Indian Journal of Chemistry
Vol. 21B, October 1982, pp. 949-952

Nitroimidazoles: Part VII—1-(1-Alkyl-5-nitroimidazol-2-yl)-aza(diaza, oxaza)cycloalkanes†‡

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

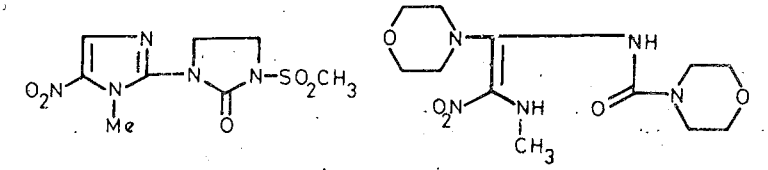
Reaction of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**2**) with pyrrolidine, piperidine and morpholine affords the amines (**3a-c**) (=**9a-c**) respectively in low yields, the reaction failing with other bases tried. Analogues (**9d-t**) have been obtained more readily by nitrating imidazoles (**8**), which are synthesised from thioureas (**5**) of cyclic secondary amines through the S-methylisothioureas (**6**) and the guanidinoacetals (**7**).

We have reported in the previous communications, the synthesis of a large number of 1-methyl-5-nitroimidazole derivatives connected at position-2 to azaheterocycles via their N-atom. These azaheterocycles were in various stages of oxidation, e.g. imidazolidinone[1], oxazolidinone[2], imidazole[3] etc. Several of these possessed marked antiprotozoal activity, among which 1-methylsulphonyl-3-(1-methyl-5-nitroimidazol-2-yl)-2-imidazolidinone** (**1**) is undergoing advanced clinical trials. A logical extension of this study would be to nitroimidazoles of the general structure (**3**), with an azacycloalkyl ring at position-2, especially pyrrolidine. Compound **3a** in fact turned out to be moderately active; hence the study was expanded to cover diverse rings and the results are presented in this paper.

The first approach to the synthesis of **3** involved treatment of the sulphone (**2**) with appropriate cyclic secondary amine. This was found to be moderately useful with pyrrolidine and piperidine. The latter yielded **3b** which was identical with the product reported earlier[4] from the reaction of 1-methyl-2-bromo-5-nitroimidazole and piperidine. **2** and morpholine gave the desired **3g** in very low yield, while with many other cyclic secondary amines, the reaction failed. Careful analysis of the product from **2** and morpholine gave in addition to unreacted **2** and **3c**, a reddish water-soluble gum which could not be induced to crystallise. Its mass spectrum (M^+ 315) indicated **4** as a possible structure. The PMR spectrum was rather complex but had the expected signals.

It was noted that the reaction of **2** with amines occasionally became exothermic suddenly and led to reddish water-soluble products. From this study and those reported earlier[1-3], it would appear that the displacement of the methylsulphonyl group in **2** by various nitrogenous anions would conform to the order, shown in Chart 1, with regard to ease and yields of clean products.

The alternate route appeared more widely applicable for the synthesis of compounds of general structure (**3**) (=**9**) (Chart 2). The route (Chart 3) con-



1 4

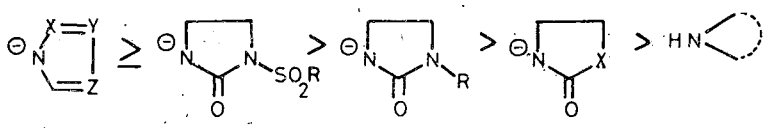
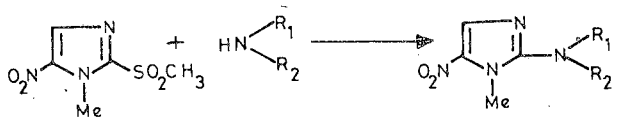


Chart 1

X = O, S

†Part VI: *Indian J Chem*, **21B** (1982) 945.
‡Contribution No. 646 from CIBA-GEIGY Research Centre.
**Code No. C 10213-Go.

