Indian Journal of Chemistry
Vol. 21B, October 1982, pp. 928-940

Nitroimidazoles: Part IV—1-Sulphonyl (carbamoyl/thiocarbamoyl)-3-(1-methyl-5-nitroimidazol-2-yl)-2-imidazolidinones†‡

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CIBA-GEIGY Research Centre, Goregaon East, Bombay 400 063

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Received 26 *May* 1982; *accepted* 22 *June* 1982

Sulphone (**5**) is condensed with sodium salts of a variety of 1-sulphonyl (**7**), 1-thiocarbamoyl (**9**) and 1-carbonyl (**10**)-2-imidazolidinones to give 3-(2-imidazolyl)imidazolidinones (**12**), (**13**) and (**14**) respectively, out of which 1-methylsulphonyl-3-(1-methyl-5-nitro-imidazol-2-yl)-2-imidazolidinone (**12a**) is undergoing clinical trials as an antiamoebic-antitrichomonal agent. **15** and **16** are analogous imidazolidinones, while **17** and **18** are benzimidazolone derivatives. The reaction of **5** with the sodium salt of 2-imidazolidinone gives rise to the mono and bis-condensation products **21** and **22** respectively. Several other minor byproducts, **23-27** have been identified. **23**, **26** and **27** arise from **21**. **24**, a transformation product of **5** leads to the ether **25** by a displacement reaction. A second synthesis of **12a** involves the nitration of imidazolylimidazolidinone (**30**) in the terminal step, with **30** becoming available from 1-methyl-2-aminoimidazole (**28**) and chloroethyl isocyanate, and subsequent reaction of resultant **29** with methanesulphonyl chloride. The higher ring homologue, **33** of **12a** is synthesised in poor yield from **5** and 1-methylsulphonylhexahydropyrimidinone. Treatment of **12a** and **13a** with KI in DMF leads to the isomeric 4-nitro derivatives **38a**, **b** and desmethyl derivatives **37a**, **b**. Treatment of **12a** with triethyloxonium fluborate affords the quaternary isothiourea (**35**) which is hydrolysed to **36**. Treatment of **12a** and **13a** with aqueous alkali leads to cleavage of imidazolidinone ring to form the ethylenediamines **31a** and **b**. Position isomers **41** and **43** of **12a** are respectively obtained by the reaction of 1-methyl-4-nitro-5-chloro-(**40**)-, and 1-methyl-5-nitro-4-chloro-(**42**)-imidazoles with 1-methylsulphonyl-ethylene urea. Treatment of the last compound with various reactive halides, e.g. 2-chlorobenzothiazole, yields several analogues **44a-i** of **12a** while niridazole (**45**) and methylsulphonyl chloride affords the nitrothiazole analogue **46**.

Since the advent of metronidazole[1] [**1**; 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole] as a potent antiprotozoal agent, a large number of 1-substituted-5-nitroimidazoles have been synthesised and studied, leading to clinically useful preparations. Most of these have at position-2 of imidazole, a methyl (e.g.: metronidazole[1], ornidazole[2], tinidazole[3]) or aryl group (flunidazole[4]) or hydrogen atom (nimorazole[5]), while one preparation has a mercaptan (SC 28536[6]). The work of Ilvespaa[7], inspired by the well-known antiparasitic properties of niridazole (**45**)[8] demonstrated for the first time the potential of nitroimidazoles carrying imidazolidinone rings at position-2, the attachment being through a N atom. We began in 1972 a large programme of synthesis and screening of nitroimidazoles, concentrating our efforts initially on molecules carrying sulphonyl, carbamoyl or thiocarbamoylimidazolidinones, with the emphasis on easy synthesis and high yields of pure products. Later we enlarged our efforts to scan fairly exhaustively 1-substituted-5-nitroimidazoles carrying an amino or modified amino function at position-2. This function ranged from plain amine and its derivatives[9] to cycloalkylenimines (e.g. pyrrolidine)[10], azoles[11] (e.g. imidazole), lactams containing one or more extra heteroatoms (e.g. triazolidinedione, oxazolidinone) and cyclic sulphamides[12]. The efforts afforded several antiprotozoal preparations out of which one, 1-methyl-sulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone (**12a**)** was studied exhaustively and is now undergoing extended clinical trials.

A considerable volume of interesting chemistry ensued in this process, two examples being the application of ^{13}C NMR spectroscopy for the structure determination of isomeric nitroimidazoles[13] and the anomalous reaction of some 2-amido-1-methyl-5-nitroimidazoles with diazomethane[14,15], the amides themselves becoming available from 2-amino-1-methyl-5-nitroimidazole[9]. A number of new nitroimidazoles were also prepared from the known and readily synthesised 4-chloro-5-nitro and 5-chloro-4-nitro-1-methylimidazoles[16]. Novel 1-substituted-5-nitroimidazoles carrying a carbon side chain at position-2 became available by acylation reactions of 1-methyl-5-nitro[17]- and 1,2-dimethyl-5-nitroimida-

†Contribution No. 643 from CIBA-GEIGY Research Centre.
‡Part III: *Indian J Chem*, **21B** (1982) 923; *Indian J Chem*, **15B** (1977) 629 and *Indian J Chem*, **19B** (1980) 383 considered as Parts I and II of this series respectively.

**Code No. C-10213-Go

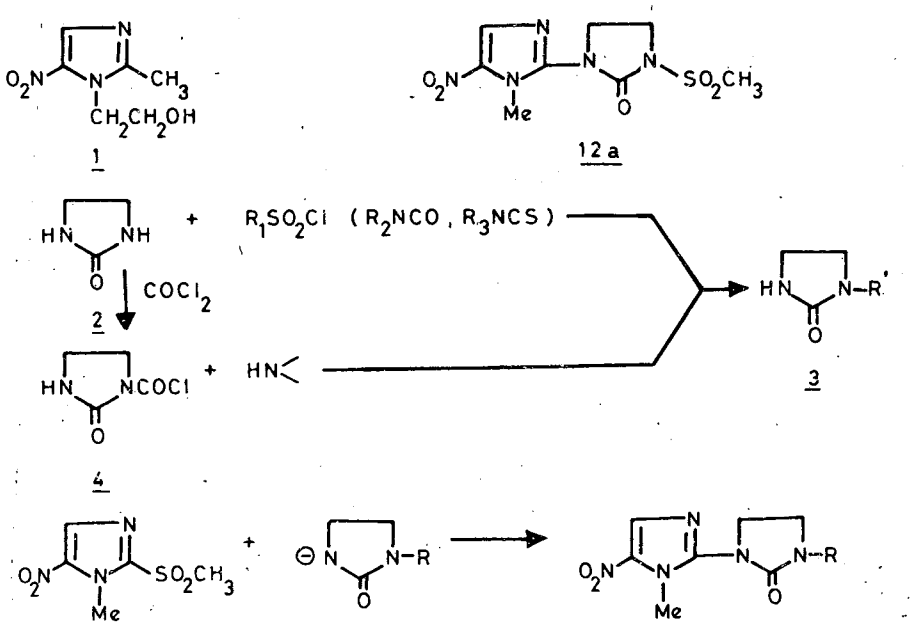


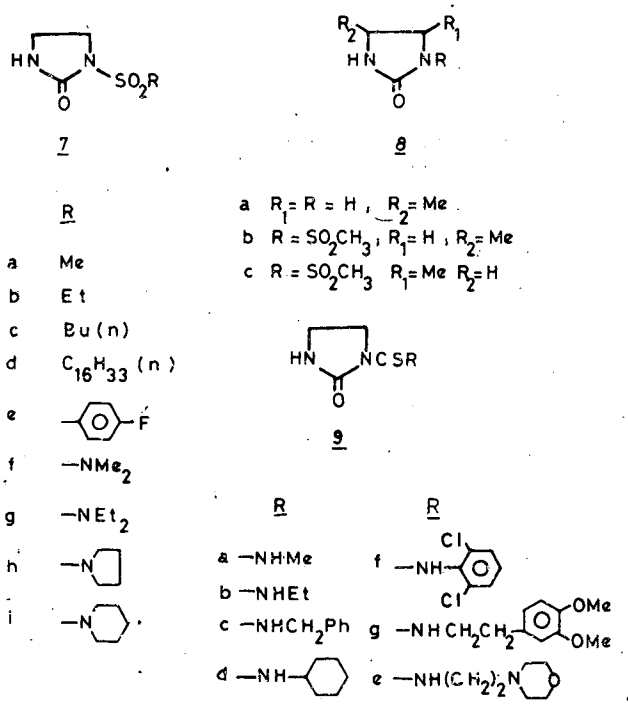
Chart 1

zoles[18,19]. The chemistry of 2-nitroimidazoles was also explored to a limited extent[20]. We describe in this paper the synthesis of 5-nitroimidazoles carrying an imidazolidinone ring at position-2 to which the clinically useful preparation, C-10213-Go (**12a**) belongs. Structure-activity relationships among the compounds synthesised under this programme are dealt with in a separate communication[21].

The title compounds were prepared by condensing 1-methyl-2-methylsulphonyl-5-nitroimidazole (**5**)[7] with the sodium salt of the monosubstituted 2-imidazolidinone (**3**) in DMF. Treatment of 2-imidazolidinone (**2**) with the appropriate sulphonyl chloride, isocyanate, carbamoyl chloride or isothiocyanate afforded most of the monosubstituted derivatives (**3**) used in this study. A few were made via carbamoyl chloride (**4**). These were treated with sodium hydride in DMF to generate the salt *in situ* for the condensation reaction (Chart 1) which was generally exothermic and had to be controlled for optimum yields of products **6**.

