.41	55.21	5.15	18.64
10e	45	CH_2Cl_2-hexane	126-28	$C_{12}H_{11}N_5O_6$	44.86	3.45	21.80	44.42	3.13	22.37
11a.HCl	41	MeOH	275	$C_{10}H_{11}N_5O_2.HCl$	44.53	4.48	25.97	44.52	4.80	26.12
11b.HCl	30	CH_3OH-EtOAc	248-50	$C_{14}H_{24}N_6O_3.HCl$	46.50	6.98	23.29	46.83	7.03	23.53
11c	38	CH_2Cl_2-hexane	120	$C_{13}H_{20}N_4O_2$	59.07	7.63	21.20	59.06	7.90	21.16
12b	52	DMF-Et_2O	253(d)	$C_6H_8N_6O_2S$	31.58	3.53	36.84	31.83	3.81	37.09
12c	90	CH_2Cl_2-hexane	225	$C_7H_{10}N_6O_2S$	34.71	4.16	34.70	34.99	4.44	34.82
12d	75	MeOH-Et_2O	294(d)	$C_7H_8N_6O_4$	35.00	3.36	34.99	35.41	3.81	34.99
12e	80	DMF-Et_2O	298(d)	$C_8H_{10}N_6O_3$	40.33	4.23	35.28	40.42	4.49	34.98
12f	50	-do-	250(d)	$C_8H_7N_5O_3S_2$	33.69	2.47	24.56	34.00	2.68	24.26
13a	22	-do-	275(d)	$C_{10}H_{11}N_5O_2$	51.49	4.75	30.03	51.10	5.18	30.12
13b	40	-do-	330(d)	$C_{10}H_{10}N_6O_3S$	40.82	3.43	28.56	40.90	3.28	28.36
13c	21	CH_2Cl_2-Et_2O	194-95	$C_{10}H_9N_5O_2$	51.94	3.92	30.29	50.92	4.04	30.05
13d	25	MeOH	293-94(d)	$C_{16}H_{19}N_7O_3$	53.77	5.36	27.44	53.68	5.64	27.54
13e	38	DMF-Et_2O	272(d)	$C_{13}H_{10}N_4O_2S$	54.55	3.52	19.58	54.44	3.88	19.73
13f	45	-do-	254(d)	$C_{15}H_{13}N_5O_3$	57.87	4.21	22.50	57.62	4.60	22.12
14	48	-do-	> 300	$C_{11}H_{11}N_5O_5$	45.05	3.78	23.88	45.10	4.21	24.20
16a	36	CH_2Cl_2-hexane	57	$C_8H_9N_3O_5$	42.29	3.99	18.50	42.56	4.22	18.91
18	30	MeOH	> 300	$C_7H_7N_7O_3$	35.45	2.97	41.34	35.84	3.31	41.55

(Contd.)

Table 1—Nitroimidazoles—(*Contd.*)