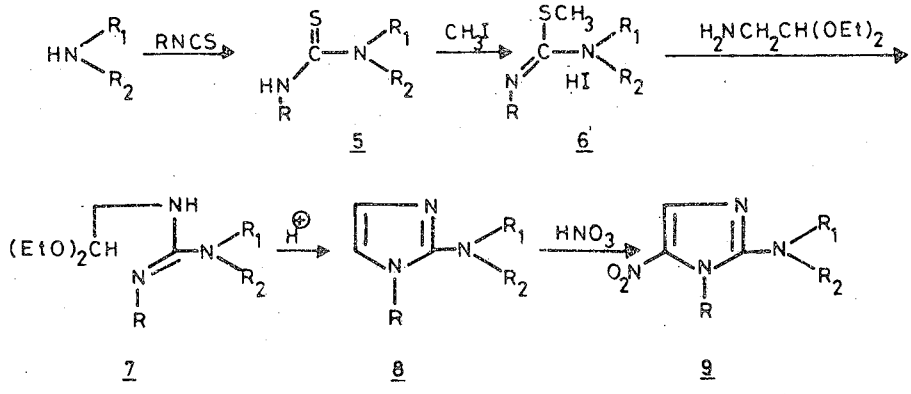
sisted of 5 steps: (i) thiocarbamoylation of azacycloalkanes (e.g. pyrrolidine, piperidine, morpholine, etc.) to **5**; (ii) conversion of **5** to isothiouronium derivatives **6** with methyl iodide; (iii) reaction of **6** with aminoacetal to form guanidines (**7**) (not isolated); (iv) acid-catalysed cyclisation of **7** to imidazoles (**8**); and (v) nitration of **8** to target **9**. Imidazoles (**8**) were characterised by their PMR spectra by an *AB* quartet centred around δ 6.7 ($\Delta\delta = 0.1$; and $J = 1.5$ Hz) which occasionally merged into a singlet, while the nitro derivatives exhibited a singlet at about 7.9. The last step invariably yielded only the 5-nitroimidazole, as was established in the cases of pyrrolidine, piperidine and morpholine by comparison of **3a-c** with **9a**, **9b** and **9g** respectively. Although the yields in the nitration reaction were low to moderate, the route was applicable to a wide variety of heterocycles and the yields in the earlier steps were high. It also offered the



2 3

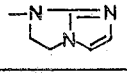
a pyrrolidino
b piperidino
c morpholino

Chart 2



5 6 7 8 9

Chart 3

for 5-9	R	$N<^{R_1}_{R_2}$	for 5-9	R	$N<^{R_1}_{R_2}$
a	Me	pyrrolidino (9a = 3a)	k	Me	4-diethylcarbamoyl piperazino
b	Me	piperidino (9b = 3b)	l	Me	4-benzylpiperazino (4-CH_3I salt)
c	Me	1,2,5,6-tetrahydro-1-pyridyl	m	Me	4-(4-chlorophenyl) piperazino
d	Me	hexahydroazepino	n	Me	4-dimethyl sulphamoyl piperazino
e	Me	octahydroazocino	o	Me	4-thiamorpholino (S,S-dioxide)
f	Me	3-azabicyclo [3,2,2] nonyl	p	Et	piperidino
g	Me	morpholino (9g = 3c)	q	Et	pyrrolidino
h	Me	2,6-dimethyl morpholino	r	cyclohexyl	pyrrolidino
i	Me	4-acetylpiperazino	s	benzyl	pyrrolidino
j	Me	4-carbethoxypiperazino	t	Me	

possibility of changing the substituent at position-1 of the nitroimidazole moiety: Me (**9a**), Et (**9p**; **9q**), cyclohexyl (**9r**) and benzyl (**9s**). Some exceptions to the versatility of this approach were: **8o** which resisted nitration and **8c** and **8m** which had either other basic centres or susceptible aromatic groups. Tables 1 and 2 give data respectively on the 2-aminoimidazoles and their 5-nitro derivatives.

Experimental Procedure

Methylthiocarbamoylpyrrolidine (**5a**)—A mixture of pyrrolidine (14.2 g) and methyl isothiocyanate (14.8 g) in benzene (150 ml) was heated under reflux for 8-10 hr. The solvent was evaporated off and the residue crystallised from benzene-hexane to afford **5a** (25.5 g), m.p. 122-23°. Compounds **5b-s** were similarly prepared and were obtained as solids or gums.

