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Nitroimidazoles: Part XVI—Some 1-Methyl-4-nitro-5-substituted Imidazoles†‡

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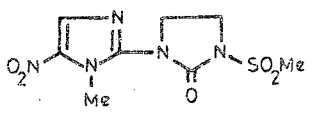
Treatment of 1-methyl-4-nitro-5-chloroimidazole (**3**) with 5-membered lactams, e.g. imidazolidinones, oxazolidinone and thiazolidinone affords N-imidazolyl derivatives (**4a-d**). Reaction of **3** with imidazole yields **4e**; amino derivatives (**4f-h**) are similarly obtained. 2-Hydroxypyrazine, 4-hydroxyquinazoline and 3,4,5-trichlorophenol and **3** react to form O-derivatives (**4i-k**), while mercaptans provide the sulphides (**4l-n**). Imidazole (**11**) is formed from 1-methyl-4-chloro-5-nitroimidazole (**10**).

Our exercises in nitroimidazole chemistry resulting in the synthesis of the potent antiprotozoal agent, 1-methyl-sulphonyl-3-(1-methyl-5-nitroimidazol-2-yl)-2-imidazolidinone[1] (**1**)** and the well-known immunosuppressive properties of azathioprine {[6-(1-methyl-4-nitro-imidazol-5-yl)thio]purine; imuran ® **2**} prompted us to synthesise some 1-methyl-4-nitroimidazoles carrying diverse substituents at position-5. These were prepared from 1-methyl-4-nitro-5-chloro imidazole (**3**)[3] by reaction with appropriate nucleophiles.

Treatment of **3** with the sodium salt of 1-acetyl-2-imidazolidinone gave a mixture of the expected **4a**; the desacetyl derivative (**4b**) and the bis condensation product (**5**) of 2-imidazolidinone with **3**, these were easily separated by chromatography. **5** was also obtained by reacting 2 mol of **3** with the sodium salt of 1 mol of 2-imidazolidinone. The reaction of 1-acetyl-2-imidazolidinone with 1-methyl-2-methanesulphonyl-5-nitroimidazole has been reported earlier to give a similar series of three products.[4] The products in these cases as well as with oxazolidinone and thiazolidinone are so formulated (heteroarylation of N rather than O) because of the presence of appropriate C=O bands in the IR spectra. Reaction products of the sodium salts of 2-hydroxypyrazine and 4-hydroxyquinazoline on the other hand appeared to be the O-imidazolyl derivatives **4i** and **4j** respectively although N-arylation is not totally ruled out. The product from 4-aminopyridine and **3** was assigned the usual nuclear N-arylated structure (**4f**), **4l** obtained from *ortho*-aminothiophenol and **3** was converted into the acetyl derivative **6**, which failed to give **7** when subjected to the usual basic conditions for the formation of phenothiazines[5]. Equally unfruitful was the effort to cyclise the amine (**8**) derived from **4m** to the imidazobenzothiazepine (**9**). The reaction of sodio-imidazole with **3** and the isomeric halide **10**[3] gave **4e** and **11** respectively which are position isomers of the potent antiprotozoal agent, 1-(1-methyl-5-nitro-imidazol-2-yl) imidazole[6].



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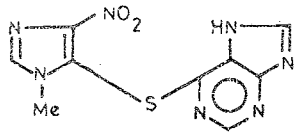

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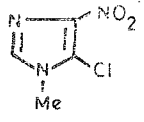

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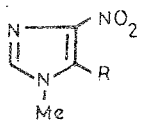

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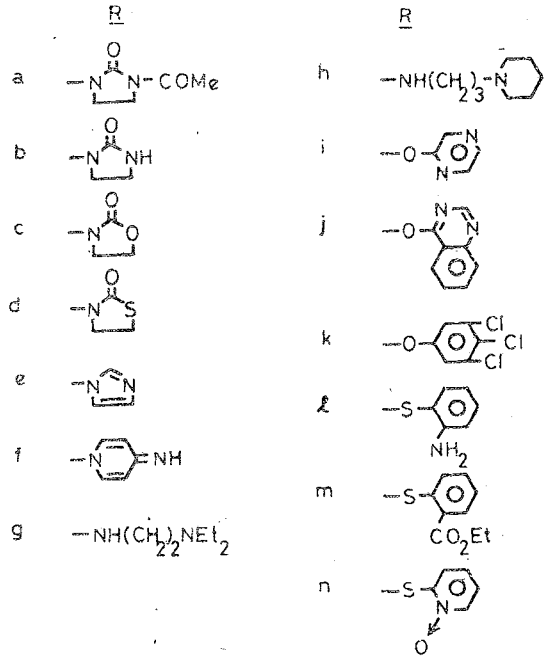

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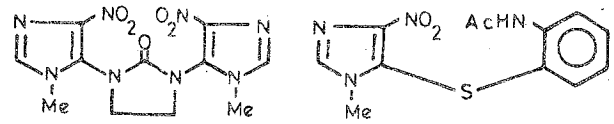