Data for the monosubstituted imidazolidinones (**7-11**; general structure **3**) are reported in Table 1. Among these compounds, **9c** showed moderate sedative activity in mice at 250 mg/kg p.o. while **9f** had good plant abscission regulating activity.

Table 2 describes the properties of nitroimidazoles (**12-16**; analogous to **6**) synthesised according to Chart 1. Compound (**12a**) was alternatively obtained from the sulphones (**19a**) and (**19b**) as also from the sulphoxide (**20**) in low to moderate yields. In the case of **19b**, a serious side reaction was the abstraction of a proton from the highly acidic benzylic group. The use



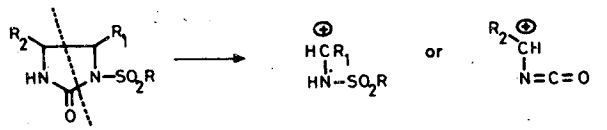
of 2-chloro-1-methyl-5-nitroimidazole for the preparation of **12a** is described in a later communication[22].

4-Methyl-2-imidazolidinone (**8a**) upon treatment with methane sulphonyl chloride yielded a derivative which could be either **8b** or **8c**. It was assigned structure (**8b**) on the grounds that the less hindered nitrogen atom would attack the sulphonyl chloride. This is also supported by a study of mass spectra of **7a**, **7b** and the above product. The mass spectrum of **7a** ($C_4H_8N_2O_3S$, M^+ 164) showed prominent peaks at

Table 1—N-Substituted-2-imidazolidinones

Comp.	Method	m.p.r b.p./mm (°C)	Crystallised from	Yield %	Mol. formula	M^+ at *m/z*	Analysis (%) Calculated C	H	N	Found C	H	N
7a	a	192-94	MeOH	61	$C_4H_8N_2O_3S$	164	29.27	4.91	17.07	29.22	5.31	17.14
7b	a	114-16	$CH_2Cl_2-Et_2O$	35	$C_5H_{10}N_2O_3S$	178	33.71	5.66	15.73	33.99	6.00	16.06
7c	a	77-79	CH_2Cl_2 – hexane	18	$C_7H_{14}N_2O_3S$	—	40.77	6.84	13.59	40.89	6.95	13.86
7d	a	122-24	$MeOH-Et_2O$	15	$C_{19}H_{38}N_2O_3S$	374	60.93	10.23	7.48	61.16	10.49	7.92
7e	a	183-85	$MeOH-Et_2O$	18	$C_9H_9FN_2O_3S$	—	44.27	3.72	11.47	44.41	3.87	11.31
7f	a	128-29	CH_2Cl_2	15	$C_5H_{11}N_3O_3S$	—	31.09	5.74	21.76	31.33	5.70	21.97
7g	a	180/0.1		18	$C_7H_{15}N_3O_3S$	—	38.00	6.84	19.00	38.18	7.02	19.12
7h	a	150-51	$CH_2Cl_2-Et_2O$	20	$C_7H_{13}N_3O_3S$	—	38.35	5.98	19.17	38.40	6.10	19.16
7i	a	201-2	$MeOH-i$PrOH	22	$C_8H_{15}N_3O_3S$	233	41.20	6.48	—	40.97	6.74	—
8b	a	129-30	CH_2Cl_2 – pet. ether	45	$C_5H_{10}N_2O_3S$	—	33.71	5.66	15.73	34.00	5.89	16.02
9a	a	167-70	$EtOH-Et_2O$	82	$C_5H_9N_3OS$	—	37.73	5.70	26.41	38.15	5.81	26.20
9b	a	135-36	$EtOH-Et_2O$	50	$C_6H_{11}N_3OS$	—	41.61	6.40	24.27	41.99	6.71	24.42
9c	a	173-75	EtOH	70	$C_{11}H_{13}N_3OS$	—	56.16	5.57	17.86	56.04	5.78	17.99
9d	a	162-64	$CHCl_3$ – EtOH	60	$C_{10}H_{17}N_3OS$	—	52.85	7.54	18.49	53.17	7.68	18.88
9e	a	124-25	Benzene-hexane	24	$C_{10}H_{18}N_4O_2S$	—	46.50	7.02	21.69	46.86	7.05	21.44
9f	a	230-32	$Me_2CO-MeOH$	38	$C_{10}H_9Cl_2N_3OS$	—	41.40	3.13	14.49	41.67	3.21	14.73
9g	a	187-88	$CHCl_3-MeOH$	79	$C_{14}H_{19}N_3O_3S$	—	54.36	6.19	13.59	54.61	6.44	13.89
10a	a	199-200	$CHCl_3-Et_2O$	38	$C_5H_9N_3O_2$	—	41.95	6.34	29.36	41.79	6.70	29.04
10b	a	139-41	$EtOH-Et_2O$	51	$C_6H_{11}N_3O_2$	—	45.85	7.05	26.74	46.10	7.35	27.14
10c	a	187-89	EtOH	57	$C_{10}H_{17}N_3O_2$	—	56.85	8.11	19.89	57.13	8.31	20.37
10d	a	122-23	CH_2Cl_2 – Hexane	30	$C_6H_{11}N_3O_2$	157	45.85	7.05	26.74	45.59	7.12	27.09
10e	a	140/2	—	40	$C_8H_{15}N_3O_2$	—	51.87	8.16	22.69	51.55	8.12	22.50
10f	a	138-40	CH_3CN	25	$C_{10}H_{17}N_3O_2$	—	56.85	8.11	19.89	57.20	8.25	19.75
10g	a	153-54	$CH_2Cl_2-Et_2O$	35	$C_8H_{13}N_3O_2$	183	52.44	7.15	22.94	52.35	7.33	23.16
10h	b	150	i-PrOH	53	$C_9H_{15}N_3O_2$	197	54.80	7.67	21.31	54.46	8.04	21.15
10i	b	163-64	i-PrOH	30	$C_8H_{13}N_3O_3$	—	48.23	6.58	21.10	47.93	6.84	20.82
10j (HCl)	b	295	MeOH	34	$C_9H_{16}N_4O_2$ HCL	—	43.46	6.89	—	43.00	7.35	—
10k	b	127-28	H_2O	28	$C_6H_{10}N_2O_3$	158	45.56	6.37	—	45.85	6.65	—
10l	b	123-24	i-PrOH	32	$C_{11}H_{12}N_2O_3$	—	59.99	5.49	—	59.71	5.79	—
11a	c	183-84	CH_2Cl_2 – hexane	83	$C_9H_{17}N_3O_3S$	—	43.72	6.93	17.00	43.66	7.19	16.65
11d	—	85-87	Et_2O	95	$C_{11}H_{13}ClN_2OS$	—	51.47	5.10	10.92	51.61	5.50	11.41
11e	—	276-78	DMF	43	$C_9H_{17}N_3O_3S$	—	43.72	6.93	17.00	43.73	7.13	17.11

m/z 108 and 56 and that of **7b** ($C_5H_{10}N_2O_3S$, M^+ 178) at *m/z* 122 and 56 pointing to fragmentation as shown in Chart 2. By analogy the mass spectrum of **8b** ($C_5H_{10}N_2O_3S$, M^+ 178) would be expected to show peaks at *m/z* 108 and 70 and that of **8c** at 122 and 56. However the mass spectrum of the compound in question showed besides mass peak, prominent peaks at *m/z* 108 and 70 and minor peaks at 122 and 56 indicating that it was predominantly **8b** with a small quantity (0.5%) of **8c**. Reaction of **8b** with sulphone (**5**) led to the expected product (**15a**), while condensation



7a	$R=CH_3$, $R_1=R_2=H$	m/z 108	m/z 56
7b	$R=C_2H_5$, $R_1=R_2=H$	m/z 122	m/z 56
8b	$R=CH_3$, $R=H$; $R_2=CH_3$	m/z 108	m/z 70
8c	$R=CH_3$; $R_1=CH_3$, $R_2=H$	m/z 122	m/z 56