S-Methyl derivative (**6a**)—Methyl iodide (30 g) was added to a solution of **5a** (25 g) in dry chloroform (150 ml) and the mixture boiled under reflux for 4 hr. The solid obtained after the evaporation of solvent was recrystallised to afford **6a** (48.5 g), m.p. 118-19°. Other S-methyl isothiouronium iodides prepared similarly were obtained as solids or gums.

Table 1—Alkyl-2-(cyclic)aminoimidazoles

Compd	Yield (%)	Crystallised from	m.p. or b.p./mm (°C)	Mol. formula	M^+ *m/z*	Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
8a HI	36	Benzene + CH_2Cl_2	173-74	$C_8H_{13}N_3.HI$	—	34.42	5.05	15.06	35.05	5.44	15.05
8b Picrate	79	Aq. EtOH	125-26	$C_9H_{15}N_3.C_6H_3N_3O_7$	—	45.68	4.60	21.31	45.96	4.87	21.20
8c	38	—	135-40/6-7	$C_9H_{13}N_3$	—	66.22	8.03	25.75	66.32	8.32	25.39
8c Picrate		Aq. EtOH	131-32/760	$C_9H_{13}N_3.C_6H_3N_3O_7$	—	45.92	4.11	21.42	50.13	4.58	20.44
8d	81	—	160-5/7-8	$C_{10}H_{17}N_3$	179	66.99	9.57	23.44	66.96	9.93	22.62
8d Picrate		Aq. EtOH	131-32	$C_{10}H_{17}N_3.C_6H_3N_3O_7$	—	47.06	4.94	20.58	47.40	5.11	20.49
8e	65	—	140-5/4	$C_{11}H_{19}N_3.\frac{1}{2}H_2O$	193	65.28	9.96	20.76	65.24	10.34	19.84
8e Picrate		Aq. EtOH	125-26	$C_{11}H_{19}N_3.C_6H_3N_3O_7$	—	48.34	5.25	19.90	48.63	5.53	20.06
8f		CH_2Cl_2-Et_2O	72	$C_{12}H_{19}N_3$	—	—	—	20.47	—	—	20.43
8f *p*-Tos.OH		MeOH-EtOAc	138-39	$C_{12}H_{19}N_3.C_7H_8O_3S$	—	60.46	7.21	11.13	59.95	7.68	10.83
8g	20	CH_2Cl_2-Et_2O	93-94	$C_8H_{13}N_3O$	167	57.46	7.84	25.13	57.87	7.92	25.27
8h Picrate	26	MeOH-EtOAc + Et_2O	127-28	$C_{10}H_{17}N_3O.C_6H_3N_3O_7$	—	45.28	4.75	19.81	45.55	4.75	19.50
8i	28	$CH_2Cl_2 - Et_2O$	129-30	$C_{10}H_{16}N_4O$	—	57.67	7.74	—	57.30	8.10	—
8j HCl	42	*i*-PrOH-EtOAc	207-8	$C_{11}H_{18}N_4O_2.HCl$	—	48.08	6.97	—	48.21	7.30	—
8k	—	—	—	—	—	—	—	—	—	—	—
8l	48	MeOH	214-15	$(C_{16}H_{23}N_4)^+I^-$	—	48.24	5.82	—	48.44	6.01	—
8m	62	EtOAc	133-34	$C_{14}H_{17}ClN_4$	—	60.75	6.19	—	60.97	6.44	—
8n	61	CH_2Cl_2-hexane	96-97	$C_{10}H_{19}N_5O_2S$	273	43.95	7.01	25.63	44.15	7.36	25.75
8o	65	$CHCl_3$-Et_2O	144-45	$C_8H_{13}N_3O_2S$	215	44.64	6.09	19.53	44.77	6.40	19.53
8p Oxalate	29	EtOH-Et_2O	118-19	$C_{10}H_{17}N_3.C_2H_2O_4$	—	53.52	7.11	15.60	53.88	7.36	15.71
8p Picrate		Aq. EtOH	115-16	$C_{10}H_{17}N_3.C_6H_3N_3O_7$		47.06	4.94	20.58	47.04	5.24	20.41
8q	97	—	95-100/1-2	$C_9H_{15}N_3$	—	—	—	—	—	—	—
8q Picrate		Aq. EtOH	160-61	$C_9H_{15}N_3.C_6H_3N_3O_7$		45.68	4.60	21.31	46.10	4.87	21.62
8r	51	—	185-90/8	$C_{13}H_{21}N_3.\frac{1}{2}H_2O$	219	68.36	9.71	18.40	68.49	9.90	18.21
8r Picrate		Aq. EtOH	180-81	$C_{13}H_{21}N_3.C_6N_3N_3O_7$	—	50.89	5.39	18.74	51.19	5.67	19.08
8s	68	—	185-90/4	$C_{14}H_{17}N_3$	227	—	—	—	—	—	—
8s Picrate		Aq. EtOH	125-26	$C_{14}H_{17}N_3.C_6H_3N_3O_7$	—	52.63	4.42	18.42	52.91	4.69	18.20

