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Nitroimidazoles: Part V—1-(1-Methyl-5-nitroimidazol-2-yl)-1,2,4-triazolidin-3,5-diones & Analogues†‡

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Condensation of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**1**) with the sodium salts of triazolidinediones affords the derivatives **2a-i**; similar reaction with the sodium salts of thiazolidinone, 2-iminothiazolidine, pyrrolidinone, oxazolidinone and its 2-methyl and 2-chloromethyl analogues leads to the formation of products **3-8** respectively. Under the reaction conditions **3** is opened by dimethylamide ion to form **10**, and **6** by methyl sulfinate ion to provide **13** respectively. Additionally, **6** is hydrolysed to the amine (**12**). Cyclic sulphamides (**17-22**) undergo reaction with **1** to provide nitroimidazoles (**23-28**).

The pronounced antiprotozoal properties of 1-methylsulphonyl-3-(1-methyl-5-nitroimidazol-2-yl)-2-imidazolidinone** reported in the previous commanication[1] prodded us to synthesise and evaluate analogues wherein the imidazolidinone moiety was replaced by other five-ring heterocycles incorporating an imide, lactam or sulphamide group. We describe in this paper the synthesis of 1-methyl-5-nitroimidazoles carrying at position-2, triazolidinedione, oxazolidinone, thiazolidinone and pyrrolidinone residues as also cyclic sulphamides.

The synthetic procedure employed was the same as the one adopted earlier[1], viz. condensation of sulphone with the sodium salt of the imide/lactam (Chart 1). The use of triazolidinediones[2] afforded compounds of the general structure (**2**) in fair to good yields (Table 1). 2-Thiazolidinone and 2-iminothiazolidine gave rise to products **3** and **4**, and pyrrolidinone, **5**, while oxazolidinone, 5-methyloxazolidinone and 5-chloromethyloxazolidinone led to **6**, **7** and **8** respectively. Since the yields of desired products in these reactions were far from satisfactory, the condensation of thiazolidinone and oxazolidinone with sulphone (**1**) was studied intensively. In the former case, a byproduct was obtained, which analysed for $C_9H_{15}N_5O_3S$. Its PMR spectrum in $CDCl_3$ displayed signals at δ 7.95 (1H, *s*), 5.55 (1H, *bs* disappearing with D_2O), 3.90 (3H, *s*), 3.50 (4H, *m*) and 2.90 (6H, *s*). These data would fit either structure (**9**) or (**10**), which would arise from **3** by opening of the thiazolidinone ring with dimethylamide ion contributed by the solvent, DMF in the condensation reaction (Chart 2). The IR spectrum (nujol) exhibited a band for C=O at 1645 cm^{-1}, while the UV spectrum (EtOH) had λ_{max} at 348 nm, which was unchanged on the addition of alkali. These data clearly favoured structure (**9**) for the byproduct, since **10** would be expected to have a C=O band in the IR spectrum at a higher frequency; λ_{max} in EtOH would also be expected ~390 nm which should be further shifted to 470 nm on the addition of alkali[3]. The mass spectrum of **9** did not exhibit a molecular ion, but only a major fragment at *m/z* 229 due to facile

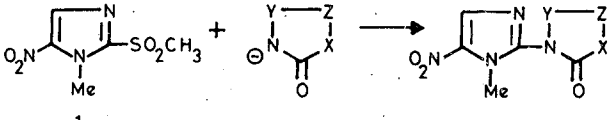
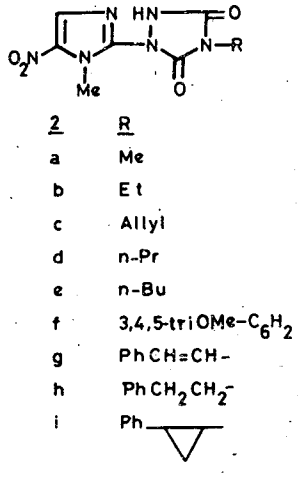
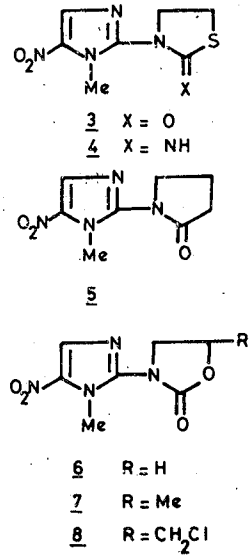


Chart 1





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$^{\delta}$PMR chemical shifts throughout the paper in δ (ppm).