Chart 2

Table 2—[1-Alkyl(aryl)-5-nitroimidazol-2-yl-)-3-substituted-2-imidazolidinones

Comp.	m.p. (°C)	Crystallised from	Yield %	Mol. formula	M^+ at *m/z*	Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
12a	184-86 202-3	Me_2CO	80	$C_8H_{11}N_5O_5S$	289	33.22	3.83	24.22	33.54	4.04	24.37
12b	176-77	$CH_2Cl_2-Et_2O$	35	$C_9H_{13}N_5O_5S$	303	35.65	4.32	23.10	35.92	4.40	23.03
12c	125-27	Me_2CO-Et_2O	48	$C_{11}H_{17}N_5O_5S$	—	39.88	5.17	21.14	40.10	5.48	20.96
12d	92-95	CH_2Cl_2 – hexane	25	$C_{23}H_{41}N_5O_5S$	499	55.29	8.27	14.02	55.44	8.51	14.41
12e	198-200	CH_2Cl_2 – hexane	10	$C_{13}H_{12}FN_5O_5S$	—	42.28	3.28	18.97	42.10	3.25	19.20
12f	217-18	$CH_2Cl_2-Et_2O$	48	$C_9H_{14}N_6O_5S$	318	33.96	4.43	26.41	34.18	4.58	26.38
12g	146-47	$CH_2Cl_2-Et_2O$	30	$C_{11}H_{18}N_6O_5S$	346	38.15	5.24	24.27	38.40	5.46	24.02
12h	226-27	$CH_2Cl_2-Et_2O$	20	$C_{11}H_{16}N_6O_5S$	344	38.37	4.68	24.41	38.08	5.00	24.42
12i	191	*i*–PrOH	18	$C_{12}H_{18}N_6O_5S$	—	40.22	5.06	—	40.30	5.27	—
13a	185-87	$CHCl_3$ – EtOH	72	$C_9H_{12}N_6O_3S$	284	38.03	4.26	29.57	37.92	4.56	29.72
13b	213-14	CH_2Cl_2 – hexane	70	$C_{10}H_{14}N_6O_3S$	—	40.27	4.73	28.18	40.00	4.41	28.18
13c	182-85	CH_2Cl_2 – EtOH	42	$C_{15}H_{16}N_6O_3S$	360	50.00	4.48	23.23	50.19	4.49	23.16
13d	165-67	EtOH	18	$C_{14}H_{20}N_6O_3S$	352	47.72	5.72	23.85	47.81	6.03	24.05
13e	150-51	Me_2CO – EtOH	40	$C_{14}H_{21}N_7O_4S$	—	43.86	5.52	25.58	44.18	5.80	25.62
14a	176-77	MeOH	13	$C_9H_{12}N_6O_4$	268	40.30	4.51	31.33	40.93	4.81	31.17
14b	145-46	EtOAc	9	$C_{10}H_{14}N_6O_4$	282	42.55	5.00	29.78	42.90	5.33	29.74
14c	113-15	EtOH	52	$C_{15}H_{16}N_6O_4$	344	52.32	4.68	24.41	52.47	4.97	24.40
14d	190-91	$CH_2Cl_2-Et_2O$	35	$C_{10}H_{14}N_6O_4$	282	42.55	5.10	29.78	42.23	5.11	29.88
14e	133-34	CH_2Cl_2 – hexane	40	$C_{12}H_{18}N_6O_4$	310	46.44	5.85	27.08	46.53	6.07	27.45
14f	177-78	CH_2Cl_2 – Pet. ether	28	$C_{14}H_{20}N_6O_4$	336	49.99	5.99	24.99	49.61	6.29	25.22
14g	155-56	CH_2Cl_2 – hexane	25	$C_{12}H_{16}N_6O_4$	308	46.75	5.23	27.26	46.84	5.57	26.98
14h	152	*i*-PrOH	23	$C_{13}H_{18}N_6O_4$	322	48.44	5.63	—	48.74	5.93	—
14i	181	*i*-PrOH	21	$C_{12}H_{16}N_6O_5$	324	44.44	4.97	—	44.14	5.38	—
14j	118-19	EtOH	16	$C_{10}H_{13}N_5O_5$	283	42.40	4.63	—	42.65	4.77	—
15a	199-200	$CH_2Cl_2-Et_2O$	49	$C_9H_{13}N_5O_5S$	303	35.65	4.32	23.10	35.96	4.68	23.35
15b	126-27	Me_2CO – MeOH – Et_2O	50	$C_{10}H_{15}N_5O_6S$	333	36.04	4.54	21.02	36.42	4.88	21.46
15c	130-31	$CH_2Cl_2-Et_2O$	20	$C_{11}H_{17}N_5O_5S$	331	39.88	5.17	21.14	39.78	5.39	21.20
15d	156	MeOH	34	$C_{13}H_{13}N_5O_5S$	—	44.45	3.73	19.94	44.70	4.10	20.07
15e	172-73	EtOAc – hexane	9	$C_9H_{13}N_5O_5S$	—	35.65	4.32	23.10	36.02	4.66	22.81

of the N-unsubstituted imidazolidinone (**8a**) with **5** afforded the bis-nitroimidazolyl derivative (**16**). Benzimidazolin-2-one, on the other hand, on condensation with **5** gave **17** and **18** arising from mono as well as bis substitution. Variations on the nitroimidazole moiety were achieved using the sulphones **19c**, **19d** and **19e** (synthesised by standard procedures) and imidazolidinone **7a**. 1,4-Dimethyl-5-nitroimidazole derivative (**15e**) was obtained using 1,4-dimethyl-2-bromo-5-nitroimidazole[23] and **7a**.

While the reaction of the sodium salts of monosubstituted **3** with **5** was clean and facile, except in the case of **12a**, unless conditions were carefully controlled, byproducts were produced in other cases, which were mainly traced to the base-induced disproportionation (Chart 3) and to some extent, the transformation of sulphone **5** to **24** under the reaction conditions. This was specially true of 1-acetyl- and some 1-carbamoyl- and 1-thiocarbamoyl-imidazolidinones. Hence the reaction of **5** with the sodium salt of imidazolidinone (**2**) was studied exhaustively and

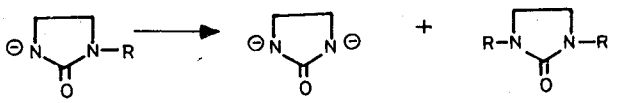
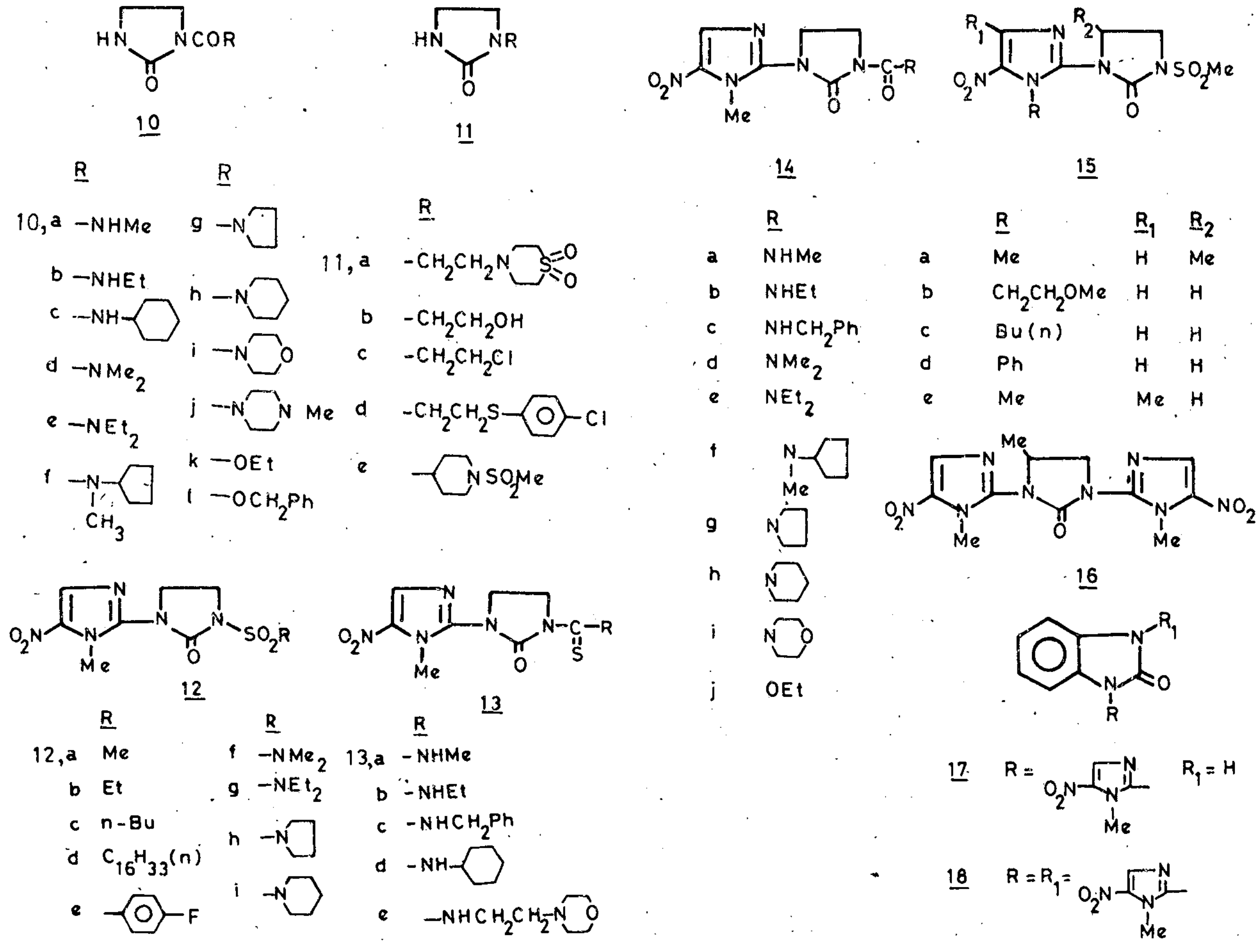
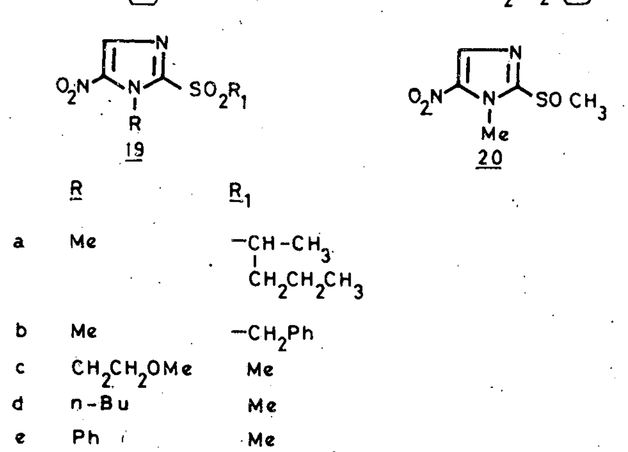


Chart 3





the products were isolated by extensive silica gel chromatography. In addition to the major products **21** and **22** described in the previous communication[7], five more, **23**-**27** were recognised as minor products (Chart 4).