Table 2—1-Alkyl-2-(cyclic)amino-5-nitroimidazoles

[Method-b was generally employed]

Compd	Yield (%)*	crystallised from	m.p. (°C)	Mol. formula	M^+ m/z	Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
9a	(31) 32	Et_2O-hexane	75-76	$C_8H_{12}N_4O_2$	196	48.97	6.17	28.56	48.86	6.55	28.29
9b	(7) 21	EtOH	88-89	$C_9H_{14}N_4O_2$	—	51.42	6.71	26.65	51.58	7.00	26.31
9c	24	Benzene-hexane	132-33	$C_9H_{12}N_4O_2$	—	51.91	5.81	26.91	51.65	6.05	27.28
9d	21	Aq. EtOH	74-75	$C_{10}H_{16}N_4O_2$	—	53.55	7.19	24.99	53.54	7.38	24.88
9e	16	Hexane	75-76	$C_{11}H_{18}N_4O_2$	—	55.44	7.61	23.52	55.75	7.92	23.82
9f	23	CH_2Cl_2-hexane	121-23	$C_{12}H_{18}N_4O_2$	250	57.58	7.25	22.39	57.85	7.25	22.20
9g	(<5) 16	CH_2Cl_2-Et_2O	155-56	$C_8H_{12}N_4O_3$	212	45.28	5.70	26.40	45.03	6.00	26.62
9h	32	Et_2O-hexane	85-86	$C_{10}H_{16}N_4O_3$	240	49.99	6.71	23.32	50.28	6.95	23.69
9i	26	*i*-PrOH	163-64	$C_{10}H_{15}N_5O_3$	—	47.42	5.97	—	47.37	6.30	—
9j	21	Do	98-100	$C_{11}H_{17}N_5O_4$	—	46.63	6.05	—	47.00	6.37	—
9k	16	Do	117-18	$C_{13}H_{22}N_6O_3$	—	50.31	7.15	—	50.53	7.35	—
9n	21	CH_2Cl_2-hexane	167-68	$C_{10}H_{18}N_6O_4S$	318	37.73	5.70	26.41	37.57	5.96	26.48
9p	29	Aq. EtOH	78-79	$C_{10}H_{16}N_4O_2$	—	53.55	7.19	24.99	53.75	7.49	25.28
9q	6	Hexane	55-56	$C_9H_{14}N_4O_2$	—	51.42	6.71	26.65	51.66	6.82	26.70
9r	6	Hexane	130-31	$C_{13}H_{20}N_4O_2$	—	59.07	7.63	21.20	59.26	7.87	20.91
9s	4	Et_2O-Hexane	82-83	$C_{14}H_{16}N_4O_2$	—	61.75	5.92	20.58	61.95	6.20	20.22
9t	38	CH_2Cl_2-Et_2O	173-74	$C_9H_{10}N_6O_2$	234	46.15	4.30	35.88	46.43	4.63	36.12

*Yields (%) by method-a are given in parentheses.

1-*Methyl*-2-*pyrrolidinoimidazole* (**8a**)—A mixture of **6a** (48.5 g), aminoacetaldehyde dimethylacetal (18 g) and isopropanol (150 ml) was heated under reflux for 6 hr. The solvent was evaporated *in vacuo* to afford the guanidine (**7a**) as an oil (57 g).