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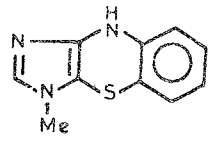

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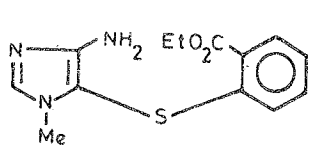

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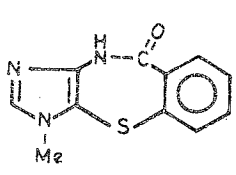

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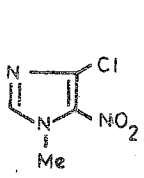

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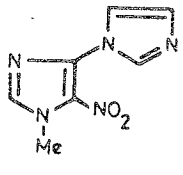

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1-Acetyl-3-(1-methyl-4-nitroimidazol-5-yl)-2-imidazolidinone (**4a**), *1-(1-methyl-4-nitroimidazol-5-yl)-2-imidazolidinone* (**4b**) *and* *1,3-bis-(1-methyl-4-nitroimidazol-5-yl)-2-imidazolidinone* (**5**)—To a suspension of 50% NaH (3.6 g) in DMF (20 ml) was added under cooling (10-15°) and stirring, a solution of N-acetylethyleneurea (9.6 g) in DMF (60 ml). After the addition was over the reaction mixture was stirred at 15-20° for 45 min. A solution of **3** (8.05 g) in DMF (30 ml) was then added and the mixture heated at 95-100° for 90 min. The solvent was removed under reduced pressure, the residue dissolved in methylene chloride, filtered and the filtrate evaporated *in vacuo*. The residue was washed with hexane to remove mineral oil and triturated with CH_3CN. The solid was filtered off and recrystallised from DMF-ether to afford **5** (2 g).

The mother liquor was evaporated *in vacuo* and the residue chromatographed over silica gel. Fractions with 2% methanolic chloroform gave N,N'-diacetylethyleneurea. Further fractions with 3% methanolic chloroform gave a solid which was recrystallised from acetonitrile-ether to afford **4a**. Fractions with 5% methanolic chloroform yielded **4b** which was recrystallised from acetonitrile-ether. Physical properties of these and other compounds made by the above method are recorded in Table 1.

1-Methyl-4-nitro-5-(4-imino-1,4-dihydro-1-pyridyl) imidazole hydrochloride (**4f**)—A mixture of **3** (8.1 g) and 4-aminopyridine (4.7 g) in absolute ethanol (100 ml) was heated under reflux for 20 hr. The reaction mixture on cooling gave **4f** as yellow crystalline solid.

1-Methyl-4-nitro-5-(2-diethylaminoethylamino) imidazole (**4g**) *and* *1-methyl-4-nitro-5-[3-[N-piperidino)propylamino]imidazole* (**4h**)—A mixture of **3** (4.85 g), 2-diethylaminoethylamine (7 g) and benzene (60 ml) was heated under reflux for 4 hr, the solvent evaporated off and the residue triturated with water. The solid was filtered off and recrystallised from methylene chloride-ether to afford **4g**.

Similarly was prepared **4h** from **3** and 3-piperidinopropylamine.

1-Methyl-4-nitro-5-(2-pyrazinyloxy)imidazole (**4i**), *1-methyl-4-nitro-5-(4-quinazolinyloxy)imidazole* (**4j**) *and* *1-methyl-4-nitro-5-(3,4,5-trichlorophenoxy)imidazole* (**4k**)—To a solution of 2-hydroxypyrazine (4.8 g) in freshly prepared sodium ethoxide, (1.2 g Na dissolved in 125 ml of absolute ethanol) was added under stirring, a solution of **3** (8.05 g) in hot absolute ethanol