Compd.	Yield (%)	Solvent of crystallisation	m.p. °C	Mol. formula	Calc. (%)			Found (%)		
					C	H	N	C	H	N
19	10	CH_2Cl_2-Et_2O	188	$C_{10}H_8N_6O_6$	38.97	2.62	27.27	38.98	2.87	27.58
22b	65	MeOH-Et_2O	190-95	$C_{16}H_{18}N_4O_6$	53.03	5.01	15.46	53.42	5.30	15.75
22d	30	EtOAc	171	$C_9H_{11}N_5O_2$	48.86	5.01	31.66	48.99	5.37	31.66
22e	35	MeOH-Et_2O	153	$C_{10}H_{13}N_5O_2.H_2O$	47.42	5.97	27.66	47.41	6.31	27.26
22f.HCl	45	MeOH-EtOAc	243-44	$C_{14}H_{22}N_4O_2.HCl$	53.41	7.36	17.80	53.41	7.60	17.41
22g.HCl	42	IPA-EtOAc	174-75	$C_{11}H_{13}N_5O_2.HCl$	46.56	4.97	24.69	46.70	5.30	25.06
23b.HCl	15	MeOH-EtOAc	220-21	$C_{11}H_{18}N_4O_3.2HCl$	40.37	6.16	17.12	40.34	6.22	17.46
23c	40	-do-	236-38	$(C_{12}H_{21}N_4O_4)^+Cl^-$	44.93	6.60	17.47	44.81	6.89	17.48
24b. Maleate	27	-do-	143-45	$C_{11}H_{18}N_4O_3.C_4H_4O_4$	48.64	5.99	15.13	48.96	6.14	14.97
24c Maleate	73	-do-	160-62	$C_{12}H_{20}N_4O_3.C_4H_4O_4$	49.99	6.29	14.58	50.04	6.25	14.50
24d Maleate	58	-do-	141-42	$C_{13}H_{22}N_4O_3.C_4H_4O_4$	51.25	6.58	14.06	51.44	6.87	14.13
24e Tris-maleate	32	-do-	160-61	$C_{12}H_{21}N_5O_3.3C_4H_4O_4$	45.64	5.27	11.09	46.53	6.02	11.01
24f Maleate	35	-do-	175-76	$C_{11}H_{18}N_4O_4.C_4H_4O_4$	46.63	5.74	14.50	46.79	6.06	14.17
24g	26	-do-	144-45	$(C_{12}H_{21}N_4O_4)^+Cl^-$	44.93	6.60	17.47	44.66	6.80	17.66
26a	24	DMF-MeOH	255	$C_7H_9N_3O_5S$	34.01	3.67	17.00	34.31	3.67	17.19
26b	20	DMF-Et_2O	282	$C_8H_{11}N_3O_5S$	36.7	4.25	16.09	37.21	4.69	16.49
30	11	MeOH	210-11	$C_{13}H_{13}N_3O_3$	60.22	5.05	16.21	60.52	5.33	16.35

under reflux for 4 hr. The solution on concentrating *in vacuo* gave **3b** as a crystalline solid. **3b** and other hydrazones are listed in Table 1.

3-(1-*Methyl*-5-*nitro*-*imidazolyloxy*)*pyridine-N-oxide* (**4b**)—**4b** was obtained from **2** (20.5 g) and 3-hydroxypyridine-N-oxide (11.1 g) in the manner described for **3a**. The mother liquor of **4b** on evaporation of the solvent *in vacuo* and chromatography over silica gel using chloroform-methanol (95:5) gave besides some **4b**, a byproduct which was identified as 1-methyl-2-methylsulphonyl-5-(1-methyl-5-nitroimidazolyloxy)imidazole[1] (methylene chloride-ether) (0.7 g), m.p. 218-20°; M^+ 301 (Found: C, 36.2; H, 3.8; N, 22.9; S, 10.6. $C_9H_{11}N_5O_5S$ requires C, 35.9; H, 3.7; N, 23.8; S, 10.6%). **4a** and **4c** were similarly prepared.

Physical data for **4a-c** are presented in Table 1.

1-*Methyl*-2-(2,4-*dinitrophenylmercapto*)*imidazole* (**5b**)—To a solution of **5a** (5.7 g) in ethanol (20 ml) was added an ethanolic solution (20 ml) of 2,4-dinitrochlorobenzene (10.15 g) and the mixture heated under reflux for 16-18 hr. The solution was cooled, the solid filtered and washed with ethyl acetate to give crude **5b**.HCl. The base was liberated by heating a suspension of **5b**.HCl in methanol with triethylamine (1 equiv.) for 20-30 min. The solvent was evaporated off, the residue treated with water and the base extracted into methylene chloride. Removal of the solvent *in vacuo* and crystallisation of the residue from methylene chloride-hexane afforded **5b** in 70% yield; m.p. 165° (Found: C, 42.6; H, 3.1; N, 20.1. $C_{10}H_8N_4O_4S$ requires C, 42.9; H, 2.9; N, 20.0%).