The structure of **23**, $C_{14}H_{17}N_9O_4$(M^+ 375), was deduced from the following data: PMR (DMSO-d_6 +$CDCl_3$)§ 3.33 (2 NCH_2, *bs*), 3.53 (N-Me, *s*), 3.80 (2 NCH_2, *bs*), 4.07 (N-Me, *s*), 6.63 (NH), 7.0 (imidazole H, *s*), 8.07 (nitroimidazole H, *s*); IR: 1720 (νC=O). Evidently, the amide ion formed from **21** had added to position-4 of the nitroimidazole moiety of another molecule of the same kind. Subsequent loss of nitrite would lead to **23**. The ^{13}C NMR spectrum provided definite proof for this formulation and against one involving a direct displacement of the NO_2 group. The signal due to C-4 of the nitroimidazole moiety was located at 131.1 as a doublet, ($^1J_{CH}$=202.1 Hz). The signal due to C-5 of the second imidazole ring at 105.3 was a large doublet ($^1J_{CH}$=200 Hz), each split into a quartet ($^3J_{CH}$=3 Hz). Displacement of the nitro group in **5** by hydroxide ion (moisture in solvent!) would afford **24** (keto form); $C_5H_8N_2O_3S$; M^+ 176; IR: 1750, 1730, 1700 cm^{-1} (νC=O). **24** probably exists in equilibrium with the enol form.

Displacement of the sulphone group in **5** by the enolate of **24** would be the genesis of byproduct **25**; $C_9H_{11}N_5O_5S$; M^+ 301; PMR: 3.40 (SO_2CH_3, NCH_3), 3.77 (NCH_3 in nitroimidazole), 7.45 (imidazole H), 8.1 (nitroimidazole H). A band in the IR spectrum at 1740 is probably due to the vinyl ether in **25**. Product **26**: $C_9H_{16}N_6O_3$; M^+ 256; PMR ($CDCl_3$): 2.93 [6H, *s*, $CON(CH_3)_2$], 3.54 (4H, *t* becoming *s* with D_2O,

§ PMR and ^{13}C NMR data in δ (ppm) and IR ν_{max} in cm^{-1} throughout the paper.

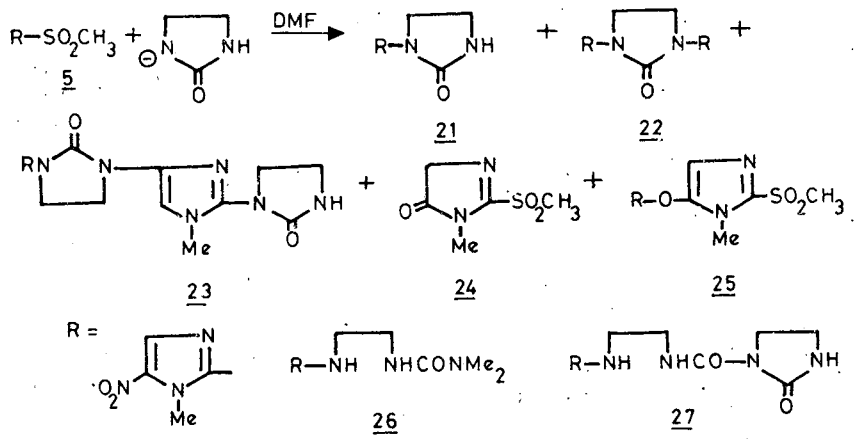


Chart 4

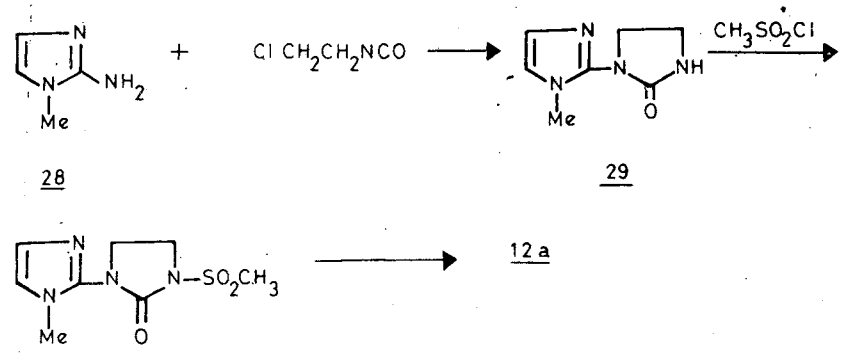


Chart 5

$HNCH_2CH_2NH$), 3.70 (3H, *s*, N-CH_3), 5.04 (1H, *bs* disappearing with D_2O, NH), 7.06 (1H, *bs* disappearing with D_2O, NH), 7.88(1H, *s*, imidazole C-4H); UV (EtOH); 390 nm log ε 4.17); +NaOH: 470(3.60) and 390 nm (3.66); IR: 1590 (νC=O); and **27**, $C_{10}H_{15}N_7O_4$; M^+ 297; PMR (DMSO-d_6): 2.98-3.50 (6H, *m*, $3CH_2$), 3.53-3.94 (2H, *m*, CH_2), 3.60 (3H, *s*, N-CH_3), 7.35 (1H, *t* disappearing with D_2O, NH), 7.48 (1H, *s* disappearing with D_2O, NH), 7.94 (1H, *s*, imidazole C-4H), 8.22 (1H, *t* disappearing with D_2O); UV (EtOH): 388 nm (log ε 4.14); +NaOH: 470 (3.92) and 388 nm (4.06); IR: 1730 (νC=O). **26** and **27** must arise from **21** by the attack of dimethylamine (from DMF?) and imidazolidinone ions respectively at the carbonyl group and preferential cleavage of one of the two N−CO bonds. The marked alkali-induced bathochromic shifts in the UV spectra of **26** and **27** demonstrate clearly the direction in which the cleavage had taken place.

As noted earlier, condensation of methanesulphonyl imidazolidinone (**7a**) with **5** was most facile and afforded **12a** in yields of 80% even in large scale runs. **12a** could also be constructed by a different route, starting from the known 1-methyl-2-aminoimidazole (**28**)[24] and proceeding through intermediates **29** and **30** (Chart 5).

Carbamoylimidazolidinone derivatives (**14b**) and (**14c**) could be synthesised by other procedures. Thus treatment of **21** with ethyl isocyanate afforded **14b** and with acetic anhydride, the acetyl derivative[7], while treatment of **13c** with sulphuric acid in DMSO furnished **14c**. **12a** and **13a** were found to be very stable to heat alone or in the presence of acids. Alkali, however, opened the imidazolidinone ring partially to afford **31a** and **31b** respectively; **31b** was isolated and characterised, while the formation of **31a** was suggested by UV data[13].

The higher homologue **33** of **12a** was synthesised in modest yield by the reaction of **5** with the sodium salt of 1-methanesulphonylhexahydropyrimidin-2-one (**32**).

Treatment of **12a** with triethyloxonium fluoborate gave the quaternary salt **34**, while **13a** afforded **35**. Acid hydrolysis of the latter led to **36**.

The high antiprotozoal activity of **12a** and **13a** prompted us to synthesise the 4-nitro-analogues **38a** and **38b** respectively. These became available in low yields by the isomerisation of the 5-nitro derivatives with potassium iodide in boiling DMF. These were accompanied by the des-methyl derivatives **37a** and **37b**, the likely precursors of **38a** and **38b** in the isomerisation reaction (Chart 6). Methylation of **37a**