Table 1—2-Substituted-1-methyl-5-nitroimidazoles

Compd	m.p. (°C)	Crystallised from	Yield %	Mol. formula	M^+ m/z	Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
2a	148-49	MeOH-Et_2O	26	$C_7H_8N_6O_4$	—	35.00	3.36	34.99	35.33	3.67	34.84
2b	121-22	CH_2Cl_2-hexane	42	$C_8H_{10}N_6O_4$	—	37.80	3.97	33.06	37.97	4.22	32.80
2c	142-43	CH_2Cl_2-Et_2O	30	$C_9H_{10}N_6O_4$	—	40.60	3.79	31.57	40.30	4.07	31.34
2d	122-23	CH_2Cl_2-hexane	58	$C_9H_{12}N_6O_4$	268	40.30	4.51	31.33	40.65	4.91	31.01
2e	129-30	CH_2Cl_2-hexane	25	$C_{10}H_{14}N_6O_4$	282	42.55	5.00	29.78	42.26	5.34	29.68
2f	242-43	CH_2Cl_2 + MeOH – Et_2O	50	$C_{15}H_{16}N_6O_7$	392	45.92	4.11	21.42	46.02	4.45	20.99
2g	183-84	DMF-Et_2O	28	$C_{14}H_{12}N_6O_4$	—	51.22	3.68	25.60	51.16	4.00	25.24
2h	145-46	CH_2Cl_2-Et_2O	26	$C_{14}H_{14}N_6O_4$	330	50.91	4.27	25.45	50.87	4.56	25.57
2i	172-73	CH_2Cl_2-Et_2O	25	$C_{15}H_{14}N_6O_4$	342	52.63	4.12	24.55	52.30	4.30	24.44
3	129-30	CH_2Cl_2-Et_2O	28	$C_7H_8N_4O_3S$	228	36.85	3.53	24.56	37.20	3.89	24.81
4	162-65	MeOH-$CHCl_3$	15	$C_7H_9N_5O_2S$	227	37.01	3.99	30.83	37.00	4.07	30.96
5	108-9	CH_2Cl_2-hexane	12	$C_8H_{10}N_4O_3$	210	45.71	4.80	26.66	46.05	4.99	27.05
6	161-62	CH_2Cl_2-Et_2O	39	$C_7H_8N_4O_4$	212	39.62	3.80	26.41	39.62	3.88	26.38
7	130-33	CH_3CN-Et_2O	23	$C_8H_{10}N_4O_4$	226	42.48	4.46	24.77	42.74	4.41	25.07
8	145-46	CH_3CN-Et_2O	10	$C_8H_9ClN_4O_4$	260, 262	36.86	3.48	21.50	37.18	3.86	21.62
9(11)	122-23	CH_2Cl_2-Et_2O	3	$C_9H_{15}N_5O_3S$[a] $[M^+ - N(CH_3)_2]$	229	39.56	5.53	25.63	39.70	5.88	25.50
12	152-53	CH_3CN-Et_2O	—	$C_6H_{10}N_4O_3$	186	38.71	5.41	30.10	39.08	5.54	29.71
13	208-9 (d)	CH_3CN-Et_2O	—	$C_7H_{12}N_4O_4S$[b]	248	33.87	4.87	22.58	34.39	5.21	22.87
23	113-14	CH_2Cl_2-Et_2O	12	$C_7H_{11}N_5O_4S$	261	32.19	4.25	26.81	32.60	4.65	26.45
24	85-86	CH_2Cl_2-hexane	16	$C_8H_{13}N_5O_4S$	275	34.91	4.76	25.45	34.78	4.98	25.31
25	87-88	CH_2Cl_2-hexane	33	$C_9H_{15}N_5O_4S$	289	37.37	5.23	24.21	37.87	5.55	24.16
26	130-31	CH_2Cl_2-hexane	55	$C_{11}H_{17}N_5O_4S$	316 $(M^+ + 1)$	41.90	5.43	22.21	41.89	5.65	22.52
27	186-88	CH_2Cl_2-Et_2O	55	$C_{10}H_{15}N_5O_4S$	301	39.87	5.02	23.25	40.05	5.33	23.38
28	142-43	CH_2Cl_2-Et_2O	46	$C_{11}H_{17}N_5O_4S$	315	41.90	5.43	22.21	42.15	5.62	22.43