1-*Methyl*-2-(*α-picolylmercapto*)*imidazole* (**5c**)—A mixture of **5a** (11.4 g) and 2-chloromethylpyridine hydrochloride (16.3 g) in methoxyethanol (95 ml) was heated under reflux for 16 hr. The solvent was evaporated off, the residue dissolved in water, basified with aq. sodium carbonate and extracted with methylene chloride. The methylene chloride solution was evaporated *in vacuo* and the residue filtered through neutral alumina column using toluene as the eluent. The eluate was evaporated under reduced pressure to afford **5c** as an oil in 60% yield. A small portion was converted into the hydrochloride salt which recrystallised from methanol-ethyl acetate; m.p. 233°(d) (Found: C, 43.5; H, 5.3; N, 14.9. $C_{10}H_{11}N_3S.2HCl$ requires C, 43.2; H, 4.7; N, 15.1%).

1-*Methyl*-2-(*β-picolylmercapto*)*imidazole* (**5d**)—**5d** was obtained in 58% yield from **5a** and 3-chloromethylpyridine hydrochloride in the manner described for **5c**. The hydrochloride salt was recrystallised from methanol-ether, m.p. 88-90° (Found: C, 40.1; H, 5.9; N, 13.8. $C_{10}H_{11}N_3S.2HCl.H_2O$ requires C, 40.6; H, 5.7; N, 14.2%).

1-*Methyl*-2-(*γ-picolylmercapto*)*imidazole* (**5e**)—**5e** was obtained as an oil in 60% yield from **5a** and 4-chloromethylpyridine hydrochloride by the method described for **5c**. A small portion was converted into the hydrochloride which recrystallised from methanol-ethyl acetate, m.p. 190° (Found: C, 43.2; H, 5.1; N,

15.1. $C_{10}H_{11}N_3S$. 2HCl requires C, 43.2; H, 4.7; N, 15.1%).

1-*Methyl-5-nitro-2-(2-pyridylmethylmercapto) imidazole* (**6b**)—To **5c** (30 g) was added dropwise under stirring, nitric acid (75 ml, $d=1.42$) keeping the temperature between 35 and 40°. After the addition, the temperature of the mixture was slowly increased to 100° and maintained there for 1 hr. The reaction mixture was then cooled at room temperature, ice (50 g) added and the solution neutralised under cooling with 50% aq. sodium hydroxide. The solid was filtered off, washed with ice cold water and recrystallised from methylene chloride-hexane to afford **6b**.

Similarly **6c** was prepared by nitrating **5d**. Compounds **6b** and **6c** are reported in Table 1.

1-*Methyl-5-nitro-2-(4-nitrophenylmercapto) imidazole* (**6e**)—**6e** was obtained from **2** and *p*-nitrothiophenol in the manner described for **3a**.

Similarly **6f-h** were obtained by the reaction of **2** with appropriate mercapto compounds.

Data for **6e-h** are given in Table 1.

2-(2,4-*Dinitrophenylsulphonyl*)-1-*methyl-5-nitro-imidazole* (**7a**)—To nitric acid (30 ml; $d=1.42$) was added portionwise under stirring **5b** (14 g), the temperature of the reaction mixture being kept between 30 and 35°. After the addition, the reaction mixture was heated at 100° for 1 hr, H_2SO_4 (5 ml) added dropwise and the heating continued for additional 1 hr. The reaction mixture was cooled under ice; 15-20 g ice were added and the solution neutralised with 50% aq. sodium hydroxide. The solid was filtered off and recrystallised from methanol-methylene chloride to give **7a** (Table 1).

2-(4-*Acetamidophenylsulphonyl*)-1-*methyl-5-nitro-imidazole* (**7b**)—To a solution of **6f** (2.9 g) in DMF (25 ml) was added dropwise under cooling (10-15°) and stirring, a solution of *m*-chloroperbenzoic acid (5.2 g) in methylene chloride during 30 min. The reaction mixture was stirred at 15-20° for 3-4 hr and then at room temperature overnight. The mixture was heated under reflux for 1 hr, cooled to room temperature and excess of *m*-chlorobenzoic acid decomposed with 10% aq. sodium bisulphite until a drop of the reaction mixture produced no instant purple colour on starch iodide paper. The solvent was evaporated off, the residue taken up in methylene chloride, treated with saturated aq. sodium bicarbonate and stirred for 30 min until free from acid. The insoluble solid was filtered off, the methylene chloride layer separated from the filtrate and evaporated *in vacuo* to get a solid which was mixed with the above insoluble solid and recrystallised from methylene chloride containing a few drops of methanol to afford **7b** (Table 1).