A solution of the above oil (57 g) in isopropanol (100 ml) and conc. hydrochloric acid (25 ml) was heated under reflux for 2 hr. The solvent was evaporated off, the residue basified under cooling with 10% aq. sodium hydroxide and extracted with methylene chloride. The methylene chloride extract was evaporated *in vacuo* to obtain a gummy residue which crystallised to afford **8a** (see Table 1).

The imidazoles (**8b-s**) were similarly prepared (Table 1).

1-*Methyl*-5-*nitro*-2-*pyrrolidinoimidazole* (**9a**): *Method a*—A mixture of sulphone (**2**, 4.1 g) and pyrrolidine (1.45 g) in dry dioxane (20 ml) was heated on a water bath at 90° for 2 hr. The solvent was removed under reduced pressure and the residue extracted with ether. The ether extract was evaporated *in vacuo* and the gummy residue obtained chromatographed over silica gel using chloroform to afford **9a** (see Table 2).

Method b—To a solution of **8a** (1 g) in glacial acetic acid (5 ml) was added dropwise under cooling (0-5°) and stirring, nitric acid (1 ml, *d*, 1.42). After the addition was over the mixture was stirred at 10-15° for 30 min, neutralised with ammonium hydroxide solution, the gummy solid obtained extracted into ether and the ether solution evaporated *in vacuo* to obtain **9a**, identical, (m.p., m.m.p. and co-TLC) with sample prepared by method a.

Compounds **9b-s** were prepared by this method (Table 1).

Reaction of sulphone (**2**) *with morpholine*—A mixture of **2** (1 g), morpholine (1 g) and benzene (10 ml) was heated under reflux for 5 hr. The solvent was evaporated off and the gummy residue which showed 3 spots on TLC was chromatographed over silica gel. The first few fractions eluted with ethyl acetate-hexane (2:3) gave unreacted **2** (0.8 g) while the later fractions gave **3c** (~10 mg), identical (m.p., m.m.p. and co-TLC) with **9g**.

Further elution of the column with $CHCl_3$-MeOH (98:2) gave **4** (reddish gum, 50 mg); M^+ 315.

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Indian Journal of Chemistry
Vol. 21B, October 1982, pp. 945-948

Nitroimidazoles: Part VI—N-(1-Alkyl-5-nitroimidazol-2-yl)-heteroarenes†‡

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

Condensation of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**2**) with imidazole affords the corresponding 2-(N-imidazolyl) derivative (**7a**) with good antiprotozoal activity. Analogous imidazoles (**7b-k**), pyrrole (**5**), indole (**6**), benzimidazole (**10**), its tetrahydro derivative (**11**), pyrazoles (**12a-d**), indazoles (**17a** and **b**), triazole (**19**), benzotriazole (**21a** and **b**) and tetrazole (**22**) are prepared similarly. Condensation of **2** with 2, 5-dimethyl-4-nitropyrazole affords the expected **12f**, which partly undergoes reaction with another molecule of **2** to yield **14**. Sulphone (**2**) and 3-methyl-5-pyrazolinone combine to form the O-alkyl derivative (**16a**), characterised further as the acetyl derivative (**16b**). ^{13}C as well as ^{1}H NMR spectra and solvent-induced shifts are used to assign unique structures, when two or more alternatives are possible, e.g. **7g**, **7h**, **12d**, **16a** and **19**. The synthesis of 1-*n*-butyl-(**9a**)- and 1-(2-methoxyethyl)-(**9b**) analogues of **7a** is also described. **25** And **26** are respectively thiazolyl and pyridyl analogues of **7a**, while **23a**, **23b** and **24** are homologues.

The outstanding antiprotozoal activity of 1-methylsulphonyl-3-(1-methyl-5-nitroimidazolyl)-2-imidazolidinone (**1**)** reported in an earlier paper[1] of this series and interesting chemistry associated with **1** and analogous oxazolidinones[2] inspired the synthesis of nitroimidazoles in combination with other five-membered rings. One of the several possibilities was 5-ring heteroaromatics, among which the earliest tried was imidazole itself which afforded **7a** with pronounced antiamoebic and antitrichomonal activities. An expanded study was thus justified and the results are reported in this paper.