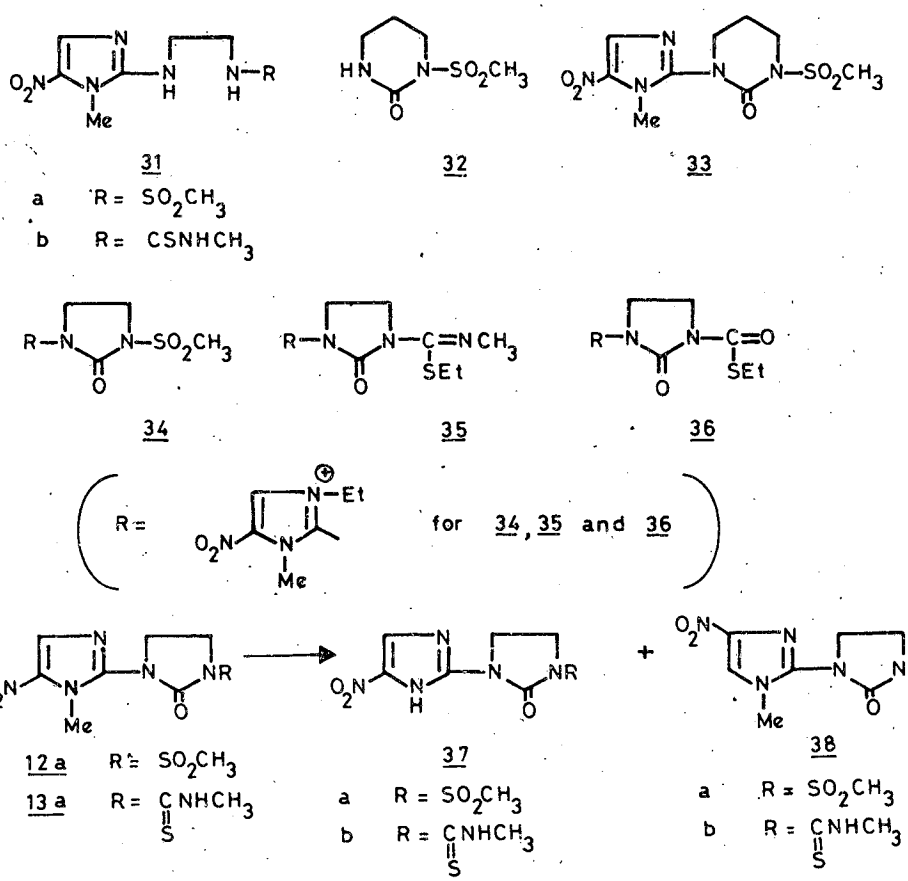


Chart 6

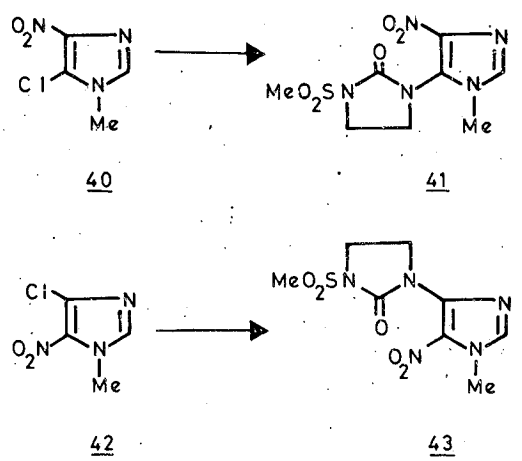
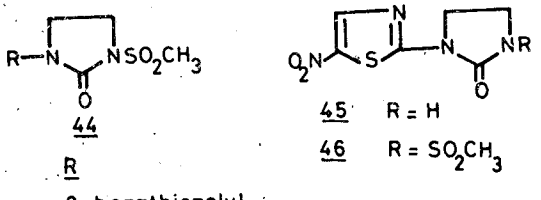


Chart 7



with methyl iodide and sodium hydride generated a mixture of **12a** and **38a**, while alkylation with morpholinoethyl chloride gave the 4-nitro derivative **39**.

Two other isomers **41** and **43** of **12a** were synthesised respectively from the known 1-methyl-5-chloro-4-nitro-(**40**)- and 1-methyl-4-chloro-5-nitro-(**42**)-imidazoles[25] and the sodium salt of **7a** (Chart 7). These are reported in Table 3.

A number of other 1-methanesulphonyl-3-substituted imidazolidin-2-ones (**44a-i**) (Table 3) were also synthesised for evaluation of antiprotozoal activity, the substituents at position-3 being mostly heterocycles. These were prepared by the reaction of the sodium salt of **7a** with the appropriate halide. Catalytic reduction of **44e** afforded the amino derivative **44f**, and not the expected tricycle, imidazobenzimidazole. Finally, a close analogue **46** of

Table 3—Miscellaneous 1-substituted-3-methyl-sulphonyl-2-imidazolidinones

Comp.	m.p. (°C)	Crystallised from	Yield %	Mol. formula	Analysis (%)					
					Calculated			Found		
					C	H	N	C	H	N
41	206-8	Me_2CO	20	$C_8H_{11}N_5O_5S$	33.22	3.83	24.22	33.51	4.04	24.59
43	199-200	Me_2CO	63	$C_8H_{11}N_5O_5S$	33.22	3.83	24.22	33.52	4.12	24.18
44a	272-74	$CHCl_3$ – MeOH	7	$C_{11}H_{11}N_3O_3S_2$	44.45	3.73	14.14	44.75	4.00	14.21
44b	251-53	$CHCl_3$ – MeOH	71	$C_{11}H_{11}N_3O_4S$	46.98	3.94	14.94	47.26	4.21	15.15
44c	265-67	DMF	70	$C_9H_{10}N_4O_5S$	37.77	3.52	19.58	37.94	3.69	19.59
44d	226-28	MeOH – Me_2CO	42	$C_8H_9ClN_4O_3S$	34.73	3.28	20.25	34.95	3.50	19.95
44e	134-36	MeOH	60	$C_{10}H_{11}N_3O_5S$	42.11	3.89	14.73	42.46	4.28	14.94
44f	217-19	Me_2CO – EtOH	12	$C_{10}H_{13}N_3O_3S$	47.06	5.13	16.47	46.90	5.43	16.25
44g	258-60	DMF	36	$C_{10}H_{11}N_3O_5S$	42.11	3.89	14.73	42.39	4.14	14.69
44h	193-94	$CHCl_3$ – MeOH	26	$C_{12}H_{13}N_3O_7S$	41.99	3.82	12.24	41.95	4.15	12.14
44i	157-58	CH_2Cl_2 – hexane	44	$C_{11}H_{12}Cl_2N_2O_3S$	40.88	3.74	8.67	40.96	4.01	8.51
46	295	Me_2CO	10	$C_7H_8N_4O_5S_2$	28.77	2.76	19.18	29.29	3.06	19.71

12a, which is the methanesulphonyl derivative of niridazole (**45**) was made in low yield by reaction of the latter with methanesulphonyl chloride.

Experimental Procedure

Melting points reported are uncorrected. IR spectra were run as nujol mulls on a Perkin-Elmer M 337 spectrophotometer; UV for 95% EtOH solutions on a Beckman M 35 spectrophotometer; PMR spectra on a Varian A 60 or EM 360 or a Bruker WH 90 spectrometer; ^{13}C NMR spectra on a Brucker WH 90 spectrometer at 22.63 MHz; and mass spectra on a Varian Mat CH 7 spectrometer. NMR chemical shifts are in ppm downfield from TMS as internal standard.

1-*Methylsulphonyl*-2-*imidazolidinone* (**7a**): *Method a*—A mixture of 2-imidazolidinone (86 g) and methanesulphonyl chloride (114.5 g) kept under N_2 atmosphere was gradually heated to 110° and stirred at this temperature for 5 hr. After cooling to room temperature the solid mass formed was warmed with water (50 ml) to dissolve unreacted 2-imidazolidinone and the solid filtered off to afford **7a**. Compounds **7b-i**, **8b**, **9a-g** and **10a-g** were similarly prepared. The physical data of these compounds are presented in Table 1.

1-*Piperidinocarbonyl*-2-*imidazolidinone* (**10h**): *Method b*—A solution of 2-imidazolidinone (34.4 g) in ethylene dichloride (400 ml) was added dropwise under stirring at 70-75° to ethylene dichloride (200 ml) into which phosgene gas was being bubbled. After the addition was over (~1 hr) bubbling of phosgene was continued for 2 hr more and then N_2 gas bubbled into the mixture for 1 hr. The reaction mixture was filtered hot and the solid obtained on cooling the filtrate was filtered off and washed with ethylene chloride to afford 2-imidazolidinone-1-carbonyl chloride (41.5 g) m.p. 155-57°.

A mixture of the above carbonyl chloride (29.6 g) and piperidine (34.2 g) in benzene (300 ml) was refluxed for 4 hr. The solid obtained on cooling the reaction mixture was filtered off and treated with saturated solution of potassium carbonate. The solid was filtered off and recrystallised from isopropanol to afford **10h** (21 g), m.p. 190-91°.

Compounds **10i-l** were similarly prepared (see Table 1).

1-[2,-*N*-(1,1-*Dioxidothiamorpholinoethyl*)]-2-*imidazolidinone* (**11a**): *Method c*—To a solution of divinyl sulphone (23.6 g) in ethyl alcohol (50 ml) was added dropwise under cooling and stirring, a solution of 1-(β-aminoethyl)-2-imidazolidinone (25.8 g) in ethyl alcohol (50 ml). After the addition was over, the reaction mixture was stirred at room temperature for 3 hr and the solid formed filtered off to afford **11a** (see Table 1).

1-[2-(*p-Chlorophenylmercapto*)]-2-*imidazolidinone* (**11d**)—A mixture of 2-aminoethylaminoethanol (36 g) and urea (20 g) was heated at 230° for 3 hr. The gummy mass formed was washed with ether and dried *in vacuo* (40 g).

To a solution of the crude **11b** (40 g) so obtained in chloroform (200 ml) was slowly added thionyl chloride (27 ml) and the mixture heated under reflux for 30 min. The solvent was evaporated off, the residue extracted with benzene, the benzene extract was evaporated *in vacuo* and the residue recrystallised from benzene-ether to afford **11c** (8.1 g), m.p. 86-88°.

To a freshly prepared solution of sodium ethoxide (11.5 g of Na dissolved in 150 ml of absolute ethanol) was added *p*-chlorothiophenol (7 g) and the mixture stirred for 10 min. **11c** (7.2 g) was then added, the resultant mixture heated under reflux for 3 hr, filtered, the filtrate evaporated under reduced pressure and the residue crystallised from ether to afford **11d** (13 g) m.p. 85-87° (see Table 1).

1-(1-*Methylsulphonyl*-4-*piperidyl*)-2-*imidazolidinone* (**11e**)—To a solution of 1-(4-piperidyl)-2-imidazolidinone (11.8 g) in DMF (100 ml) containing triethylamine (7.1 g) was added dropwise under cooling and stirring methanesulphonyl chloride (8 g) during 30 min. After the addition was over, the reaction mixture was stirred for 1 hr at 60° and then overnight at room temperature. The solid formed was filtered off, washed with water (10 ml) and recrystallised from DMF to afford **11e** (7.5 g), m.p. 276-78° (Table 1).