1-*Methyl-5-nitro-2-(4-pyridylmethyl mercapto) imidazole-S-oxide* (**8**) *hydrochloride*—The sulphoxide (**8**) was formed by the action of nitric acid on **5e** under the conditions used for **6b** and characterised as the hydrochloride (Table 1).

2-(*Methanesulphonyloxymethyl*)-1-*methyl-5-nitro-imidazole* (**9b**)—To a mixture of **9a** (4.8 g) and triethylamine (3.3 g) in dioxane (40 ml) was added dropwise under stirring and cooling a solution of methanesulphonyl chloride (3.5 g) in dioxane (20 ml) during 1 hr. The reaction mixture was stirred at room temperature overnight and then refluxed for 1 hr. The solvent was evaporated off, the residue triturated with water and extracted with ethyl acetate. Removal of the solvent *in vacuo* and crystallisation of the residue from methylene chloride-hexane afforded **9b**.

Similarly, **9c** was prepared from **9a** and *p*-bromotoluenesulphonyl chloride. Physical properties of **9b** and **9c** are reported in Table 1.

2-(2,6-*Dichlorophenylcarbamoyloxy*)*methyl*-1-*methyl-5-nitroimidazole* (**10c**)—To a solution of **9a** (3.05 g) in dry dioxane (20 ml was added dropwise under stirring and cooling a solution of 2,6-dichlorophenyl isocyanate (3.8 g) in dry dioxane (20 ml). After the addition, the reaction mixture was stirred at room temperature for 1 hr and then heated under reflux for 1 hr. The solvent was evaporated off and the residue crystallised from methylene chloride-hexane to afford **10c**.

Compounds **10a-e** are listed in Table 1.

2-(4-*Imino*-1,4-*dihydropyridyl*-1-*methyl*)-1-*methyl-5-nitroimidazole* (**11a**)—A mixture of 1-methyl-2-chloromethyl-5-nitroimidazole (**9d**)[5] hydrochloride (10.6 g) and 4-aminopyridine (9.4 g) in ethanol (100 ml) was heated under reflux for 16 hr. The solvent was evaporated *in vacuo*, the residue triturated with water and ether, the solid filtered off and crystallised from methanol to afford **11a** hydrochloride (Table 1).

1-(1-*Methyl-5-nitro-imidazol-2-yl*)*methyl*-4-(*diethyl-carbamoyl*) *piperazine hydrochloride* (**11b**) *and* 2-{3-(3-*azabicyclo*[3,2,2]*nonylmethyl*)}-1-*methyl-5-nitro-imidazole* (**11c**)—A mixture of **9c** (18.5 g) and diethylcarbamoylpiperazine (37.6 g) in dioxane (100 ml) was heated under reflux for 20 hr. The solvent was evaporated off, the residue treated with water and extracted with ethyl acetate. The ethyl acetate extract was evaporated *in vacuo* and the residue converted into hydrochloride salt, which recrystallised from methanol-ethyl acetate to afford **11b**. Similarly **11c** was prepared from **9c** and azabicyclo [3,2,2] nonane. Physical data of **11b** and **11c** are presented in Table 1.

1-*Methyl-5-nitroimidazole-2-carboxaldehyde thio-semicarbazone* (**12b**)—A solution of **12a** (2.3 g) in ethanol (30 ml) was mixed with a solution of thiosemicarbazide (1.4 g) in 10% aq. acetic acid (50 ml) and the mixture heated under reflux for 4 hr. On leaving the reaction mixture overnight at room

temperature, a crystalline solid separated out, which was filtered off and recrystallised from DMF-ether to afford **12b** (Table 1).