[a]Calc., S, 11.71; found S, 11.90%.
[b]Calc., S, 12.89; found S, 13.25%.

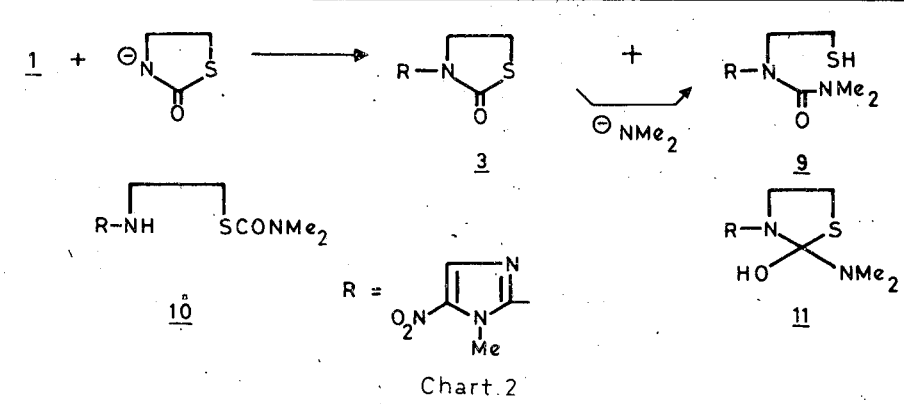


Chart 2

loss of Me_2N moiety. The IR spectrum (nujol) in the solid state rather intriguingly showed a sharp band at 3490 cm^{-1}, which can be reconciled with **9** only by proposing that in the solid state (and perhaps also in solutions in non-polar solvents) it exists partly as the cyclic hemiketal (**11**). On the other hand, in ethanol, the open chain form (**9**) is preferred. This was also supported by the strong similarity of the UV spectrum of **9** with those of ureas of 1-methyl-2-amino-5-nitroimidazole[4].

The reaction of sulphone (**1**) with oxazolidinone gave rise to a mixture of three products which were separated by silica gel chromatography. The major product was the expected oxazolidinone (**6**, 39%), $C_7H_8N_4O_4$, M^+ 212: PMR: 3.80 (3H, *s*, N-Me), 4.17 (2H, approx. *t*, OCH_2), 4.63 (2H, approx. *t*, NCH_2)