The synthetic sequence (Chart 1) employed involved, as in earlier work[1,2], the condensation of the sulphone (**2**) with the sodium salt of the heteroaromatic **3**, affording **4** in moderate to very good yields. Some benzologues of **3** were also utilised.

Condensation of **2** with pyrrole, indole, imidazole and 2-substituted imidazoles proceeded uneventfully to provide **5**, **6**, **7a** and **7b-e** respectively. The yield of **5** was moderate (26%); with indole the yield rose to 45% while **7a** was formed in 60% yield, demonstrating the better nucleophilicity of imidazolyl versus indolyl and pyrryl anion. Sulphone (**7f**) arose from **7e** by peroxide oxidation. 4-Nitroimidazole and 2-methyl-4-nitroimidazole can lead to either 4- or 5-nitro-derivative. The single product isolated in the two instances were formulated as **7g** and **7h** respectively rather than as **8a** and **8b** for the following reasons: (i) alkylation of 4-nitroimidazoles under basic conditions is known to yield 4-nitro-derivatives as the sole or main product[3]; (ii) **7g** and **7h** incorporate nitroimidazole rings with protons at C-4 and C-5′ respectively, while the alternatives **8a** and **8b** would have protons at C-4 and C-4′. It is known that protons at C-5 in 1-substituted imidazoles undergo a considerable shift ($\Delta\delta$) in their PMR spectra in switching from $CDCl_3$ to DMSO-d_6 as solvent, while $\Delta\delta$ for C-4 protons is much less[4,5]. The $\Delta\delta$ observed for **7g** was: C-4H 0.20; C-2′H, 0.53; and C-5′H, 0.80; and for **7h**: C-4H 0.34; and C-5′H 0.65. (iii) δC-4 for 5-nitroimidazoles is around 132 and for C-5 in 4-nitroimidazoles 121 ppm. The ^{13}C NMR spectrum of **7h** displayed signals of C-4 at 130.2 and C-5′ at 121.0 ppm. The products from 2, 4-dimethyl-, 2-ethyl-4-methyl- and 4-phenyl-imidazoles are formulated respectively as **7i**; **7j** and **7h** for similar reasons.

Two analogues of **7a** were also synthesised for structure-activity relationship wherein the methyl group was replaced by *n*-butyl (**9a**) and methoxyethyl (**9b**) groups using the appropriate analogues of **2**[1]. The benzimidazole derivative (**10**) was also synthesised for a similar reason. The structure of **10** rested especially on PMR data (DMSO-d_6) [C-4H 8.20 (*s*), C-2′ 8.60 (*s*)].