1-*Methylsulphonyl*-3-(1-*methyl*-5-*nitroimidazol*-2-*yl*)-2-*imidazolidinone* (**12a**)—To a suspension of **7a** (16.4 g) in dry DMF (100 ml) kept under stirring at 5-10° was added NaH (50%, 4.8 g). The mixture was stirred at 15° for 45 min and treated dropwise with a solution of **5** (20.5 g) in dry DMF (70 ml). After the addition was over the mixture was stirred at 25° for 5 hr, poured into ice-water under stirring, the yellow solid obtained filtered off, washed with water and recrystallised from acetone to afford **12a** (see Table 2). **12a** was obtained in two crystalline forms, the one melting at 184-86° being more frequently encountered than the other melting at 202-3°.

Compounds **12b-i**, **13a-e**, **14a-j** and **15a-e** were similarly prepared. The physical data of these compounds are given in Table 1.

4-*Methyl*-1,3-*bis*-(1-*methyl*-5-*nitroimidazol*-2-*yl*)-2-*imidazolidinone* (**16**)—**5** (2 mol) was reacted with di-Na salt of **8a** (1 mol) in the manner described for **12a** and the crude product obtained recrystallized from methylene chloride-ether to afford **16** in 15% yield; m.p. 179-80°; M^+ 350 (Found: C, 39.2; H, 4.4; N, 29.9. $C_{12}H_{14}N_8O_5$ requires C, 39.1; H, 4.4; N, 30.4%).

1-(1-*Methyl*-5-*nitroimidazol*-2-*yl*)-2(3*H*)-*benzimidazolinone* (**17**) *and* 1,3-*Bis*-(1-*methyl*-5-*nitroimidazol*-2-*yl*)-2-*benzimidazolinone* (**18**)—**5** was reacted with the sodium salt of 2-benzimidazolinone under the conditions used for **12a**. The crude product was chromatographed over silica gel. Fractions eluted with $CHCl_3$-MeOH (98:2) gave a solid which recrystallized from acetonitrile-ether to afford **18** in 25% yield; m.p. 245-46°; M^+ 384 (Found: C, 47.1; H, 3.4; N, 28.9. $C_{15}H_{12}N_8O_5$ requires C, 46.9; H, 3.2; N, 29.2%).

Fractions with 5% methanolic chloroform gave **17** which was recrystallized from methylene chloride-ether (yield 10%); m.p. 303-4° (d); M^+ 259 (Found: C, 50.3; H, 4.0; N, 26.9. $C_{11}H_9N_5O_3$ requires C, 51.0; H, 3.5; N, 27.0%).

1-*Methyl*-2-(2-*pentylsulphonyl*)-5-*nitroimidazole* (**19a**)—To a 1.5 litre flask through which oxygen-free nitrogen was being passed was added 1-methyl-2-mercaptoimidazole (49 g) and methanol (400 ml). The mixture was cooled to 10° and sodium hydroxide solution (10 *N*, 46 ml) added in one lot. To this was added with stirring, 2-bromopentane (69 g) in methanol (100 ml) during 15 min keeping the temperature below 15°. The mixture was stirred at room temperature for 3 hr and left overnight at under N_2. The solvent was removed *in vacuo* at 40-45°, the residue dissolved in water (400 ml), repeatedly extracted with methylene chloride, the extract washed with saturated sodium chloride solution, dried (Na_2SO_4) and the solvent removed under reduced pressure to yield 1-methyl-2-(2-pentylmercapto)imidazole as an oil (52 g); PMR ($CDCl_3$): 7.00 (1H, *d*, C-4H or C-5H), 6.92 (1H, *d*, C-5H or C-4H), 3.62 (3H, *s*, NCH_3), 3.30 (1H, *q*, $CH-CH_3$), 1.28 (3H, *d*, CH_3-CH), 0.80-1.70 (7H, complex signals, $CH_2CH_2CH_3$).

The above crude product (52 g) was added dropwise with stirring to nitric acid (150 ml, $d=1.42$) heated at 80°. The internal temperature was maintained between 80 and 90°. There was a copious evolution of oxides of nitrogen. The mixture was heated at 90-95° for 1 hr, cooled, poured into ice, treated with acetic acid (30 ml) and neutralised to *p*H 8 with sodium hydroxide solution (30%) at 0°. The mixture then extracted with methylene chloride, dried (Na_2SO_4) and the solvent removed under reduced pressure to yield 1-methyl-2-(2-pentylmercapto)-5-nitroimidazole as an oil (39 g); PMR ($CDCl_3$), δ 7.95 (1H, *s*, C-4H), 3.90 [(3H, *s*, N$-CH_3$)+(1H, *q*, $CH-CH_3$)], 1.40 (3H, *d*, CH CH_3), broad signals between 0.8 and 1.8 (7H, $CH_2CH_2CH_3$).

The above crude product (38 g) was dissolved in methylene chloride (500 ml) cooled in an ice bath and treated with stirring during 10 min with formic acid (17 ml) followed by hydrogen peroxide (30%, 45 ml). The mixture was stirred at room temperature for 3 hr and gently refluxed on a water bath for 3 hr. The methylene chloride was tapped off and the aqueous layer repeatedly extracted with the same solvent. The methylene chloride extract was washed successively with solutions of sodium bicarbonate, sodium metabisulphite, sodium bicarbonate and saturated sodium chloride and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield **19a** as an oil (38 g); PMR ($CDCl_3$): 8.00 (1H, *s*, C-4H), 4.33 (3H, *s*, N$-CH_3$), 3.60 (1H, *q*, $CHCl_3$), 1.42 (3H, *d*, CH_3 CH) and complex signals between 0.9 and 2.00 (7H, $CH_2CH_2CH_3$).

2-Benzylsulphonyl-1-methyl-5-nitroimidazolo (**19b**)—1-Methyl-2-mercaptoimidazole (54 g) was allowed to react with benzyl chloride (63 g) by the method described for 1-methyl-2-(2-pentylmercapto) imidazole to obtain 2-benzylmercapto-1-methyl imidazole as an oil (100 g); PMR ($CDCl_3$); 7.30 (5H, Ar-H), 7.12 (1H, *d*, C-4H or C-5H), 6.92 (1H, *d*, C-5H or C-4H), 4.2 (2H, *s*, CH_2-Ph), 3.25 (3H, *s*, N-CH_3).

The above crude product (20 g) was nitrated under the conditions used for 1-methyl-2-(2-pentylmercapto)-5-nitroimidazole and the gummy product obtained filtered through silica gel column using $CHCl_3$-MeOH (98:2) as the eluent. The solid obtained was recrystallised from CH_2Cl_2-ether to afford 2-benzylmercapto-1-methyl-5-nitroimidazole (15 g), m.p. 90-92°; M^+ 249; PMR ($CDCl_3$): 8.07 (1H, *s*, C-4H), 7.37 (5H, *bs*, Ar-H), 4.52 (2H, *s*, CH_2-Ph), 3.75 (3H, *s*, N-CH_3) (Found: C, 53.3; H, 4.7; N, 16.8. $C_{11}H_{11}N_3O_2S$ requires C, 53.0; H, 4.5; N, 16.9%).

To a solution of 2-benzylmercapto-1-methyl-5-nitroimidazole (7.5 g) in methylene chloride (200 ml) was added a solution of monoperphthalic acid (0.075 m) in ether (150 ml) at 0°. The mixture was stirred overnight at room temperature and gently refluxed for 2 hr. The precipitated phthalic acid was filtered off, washed with methylene chloride and the filtrate cooled in ice and stirred with potassium bicarbonate solution until a small aliquot of organic layer did not give colour with starch and potassium iodide solution. The organic layer was dried (Na_2SO_4), the solvent evaporated and the residue crystallised from methylene chloride-ether to yield **19b** (4.8 g) m.p. 160-63°; PMR ($DMSOd_6 + CDCl_3$): 3.88 (3H, *s*, N-CH_3), 4.93 (2H, *s*, CH_2-C_6H_5), 7.38 (5H, *bs*, C_6H_5), 8.27 (1H, *s*, C-4H) (Found: C, 47.2; H, 4.2; N, 15.2. $C_{11}H_{11}N_3O_4S$ requires C, 47.0; H, 3.9; N, 14.9%).

1-(2-Methoxyethyl)-2-methylsulphonyl-5-nitroimidazole (**19c**)—A mixture of 2-methoxyethylamine (65% aqueous solution, 170 ml) and bromoacetaldehyde diethyl acetal (90 g) was heated in a steel tube for 16 hr at 120°. After cooling, the contents were treated with potassium hydroxide pellets (75 g) and set aside for 15-20 min. The liquid product was dried over anhydrous potassium carbonate, filtered and the solid washed with ethyl acetate. The filtrate and ethyl acetate washings were mixed and distilled under reduced pressure. After the removal of ethyl acetate, unreacted methoxyethylamine distilled off at 50-55°. The residual oil was then distilled under reduced pressure to afford 2-methoxyethylaminoacetaldehyde diethyl acetal (30 g), b.p. 115-20°/12 mm (Found: C, 56.5; H, 11.2; N, 7.6. $C_9H_{21}NO_3$ requires C, 56.5; H, 11.1; N, 7.3%).

To a solution of the above aminoacetal (28.8 g) in absolute ethyl alcohol (150 ml) was added potassium thiocyanate (6 g) and 2 *N* HCl (82.5 ml) and the mixture stirred under reflux for 16 hr. The solvent was evaporated off and the residue extracted with acetone. The acetone solution was concentrated *in vacuo* and the residue crystallised from acetone-ether to afford 2-mercapto-1-(2-methoxyethyl)imidazole (19.4 g), m.p. 92.95° (Found: C, 45.4; H, 6.7; N, 18.0. $C_6H_{10}N_2OS$ requires C, 45.6; H, 6.4; N, 17.7%).