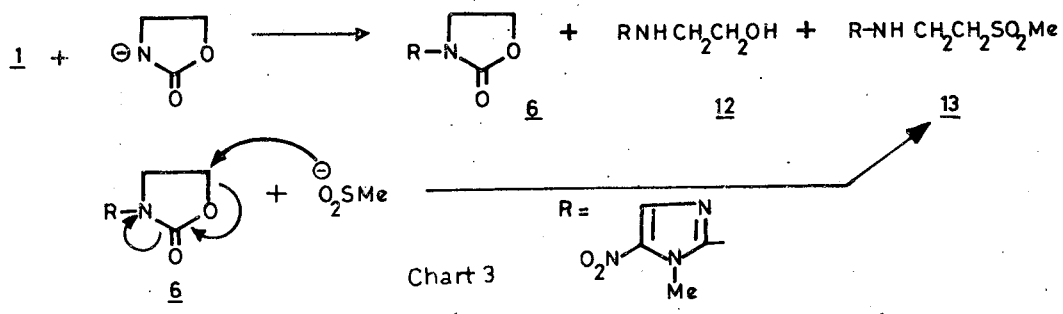
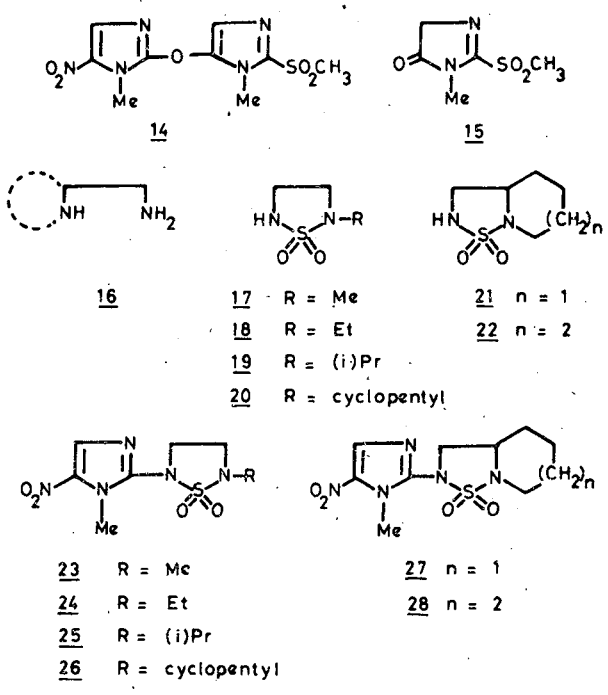


Chart 3

and 8.00 (1H, *s*, C-4H); IR: 1780 cm^{-1} ($\nu C=O$). The second product was the hydrolysis product, the substituted aminoethanol (**12**), $C_6H_{10}N_4O_3$, M^+ 186; UV (EtOH): 380 nm (log ε 4.11), identical with a sample synthesised by another route[4]. The third product contained sulphur and was obviously anomalous. Analysis ($C_7H_{12}N_4O_4S$) and spectral data pointed to the structure (**13**): M^+ 248; PMR: δ 3.03 (3H, *s*, SO_2Me), 3.42 (2H, *t*, $J=6$ Hz, SO_2CH_2), 3.63 (3H, *s*, N-Me), 3.83 (2H, *q*, $J=6$ Hz, NCH_2), 7.37 (1H, *t*, $J=6$ Hz, NH) and 7.87 (1H, *s*, C-4H). Its UV spectrum in particular with λ_{max} at 380 nm (log ε 4.15), resembled that of **12** providing definitive support for the structure. Obviously methyl sulphinate generated in the displacement reaction by oxazolidinone on **1** had opened the lactone ring in **6** as shown in Chart 3 to lead to **13**.

In the case of 5-chloromethyloxazolidinone, chromatographic analysis indicated that in addition to the expected **8**, two minor products were formed. These were identified as **14** and **15**. The formation of these in condensation reactions of **1** has been noted in an earlier paper and rationalised[1].

After ascertaining that sulphamide ion could displace the sulphone group in **1**[4], we looked at some cyclic sulphamides. Successful condensation was achieved with the sulphamides (**17-22**) to afford the nitroimidazole derivatives (**23-28**). The starting materials were obtained by the reaction of the appropriate diamines (**16**) with sulphamide.



14 **15**

16

17 R = Me
18 R = Et
19 R = (i)Pr
20 R = cyclopentyl

21 n = 1
22 n = 2

23 R = Me
24 R = Et
25 R = (i)Pr
26 R = cyclopentyl

27 n = 1
28 n = 2

Experimental Procedure

1-(1-*Methyl-5-nitroimidazol-2-yl*)-4-*methyl*-1, 2, 4-*triazolidine*-3, 5-*dione* (**2a**)—To a suspension of NaH (50%, 2 g) in DMF (30 ml) was added dropwise under cooling (10-15°) and stirring a solution of 4-methyl-1, 2, 4-triazolidine-3, 5-dione[2] (4.6 g) in DMF (20 ml). After the addition was over the mixture was stirred at room temperature for 1 hr. To this was added a solution of the sulphone (**1**, 8.2 g) in DMF (15 ml) dropwise at 10-15°, and the reaction mixture stirred overnight at room temperature. The solvent was removed *in vacuo*, the residue triturated with water, the solid obtained filtered off and recrystallised from MeOH-Et_2O to afford **2a** (see Table 1).