Table 1—1-Methyl-4-nitro-5-substituted imidazoles

Compd.	Yield %	Crystallised from	m.p. (°C)	Mol. formula	Analysis (%)					
					Calculated			Found		
					C	H	N	C	H	N
4a	4	CH_3CN-Et_2O	105-9	$C_9H_{11}N_5O_4$	42.69	4.38	27.67	43.06	4.58	27.72
4b	15	CH_3CN-Et_2O	186	$C_7H_9N_5O_3$	39.81	4.30	33.17	40.20	4.44	32.98
4c	40	CH_3CN-Et_2O	134	$C_7H_8N_4O_4$	39.62	3.80	26.41	40.22	3.90	27.02
4d	83	CH_3CN-Et_2O	233-35	$C_7H_8N_4O_3S$	36.85	3.53	24.56	37.12	3.57	24.97
4e	20	H_2O	160-61	$C_7H_7N_5O_2$	43.52	3.65	36.26	43.75	3.83	36.58
4f HCl	78	MeOH–EtOAc	291(d)	$C_9H_9N_5O_2.HCl$	42.28	3.94	27.39	42.05	4.65	27.69
4g	66	$CH_2Cl_2-Et_2O$	78-82	$C_{10}H_{19}N_5O_2$	49.77	7.94	29.03	49.41	8.03	29.23
4h	62	$CH_2Cl_2-Et_2O$	86-88	$C_{12}H_{21}N_5O_2$	53.92	7.92	26.20	53.72	8.07	25.86
4i	45	DMF–MeOH	>300	$C_8H_7N_5O_3$	43.44	3.19	31.67	43.40	3.28	31.42
4j	45	$CHCl_3-Et_2O$	186-87	$C_{12}H_9N_5O_3$	53.14	3.34	25.82	53.50	3.52	25.72
4k	32	$CHCl_3$–hexane	234	$C_{10}H_6Cl_3N_3O_3$	37.24	1.88	13.03	37.49	1.99	12.89
4l	60	Benzene	134-36	$C_{10}H_{10}N_4O_2S$	48.00	4.02	22.39	48.02	4.26	22.67
4m	70	EtOAc–hexane	182	$C_{13}H_{13}N_3O_4S$	50.81	4.26	13.68	51.12	4.37	13.09
4n	72	MeOH	154(d)	$C_9H_8N_4O_3S$	42.86	3.20	22.22	42.80	3.33	21.83
5	25	DMF–Et_2O	286-87(d)	$C_{11}H_{12}N_8O_5$	39.29	3.60	33.33	39.80	3.88	33.42
6	68	EtOH	166-67	$C_{12}H_{12}N_4O_3S$	49.31	4.14	19.17	49.54	4.51	19.45

(100 ml) and the reaction mixture boiled under reflux for 18-20 hr. The solvent was evaporated off, the residue treated with water (30 ml) and extracted with methylene chloride. The methylene chloride extract was evaporated *in vacuo* and the residue crystallised from DMF-methanol to afford **4i**.

Similarly were synthesised **4j** and **4k** by the action of **3** on sodium salts of 4-hydroxyquinazoline and 3,4,5-trichloro-phenol respectively.

1-Methyl-4-nitro-5-(o-aminophenyl)mercaptoimidazole (**4l**)—A solution of **3** (4 g) in hot ethanol (50 ml) was added to a solution of *o*-aminothiophenol (3.13 g) in ethanol (30 ml) containing 12.5% aq. sodium hydroxide (8 ml). The reaction mixture was heated under reflux for 30 min, concentrated *in vacuo*, cooled and the solid obtained filtered off and recrystallised from benzene to afford **4l**.

1-Methyl-4-nitro-5-(2-carbethoxyphenyl)mercaptoimidazole (**4m**)—To a solution of ethyl thiosalicylate in sodium ethoxide (2.4 g of Na dissolved in 100 ml of absolute ethanol) was added under stirring a hot solution of **3** (16.15 g) in absolute ethanol (200 ml). The reaction mixture was heated under reflux for 16-18 hr, allowed to cool to room temperature, the solid filtered off, triturated with water and filtered again. Recrystallisation from methanolic chloroform afforded **4m**.

2-(1-Methyl-4-nitroimidazol-5-yl)mercaptopyridine N-oxide (**4n**)—A warm solution of **3** (8.05 g) in ethanol (100 ml) was added under stirring to 2-mercaptopyridine N-oxide sodium salt in warm ethanol (80 ml) and the reaction mixture stirred overnight at room temperature. The yellow solid separated was filtered off, triturated with water, filtered again and recrystallised from methanol at $<50°$ (the solution turned dark at higher temperature) to afford **4n**.

1-Methyl-4-nitro-5-(o-acetamidophenyl)mercaptoimidazole (**6**)—A mixture of **4l** (1 g) and acetic anhydride (5 ml) containing a drop of pyridine was heated on a water-bath at 90° for 3 hr. The reaction mixture was cooled, poured into water and left at room temperature for 2-3 hr. The solid was filtered off and recrystallised from ethanol to afford **6**.

1-Methyl-4-amino-5-(2-carbethoxyphenyl)mercaptoimidazole (**8**)—A solution of **4m** (6.15 g, 20 mmol) in 2-methoxyethanol (150 ml) was hydrogenated in a Parr apparatus at 40 psi at 45° in the presence of Raney nickel (2 g) until 60 mmol of hydrogen was absorbed (3 hr). The solution was filtered, the filtrate evaporated *in vacuo* and the residue recrystallised from methylene chloride-hexane to afford **8** (1.6 g), m.p. 162-63° (Found: C, 56.6; H, 5.8; N, 15.0. $C_{13}H_{15}N_3O_2S$ requires C, 56.3; H, 5.5; N, 15.2%).

1-Methyl-4-(1-imidazolyl)-5-nitroimidazole (**11**)—**11** was obtained from **10** and imidazole by the method described for **4a**. The crude product was converted into the nitrate salt which crystallised from methanol-ether, yield 42%, m.p. 185-86° (Found: C, 33.2; H, 3.5; N, 33.0. $C_7H_7N_5O_2.HNO_3$ requires C, 32.8; H, 3.2; N, 32.8%).

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