The above mercapto compound (15.8 g) was reacted with methyl iodide by the method described for 1-methyl-2-(2-pentylmercapto)imidazole to afford 1-(2-methoxyethyl)-2-methylmercaptoimidazole as an oil (15.3 g).

The above crude product (15.3 g) was nitrated by the method described for 1-methyl-2-(2-pentyl mercapto)-5-nitroimidazole. The gummy product obtained was filtered through silica gel column using $CHCl_3$-MeOH (95:5) as the eluent. The solid obtained was recrystallised from methylene chloride-hexane to afford 1-(2-methoxyethyl)-2-methylmercapto-5-nitroimidazole (5 g) m.p. 44-45°; PMR ($CDCl_3$): 8.00 (1H, *s*, C-4H), 4.50 (2H, *t*, N-CH_2), 3-70 (2H, *t*, CH_2OCH_3), 3.30 (3H, *s*, OCH_3), 2.70 (3H, *s*, SCH_3) (Found: C, 39.0; H, 5.4; N, 19.5. $C_7H_{11}N_3O_3S$ requires C, 38.7; H, 5.1; N, 19.4%). The above (4.5 g) was oxidised to **19c** by monoperphthalic acid in the manner described for **19b**. The crude product obtained was recrystallised from CH_2Cl_2-hexane (4 g), m.p. 92-93°; M^+ 249; PMR ($CDCl_3$): 8.00 (1H, *s*, C-4H), 5.08 (2H, *t*, N-CH_2), 3.75 (2H, *t*, CH_2OCH_3), 3.45 (3H, *s*, SO_2CH_3), 3.30 (3H, *s*, OCH_3) (Found: C, 33.9; H, 4.5; N, 17.0. $C_7H_{11}N_3O_5S$ requires C, 33.7; H, 4.5; N, 16.9%).

1-Butyl-2-methylsulphonyl-5-nitroimidazole (**19d**)—*n*-Butylamine (146 g) was reacted with bromoacetaldehyde diethyl acetal (118.2 g) by the method described for the synthesis of 2-methoxyethylaminoacetaldehyde diethyl acetal and the crude product obtained distilled under reduced pressure to afford *n*-butylaminoacetaldehyde diethyl acetal as an oil (70 g), b.p. 103°/15 mm.

The above product (70 g) was reacted with potassium thiocyanate (44.4 g) in the manner described for 1-methoxyethyl-2-mercaptoimidazole. The crude product was recrystallised from acetone to afford 1-(*n*-butyl)-2-mercaptoimidazole (38 g); m.p. 80°; M^+ 156 (Found: C, 54.0; H, 8.1; N, 18.2. $C_7H_{12}N_2S$ requires C, 53.8; H, 7.7; N, 17.9%).

The above mercapto compound was methylated with methyl iodide under the conditions used for 1-methyl-2-(2-pentylmercapto)imidazole to afford 1-(*n*-butyl)-2-methylmercapto imidazole as an oil in 93% yield. This was nitrated by the method described for 1-methyl-2-(2-pentylmercapto)imidazole. The crude product was filtered through silica gel column using chloroform-methanol (98:2) as the eluent to obtain 1-(*n*-butyl)-2-methylmercaptoimidazole as an oil in 42% yield; PMR ($CDCl_3$): 7.95 (1H, *s*, C-4H), 4.30 (2H, *t*, N-

CH_2), 2.70 (3H, *s*, S-CH_3), 1.08 (3H, *t*, CH_2CH_3), 1.15-2.00 (4H, complex signals, $CH_2CH_2CH_3$). This was converted as usual by monoperphthalic acid to **19d**. This was obtained as a gum and used as such for the synthesis of **15c**.

2-*Methylsulphonyl*-5-*nitro*-1-*phenylimidazole* (**19e**)—To phenyl isothiocyanate (64 g) was added gradually under stirring aminoacetaldehyde diethyl acetal (50.4 g). The reaction was exothermic and the temperature of the stirred solution rose to 90°C. After 15 min, water (400 ml) was added followed by conc. H_2SO_4 (240 ml). After stirring for 6 hr, the mixture was allowed to stand overnight, heated on a water-bath at 90° (inside temperature) for 2 hr, cooled, diluted with water (1.5 litres) and neutralised with ammonia. The precipitate formed was filtered off, washed well with water and recrystallised from the same solvent, m.p. 146-47°.

The above product was heated with 300 ml of 50% H_2SO_4 at 95° for 2 hr. After dilution with water (1.5 litres) it was neutralised with ammonia, the solid obtained dissolved in methylene chloride (400 ml) and extracted with 200 ml of 5*N* aqueous NaOH. The aqueous extract was neutralised with acetic acid, the solid filtered off and recrystallised from water to get 2-mercapto-1-phenylimidazole (9 g), m.p. 186-87°.

The above mercapto compound (5.2 g) was methylated as described for 1-methyl-2-methylmercaptoimidazole, to afford 2-methylmercapto-1-phenylimidazole as a homogenous oil (4.8 g) which was nitrated under the conditions used for 1-methyl-2-methylmercapto-5-nitroimidazole. The crude solid obtained was recrystallised from ether-hexane to afford 2-methylmercapto-5-nitro-1-phenylimidazole (2 g), m.p. 120° (Found: C, 51.3; H, 4.2. $C_{10}H_9N_3O_2S$ requires C, 51.1; H, 3.9%).

Oxidation of the above compound by monoperphthalic acid in the manner described for **19b** afforded **19e** in 60% yield which was recrystallised from methanol; m.p. 157-58° (Found: C, 45.0; H, 3.7. $C_{10}H_9N_3O_4S$ requires C, 45.0; H, 3.4%). This was used for the synthesis of **15d**.

1-*Methyl*-2-*methylsulphinyl*-5-*nitroimidazole* (**20**)—1-Methyl-2-methylmercapto-5-nitroimidazole (35 g) was reacted with an ethereal solution of monoperphthalic acid (1M, 200 ml) in the manner described for **19b**. The crude product obtained was recrystallised from CH_2Cl_2-ether to afford **20** (21 g), m.p. 99° (Found: C, 31.5; H, 3.7; N, 21.9. $C_5H_7N_3O_3S$ requires C, 31.8; H, 3.7; N, 22.2%).

Reaction of sulphone (**5**) *with sodium salt of imidazolidinone* (**2**)—To a suspension of NaH (50%, 4.8 g) in dry DMF (40 ml) was added under cooling and stirring imidazolidinone (**2**, 11.3 g) and the mixture stirred at 50° for 30 min. **5** (20.5 g) in DMF (20 ml) was then added and the dark red reaction mixture stirred overnight at 85°. The solvent was evaporated under reduced pressure, the residue triturated with water and extracted with methylene chloride. The aqueous solution was carefully acidified with acetic acid and extracted with methylene chloride. The methylene chloride extracts were combined, concentrated *in vacuo* and the gummy residue chromatographed over silica gel using $CHCl_3$-MeOH (95:5) as eluent. The products obtained are given below in the order they were eluted.

25 (CH_2Cl_2-ether), 0.5 g, m.p. 220-22° (Found: C, 36.2; H, 3.9; N, 22.9; S, 10.6. $C_9H_{11}N_5O_5S$ requires C, 35.9; H, 3.7; N, 23.3; S, 10.6%).

27[7] (MeCN), 4 g, m.p. and m.m.p. with an authentic sample, 210-11°.

21[7] (water), 0.75 g, m.p. and m.m.p. with an authentic sample, 203-5°.

24 (MeCN-ether), 0.25 g, m.p. 204-6° (Found: C, 33.9; H, 4.7; N, 16.4; S, 18.1. $C_5H_8N_2O_3S$ requires C, 34.1; H, 4.6; N, 15.9; S, 18.2%).

23 (MeCN-MeOH), 0.2 g, m.p. 283° (d) (Found: C, 44.8; H, 4.8; N, 32.6. $C_{14}H_{17}N_9O_4$ requires C, 44.8; H, 4.6; N, 33.6%).

26 (CH_2Cl_2-ether), 0.2 g, m.p. 170-72° (Found: C, 42.2; H, 6.3; N, 31.8. $C_9H_{16}N_6O_3$ requires C, 42.2; H, 6.3; N, 32.8%).

27 (CH_2Cl_2 + MeOH-ether), 0.65 g, m.p. 218-22° (Found: C, 40.3; H, 5.4; N, 31.9. $C_{10}H_{15}N_7O_4$ requires C, 40.4; H, 5.1; N, 33.1).

Alternative synthesis of **12a**—To a suspension of 2-amino-1-methylimidazole (**28**) hydrochloride (48.5 g) in dry methylene chloride (300 ml) containing triethylamine (34 g) was added dropwise under cooling (0-5°) and stirring β-chloroethyl isocyanate (39.1 g). After the addition, the mixture was stirred at 0-5° for 1 hr and then at 45° for 3 hr. The mixture was cooled, filtered, the filtrate evaporated under reduced pressure, the residue treated with water (10 ml) and extracted with methylene chloride. The methylene chloride extract was evaporated *in vacuo* and the residue recrystallised from ethanol to afford 1-(1-methyl-2-imidazolyl)-2-imidazolidinone (**29**) as the hydrochloride salt (5.6 g), m.p. 187-88° (Found: C, 41.6; H, 5.8; Cl (ionic) 17.4. $C_7H_{10}N_4O$. HCl requires C, 41.5; H, 5.5; Cl, 17.5%).