Physical data of compounds **12b-d** and **12f** are listed in Table 1.

N-(2-Oxo-1-imidazolidino)-1-methyl-5-nitroimidazole-2-carboxaldehyde-imine (**12e**)—A mixture of **12a** (1.6 g) and N-aminorhodanine (1.5 g) in ethanol (90 ml) was boiled under reflux for 4 hr and left overnight at room temperature when **12e** separated out as a crystalline solid (Table 1).

1-(1-Methyl-5-nitroimidazo-2-yl)-2-(1-acetylbenzimidazol-2-yl)-ethylene (**13f**)—A mixture of **12a** (3.1 g) and 2-methylbenzimidazole (2.6 g) in acetic anhydride (30 ml) was heated under reflux for 8 hr and left overnight at room temperature to obtain **13f** as crystalline solid. Compounds **13a-e** and **14** were prepared similarly (Table 1).

Ethyl(1-methyl-5-nitroimidazol-2-yl)glyoxalate (**16a**)—To a solution of **15** (12.7 g) and triethylamine (10.1 g) in dry acetonitrile (100 ml) was added dropwise at 0°, ethyl oxalyl chloride (14 g). After the addition, the reaction mixture was stirred overnight at room temperature. The insoluble solid was filtered off, the filtrate evaporated and the gummy residue chromatographed over silica gel. Elution with chloroform gave **16a** (Table 1) as a gum which solidified on chilling under ice-salt mixture. Fractions with $CHCl_3$ – MeOH (98:2) gave **17a** (CH_2Cl_2-ether) (1 g), m.p. 208-10°; M^+ 354 and a prominent fragment at *m/z* 281 ($M^+ - CO_2Et$); PMR ($CDCl_3$ + DMSO-d_6): δ 7.90 (2H, *s*, C-4H and C-4'H), 4.2 (2H, *q*, CO_2CH_2), 3.95 (6H, *s*, 2N-Me), 1.33 (3H, *t*, CH_2CH_3); IR (nujol): 3500 (νOH), 1740 cm^{-1} (νC=O) (Found: C, 40.8; H, 4.2; N, 24.3. $C_{12}H_{14}N_6O_7$ requires C, 40.7; H, 4.0; N, 23.8%). (A similar product has been obtained earlier from the reaction of **15** with methoxalyl chloride[9]).

Further elution with $CHCl_3$ – MeOH (95:5) yielded **15** formic acid salt (CH_3OH – EtOAc) (0.8 g), m.p. 120-22°; M^+ 127 (Found: C, 34.5; H, 4.0; N, 23.7. $C_4H_5N_3O_2.HCO_2H$ requires C, 34.7; H, 4.1; N, 24.3%).

6-Amino-4,5-dihydro-3-(1-methyl-5-nitro-imidazol-2-yl)-4-oxo-1,2,4-triazine (**18**)—A mixture of **15** (16.8 g) and aminoguanidine hydrochloride (4.7 g) in ethanol (150 ml) was heated under reflux for 4 hr. The solvent was removed under reduced pressure, the gummy residue dissolved in methanol and heated under reflux with triethylamine (1 equiv.) for 20-30 min. Removal of the solvent and trituration of the residue with water gave a solid which was warmed with methanol and filtered off to afford **18** (Table 1).

1,2-Bis(1-methyl-5-nitro-2-imidazolyl)glyoxal (**19**)—**15** (28 g) was reacted with oxalyl chloride (14 g) in the manner described for **16**. The crude residue obtained after the removal of solvent was chromatographed over silica gel using $CHCl_3$ – MeOH (97:3) as the eluent. The products obtained are given below in the same order as they were eluted; **19** (see Table 1).

21 (CH_2Cl_2-ether), 0.2 g; m.p. 110-12° (lit.[10] m.p. 108-10°); M^+ 185, fragments at *m/z* 154 ($M^+ - OMe$), 127 ($MH^+ - CO_2Me$). (Found: C, 39.4; H, 4.1; N, 22.9. $C_6H_7N_3O_4$ requires C, 38.9; H, 3.8; N, 22.7%).