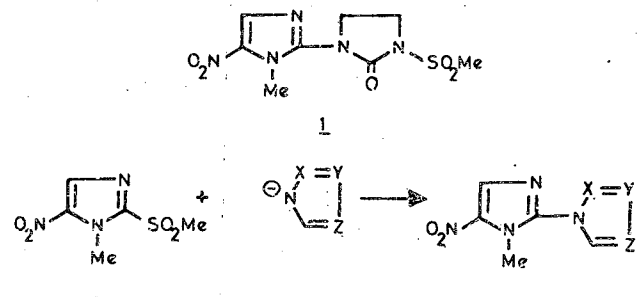
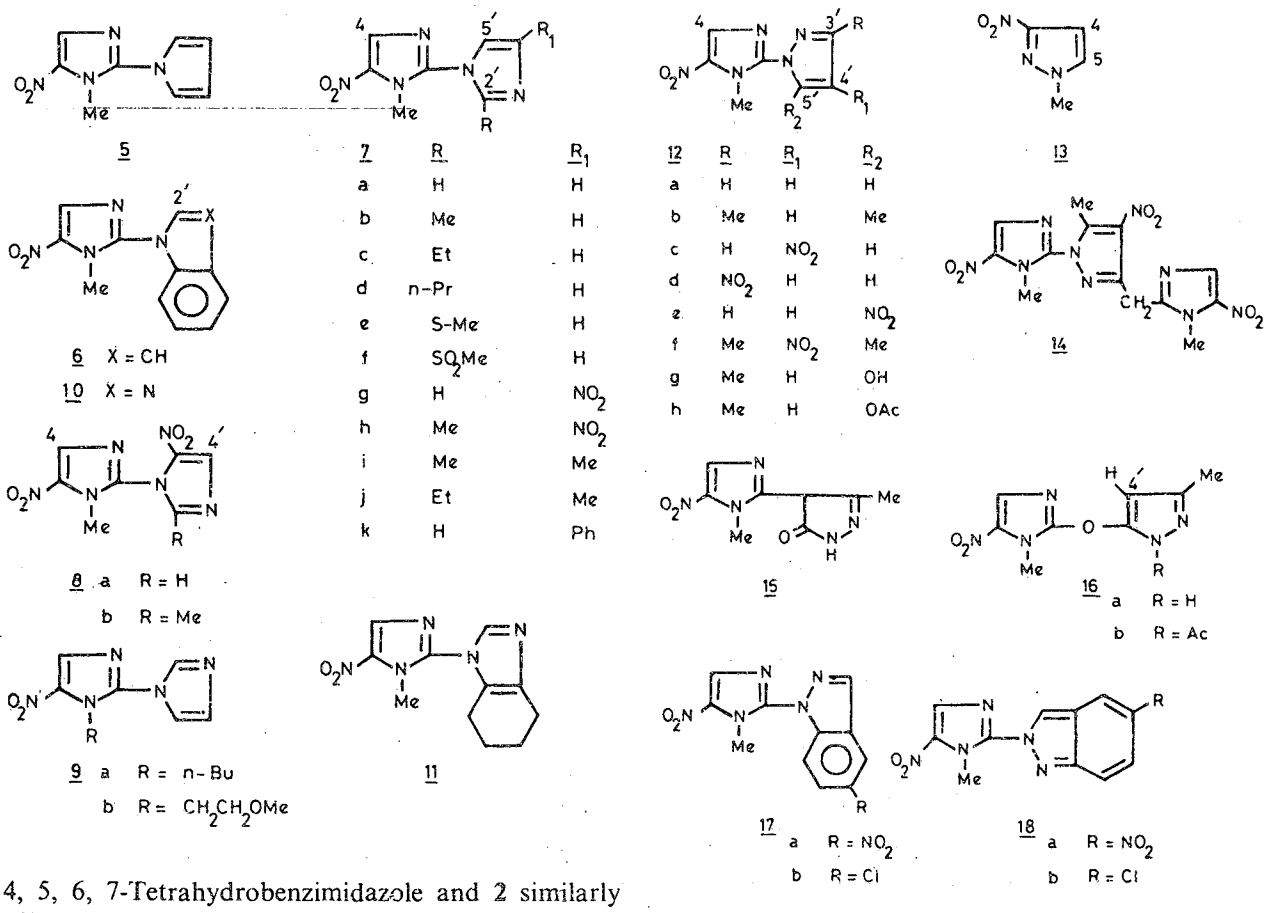


Chart 1

†Contribution No. 645 from CIBA-GEIGY Research Centre.
‡Part V: *Indian J Chem*, **21B** (1982) 941.
**Code No. C 10213-Go.



4, 5, 6, 7-Tetrahydrobenzimidazole and **2** similarly afforded **11**.

Reaction of **2** with the sodium salt of pyrazole afforded **12a** in 34% yield, but with 3, 5-dimethylpyrazole, the yield of **12b** dropped to 20%, perhaps due to crowding at the anionic centre. 4-Nitropyrazolyl ion proved to be a better nucleophile affording **12c** in 54% yield. 3-Nitropyrazole and **2** can lead to either **12d** or **12e**; structure (**12d**) was preferred for the following reasons: (i) 3-Nitropyrazole leads to 1-methyl-3-nitro derivative (**13**) under alkaline conditions; and (ii) ^{13}C NMR data for the proton bearing aromatic carbon atoms in **12d** (δC-4 130.0, C-4′ 104.6 and C-5′] 134.5 ppm). The last two shifts are very close to those observed for the analogue **13** (δC-4 103.1 and δC-5 133.3 ppm). We felt that solvent-induced shift of the pyrazole protons could also be used to differentiate between **12d** and **12e**. Hence a limited study was carried out on these pyrazole derivatives, the results of which are reported in Table 1. $\Delta\delta[=(\delta_{DMSO\text{-}d_6}-\delta_{CDCl_3})]$ for C-5′H in **13** was of the order observed for 4-nitroimidazole derivatives[4,5] (0.53), but only 0.14 as expected for C-4′H.