To a solution of **29** HCl in a mixture of DMF (10 ml) and dioxane (30 ml) was added under cooling (0-5°) and stirring, sodium hydride (50%, 1.4 g) and the mixture stirred at this temperature for 30 min. Methanesulphonyl chloride (3 g) was then added dropwise at 0-5° and the mixture stirred at this temperature for 1 hr and at room temperature for 12 hr after which it was filtered. The filtrate was evaporated *in vacuo* and the residue (viscous oil, 0.7 g) chromatographed over silica gel (25 g). The fraction eluted with 2% methanolic

chloroform gave a solid which recrystallised from isopropanol to afford 1-methylsulphonyl-3-(1-methyl-2-imidazolyl)-2-imidazolidinone (**30**) (0.1 g), m.p. 171-72°; M^+ 244; UV: 225 nm; IR: 1720 ($\nu C=O$).

30 (68 mg) was added at room temperature to nitric acid (0.4 ml; *d* 1.42) containing conc. sulphuric acid (3-4 drops). The mixture was heated gradually to 120° on an oil-bath, and maintained at this temperature for 1.5 hr. The reaction mixture was cooled, poured onto crushed ice, neutralised with aq. sodium bicarbonate and extracted with methylene chloride. After evaporation of the solvent *in vacuo* the residue was chromatographed over silica gel (2 g). The fraction eluted with 2% methanolic chloroform gave 15 mg of a solid; m.p. and m.m.p. with **12a**, 202-3°; M^+ 289; TLC identical with that of **12a**; UV: 316 nm.

Alkaline hydrolysis of **13a**—To a solution of **13a** (2.85 g) in dioxane (10 ml) was added aq. sodium hydroxide (1*N*, 10 ml) and the mixture set aside at room temperature for 5 days. The solvent was evaporated off, the residue treated with water and extracted with chloroform. The chloroform solution on concentration *in vacuo* gave a yellow solid which recrystallised from acetone to afford **31b** (0.5 g) m.p. 200-201° (d); PMR (DMSO-d_6): 7.93 (1H, *s*, C-4H), 7.53, 7.45, 7.38 (3H, 3 broad singlets disappearing with D_2O, 3 NH), 3.67 (4H, *bs*, CH_2CH_2), 3.58 (3H, *s*, N-CH_3); 2.87 ppm (3H, *d*, $NHCH_3$, becoming a singlet with D_2O) (Found: C, 37.5; H, 5.6; N, 32.8. $C_8H_{14}N_6O_2S$ requires C, 37.2; H, 5.5; N, 32.6%).

1-*Methylsulphonylhexahydro-2-pyrimidinone* (**32**)—**32** was obtained in 12% yield by the action of methanesulphonyl chloride on hexahydro-2-pyrimidinone (see synthesis of **7a**). The crude product was recrystallised from methanol-ether; m.p. 172-73°; M^+ 178 (Found: C, 34.0; H, 5.8; N, 16.1. $C_5H_{10}N_2O_3S$ requires C, 33.7; H, 5.7; N; 15.7%).

1-*Methylsulphonyl*-3-(1-*methyl*-5-*nitroimidazol*-2-*yl*)-*hexahydro*-2-*pyrimidinone* (**33**)—**32** was reacted with **5** in the manner described for **12a** and the gummy product obtained chromatographed over silica gel to afford **33** which recrystallised from acetone (yield < 5%), m.p. 134-37°; M^+ 303; PMR ($CDCl_3$): 7.95 (1H, *s*, C-4H), 3.95 (4H, *t*, 2N-CH_2), 3.80 (3H, *s*, N-CH_3), 3.38 (3H, *s*, SO_2CH_3), 2.25 (2H, $CH_2CH_2CH_2$) (Found: C, 36.5; H, 4.6; N, 25.0. $C_9H_{13}N_5O_5S$ requires C, 35.7; H, 4.3; N, 23.1%).

3-*Ethyl*-1-*methyl*-5-*nitro*-2-(3-*methylsulphonyl*-2-*oxotetrahydroimidazolyl*-1) *imidazolium fluoborate* (**34**)—A mixture of **12a** (2.9 g) and triethyloxonium fluoborate (1.9 g) in dry chloroform (200 ml) was left at room temperature for 3 days. The oil separated was triturated with ethanol and the solid obtained recrystallised from ethanol-acetone mixture to afford **34** (0.85 g), m.p. 265-67° (Found: C, 29.8; H, 4.2; N, 17.6. $(C_{10}H_{16}N_5O_5S)^+(BF_4)^-$ requires C, 29.7; H, 4.0; N, 17.3%).

3-*Ethyl*-1-*methyl*-5-*nitro*-2-[3-(*ethylmercaptocarbonyl*)-2-*oxotetrahydroimidazolyl*-1]*imidazolium fluoborate* (**36**)—A mixture of **13a** (7.1 g) and triethyloxonium fluoborate (9.5 g) was left overnight at room temperature. The oil separated was crystallised from aq. ethanol to afford **35** (1.1 g), m.p. 205-8° (Found: C, 35.7; H, 4.6; N, 19.2. $(C_{13}H_{21}N_6O_3S)^+(BF_4)^-$ requires C, 36.5; H, 4.9; N, 19.6%).

A mixture of **35** (1.4 g) and 3*N* HCl (10 ml) was warmed slightly and the solution set aside at room temp. for 16-18 hr. The crystalline solid separated was filtered off, washed with water and recrystallised from methanol to afford **36** (0.6 g), m.p. 224-26°; PMR (DMSO-d_6): 9.2 (1H, *s*, C-4H), 4.05 (7H, *s*, NCH_3 and $-NCH_2CH_2N-$), 4.33 (2H, *q*, N^+-CH_2), 2.95 (2H, *q*, $S-CH_2$), 1.48 (3H, *t*, $N-CH_2CH_3$), 1.28 (3H, *t*, SCH_2CH_3).

1-*Methylsulphonyl*-3-(1-*methyl*-4-*nitroimidazol*-2-*yl*)-2-*imidazolidinone* (**38a**) *and* 1-*methylsulphonyl*-3-(4-*nitro*-1*H*-*imidazol*-2-*yl*)-2-*imidazolidinone* (**37a**)—A mixture of **12a** (10 g) and potassium iodide (10 g) in DMF (70 ml) was heated under reflux for 20 hr, the solvent evaporated under reduced pressure, the residue triturated with water and the solid filtered off. The solid was boiled with acetone and filtered off to afford **37a** which recrystallised from DMF (1.8 g), m.p. 306° (d); M^+ 275 (Found: C, 30.8; H, 3.5; N, 25.8. $C_7H_9N_5O_5S$ requires C, 30.5; H, 3.3; N, 25.5%).

The above aqueous and acetone filtrates gave **38a** which was recrystallised from acetone-methanol; (2.1 g), m.p. 170-71°; M^+ 289; PMR (DMSO-d_6): 8.42 (1H, *s*, C-5H), 4.00 (4H, *s*, CH_2CH_2), 3.66 (3H, *s*, N-CH_3), 3.39 (3H, *s*, SO_2CH_3). (Found: C, 33.4; H, 4.1; N, 24.6. $C_8H_{11}N_5O_5S$ requires C, 33.2; H, 3.8; N, 24.2%).

37b and **38b** were similarly obtained from **13a**:**37b** (acetone), 5% yield; m.p. 290° (d) (Found: C, 35.9; H, 3.9; N, 31.5. $C_8H_{10}N_6O_3S$ requires C, 35.6; H, 3.7; N, 31.1%).

38b (acetone-methanol), 20% yield, m.p. 239-41°; M^+ 284; PMR (DMSO-d_6): 9.97 (1H, *bq*, NH), 8.32 (1H, *s*, C-5H) 4.30 (2H, *t*, $N-CH_2$), 3.95 (2H, *t*, N-CH_2), 3.73 (3H, *s*, $N-CH_3$), 3.12 (3H, *d*, $NHCH_3$) (Found: C, 38.3; H, 4.5; N, 29.5. $C_9H_{12}N_6O_3S$ requires C, 38.0; H, 4.3; N, 29.6%).

1-*Methylsulphonyl*-3-(1-*methyl*-4-*nitroimidazol*-5-*yl*)-2-*imidazolidinone* (**41**)—The sodium salt of **7a** was reacted with **40** by the method used for **12a** and the crude product obtained recrystallised from acetone to afford **41** in 20% yield (see Table 3).

Compounds **43**, **44a-e** and **44g-i** were similarly prepared. The physical data of these compounds are listed in Table 3.

1-(2-*Aminophenyl*)-3-*methylsulphonyl*-2-*imidazolidinone* (**44f**)—A solution of **44e** in methanol was hydrogenated in an Ente apparatus at room temperature and 15 psi over 10% Pd/C catalyst until 3 mol of hydrogen were absorbed (~16 hr). The solution was filtered, evaporated under reduced pressure and the residue recrystallised from acetone-ethanol to afford **44f** (Table 3).

1-*Methylsulphonyl*-3-(5-*nitrothiazol*-2-*yl*)-2-*imidazolidinone* (**46**)—Niridazole (**45**)[8] was reacted with methanesulphonyl chloride in the manner described for **7a** to afford **46** (see Table 3).

Acknowledgement

We thank Dr T R Govindachari and Dr R S Grewal for their interest in the work. Dr S Selvavinayakam and his associates—Messrs R K Agashe and T P Vaikuntaraman (PMR spectra), A N Bhale Rao (UV), R K Sundaram (IR) and K Umesh Rao (mass), S S Kulkarni, S M Atre and D S Varde (elemental analyses) and Mr M S Kirtikar for TLC data and help with the charts.

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