Compounds **2b-i**, **4**, **5**, **7** and **8** were similarly prepared. The physical data for these compounds are given in Table 1.

3-(1-*Methyl-5-nitroimidazol-2-yl*)-2-*thiazolidinone* (**3**) *and N-dimethylcarbamoyl-N*-(1-*methyl-5-nitroimidazol-2-yl*)*cysteamine* (**9**)—Sulphone (**1**) was reacted with the sodium salt of thiazolidin-2-one in the manner described for **2a** and the crude gummy product chromatographed over silica gel. The fractions with 1% methanolic chloroform gave **3** (Table 1) and those with methanol-chloroform (97:3) gave **9**(**11**) (See Table 1).

3-(1-*Methyl-5-nitroimidazol-2-yl*)-2-*oxazolidinone* (**6**), 2-*hydroxy-N*-(1-*methyl-5-nitroimidazol-2-yl*)*ethylamine* (**12**). *and N*-(1-*methyl-5-nitroimidazol-2-yl*)-2-*methylsulphonylethylamine* (**13**)—The sodium salt of 2-oxazolidinone was reacted with the sulphone (**1**) by the method used for **2a** and the gummy product obtained was triturated with chloroform-ether to afford **6** (Table 1). The mother liquor was chromatographed over silica gel. Fractions eluted with $CHCl_3$-MeOH (99:1) gave **12** (Table 1) whereas **13** was obtained from those with 3% methanolic chloroform.

2-Methyl-1, 2, 5-thiadiazolidine-1, 1-dioxide (**17**)—To a boiling solution of sulphamide (28.8 g) in pyridine (240 ml) was added dropwise under stirring N-methylethylenediamine (22.2 g) during 3 hr. After the addition was over, boiling under reflux was continued until the evolution of NH_3 ceased (~50 hr). The reaction mixture was filtered, the filtrate evaporated *in vacuo* and the residue chromatographed over silica gel. The fractions eluted with 3% methanolic chloroform were evaporated *in vacuo* to afford **17** as an oil (15.5 g), PMR ($CDCl_3$): 5.63 (1H, *bs*, disappearing with D_2O, NH), 3.40 (4H, *s*, CH_2CH_2) and 2.67 (3H, *s*, CH_3).

Compounds **18-22** were similarly prepared.

18: oil (35% yield); PMR ($CDCl_3$): 5.25 (1H, *bs*, disappearing with D_2O, NH), 3.45 (4H, *s*, CH_2CH_2), 3.08 (2H, *q*, CH_2CH_3), 1.23 (3H, *t*, CH_2CH_3).

19: oil (35% yield); PMR ($CDCl_3$): 5.50 (1H, *bs*, disappearing with D_2O, NH), 3.63 [1H, *septet*, $CH(CH_3)_2$], 3.43 (4H, *s*, CH_2CH_2) and 1.25 [6H, *d*, $CH(CH_3)_2$].

20: (CH_2Cl_2-hexane) (30% yield); m.p. 65-66°; M^+ 190 (Found: C, 44.4; H, 7.5; N, 14.4. $C_7H_{14}N_2O_2S$ requires C, 44.2; H, 7.4; N, 14.7%).

21: (hexane) (27% yield); m.p. 49-50°; M^+ 176 (Found: C, 41.3; H, 7.1; N, 15.9. $C_6H_{12}N_2O_2S$ requires C, 40.9; H, 6.9; N, 15.9%).

22: (*n*-pentane) (22% yield); m.p. 43-44° (Found: C, 44.1; H, 7.6; N, 14.5. $C_7H_{14}N_2O_2S$ requires C, 44.2; H, 7.4; N, 14.7%).

2-N-(1-Methyl-5-nitroimidazol-2-yl)-2-substituted-1, 2, 5-thiadiazole 1, 1-dioxides (**23-28**)—Sulphone (**1**) was reacted with the sodium salts of sulphamides (**17-22**) to afford the compounds (**23-28**) respectively. Physical properties of these compounds are listed in Table 1.

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