20 (CH_2Cl_2-ether), 0.7 g; m.p. 191-93°; M^+ 282 (Found: C, 37.5; H, 4.0; N, 29.2. $C_9H_{10}N_6O_5$ requires C, 38.3; H, 3.6; N, 29.8%).

1-[β-(4-Carboethoxyphenylcarbamoyloxy)ethyl]-2-methyl-5-nitroimidazole (**22b**)—To a solution of **22a** (5.13 g) in dry dioxane (60 ml) was added dropwise under stirring a solution of ethyl *p*-isocyanobenzoate (5.7 g) in dry dioxane (50 ml). After the addition, the mixture was heated under reflux for 3 hr. Removal of the solvent and trituration of the residue with dry ether yielded **22b** (Table 1).

1-[2-(1-Imidazolyl)-1-ethyl]-2-methyl-5-nitroimidazole (**22d**)—Thionyl chloride (21.5 ml) was added slowly to a solution of **22a** (8.6 g) in chloroform (50 ml) and the mixture heated under reflux for 1 hr. The residue (**22c**) obtained after the removal of solvent and flushing with toluene was dissolved in DMF (80 ml), mixed with imidazole and the mixture heated at 120° for 20 hr. The solvent was removed under reduced pressure and the residue extracted with ethyl acetate. The ethyl acetate extract was evaporated *in vacuo* and the residue crystallised from the same solvent to afford **22d** (Table 1). Compounds **22e-g** were similarly prepared by reacting **22c** with appropriate bases.

1-[2-Hydroxy-3-(N-pyrrolidino)-1-n-propyl]-2-methyl-5-nitroimidazole dihydrochloride (**23b**)—A mixture of **23a** (3 g) and pyrrolidine (3 g), in ethanol (30 ml) was heated under reflux for 8 hr. The residue obtained after the removal of solvent was triturated with water and extracted with ethyl acetate. The ethyl acetate extract was evaporated *in vacuo*, the gum obtained dissolved in ether and treated with isopropanolic HCl to obtain **23b** as dihydrochloride salt (Table 1).

1-[2-Hydroxy-3-(N-methyl-N-morpholinium)-1-n-propyl]-2-methyl-5-nitroimidazole chloride (**23c**)—A mixture of **23a** (2 g) and N-methylmorpholine (8 ml) was heated under reflux for 2 hr. The reaction mixture was cooled, ether was added and the solid was filtered off to afford **23c** (Table 1).

1-(3-Hydroxy-4-sulpholanyl)-4-nitroimidazole (**26a**)—It was prepared by the method described for **3a** by heating a mixture of the sodium salt of 4(5)-nitroimidazole and 3-chloro-4-hydroxysulpholane in DMF at 130° for 18 hr. The solution was filtered, the filtrate evaporated *in vacuo* and the residue triturated with MeOH to afford **26a**. **26b** was prepared similarly

from 2-methyl-4-nitroimidazole. Data for **26a** and **26b** are presented in Table 1.

1-(2-*Hydroxy*-1-*indanyl*)-2-*methyl*-4-*nitroimidazole* (**30**)—To a suspension of 2-methyl-4-nitroimidazole (6.35 g) in absolute methanol (35 ml) was added sodium methoxide (1.15 g Na dissolved in 30 ml of absolute methanol), and the mixture heated under reflux for 30 min. About 30 ml of the solvent was distilled off, DMF (100 ml) added and the mixture treated at 100° without using condenser until all the methanol was evaporated off. A solution of 2-bromo-1-indanol in DMF (100 ml) was then added and the reaction mixture heated at 130° for 16 hr. The solution was filtered from insolubles, the filtrate evaporated off and the residue chromatographed over silica gel. Fractions with $CHCl_3$ – MeOH (98:2) gave **30** (Table 1) with further fractions giving the starting material.

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