However for the other pyrazoles, $\Delta\delta$ observed had the following values: C-5′H, 0.07-0.30; C-4′H 0.03-0.18; C-3′H 0.05-0.44. Extension of the experience with 4-nitroimidazoles would have predicted a much larger $\Delta\delta$ values for C-5′H. However, while the assignment of

Table 1—PMR Data for Some Pyrazoles

Compd	δH (ppm) ($CDCl_3$)				δH (ppm (DMSO-d_6)			
	C-4	C-3′	C-4′	C-5′	C-4	C-3′	C-4′	C-5′
12a	7.96	8.20	6.52	7.83	8.10	8.25	6.55	7.90
12b	7.90	—	6.03	—	8.17	—	6.21	—
12c	7.98	8.91	—	8.35	8.05	9.35	—	8.65
12d	7.98	—	7.16	8.32	8.20	—	7.33	8.60
12f	8.01	—	—	—	—	—	—	—
13	—	—	6.88	7.45	—	—	7.02	7.98
16a	7.75	—	5.95	—	—	—	—	—
16b	7.75	—	6.28	—	7.95	—	6.45	—

PMR signals in **12d** is clear, there is some ambiguity in the case of **12a** and **12c** where C-3′ and C-5′H signal assignments are not as rigorous.

Condensation of the sulphone (**2**) with the sodium salt of 3, 5-dimethyl-4-nitropyrazole gave an apparently homogenous product which was considered to be the desired derivative **12f** on the basis of analytical and mass spectral data (80% yield as **12f**), but the PMR spectrum had far more signals in the aromatic and methyl regions than expected. Careful chromatography on silica gel resolved the problem by providing two pure compounds **12f** and **14** in the ratio of about 3 : 1 (PMR). The structural assignments were

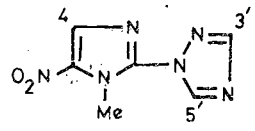
especially supported by PMR data: **12f** C-4H, 8.01 (*s*), N-Me, 3.98 (*s*), 2C-Me, 2.74 (*s*), 2.00 (*s*); **14** 2C-4H, 7.88 (*s*), 7.68 (*s*); $-CH_2$, 4.83 (*s*); 2N-Me, 4.04 (*s*), 4.01 (*s*), one C-Me, 2.66 (*s*). Obviously the initially formed **12f** had given rise to a carbanion which became involved with **2** in a substitution reaction. We expect the methyl group at C-3′ in **12f** to be more activated than the one at C-5′ and formulate the product accordingly as **14**.

The reaction of 3-methylpyrazolin-5-one with **2** can give rise to a product by heteroarylation on nitrogen, oxygen or carbon atom. The first can again exist in the enol **12g** or its keto form. C-Alkylation would lead to **15** which can also go over to an enol. O-Alkylation should afford **16a**. The presence in the PMR spectrum ($CDCl_3$) of the product of a singlet at 5.95 (C-4′H) and a broad singlet at 11.1 which disappeared with D_2O ruled out **15**, leaving **12g** and **16a** for consideration. A study of the acetyl derivative allowed us to differentiate between the two and settle in favour of **16a**. The PMR spectrum ($CDCl_3$) of the acetyl derivative had signals at 6.28 (C-4′H, *s*), 3.95 (N-Me, *s*) and 2.63 (C-3′ Me, OCOMe, *s*). More importantly its IR spectrum exhibited a band at 1740 cm^{-1} resembling those of N-acetylpyrazole ($\nu C=O$ at 1730 cm^{-1}) and 1, 4-diacetyl-5-methylpyrazole ($\nu C=O$ at 1730 cm^{-1}). Thus the acetyl derivative is formulated as **16b** and the precursor as **16a**. The O-acetyl derivative **12h**, being an enol acetate, would be expected to show a band at 1780 cm^{-1} in the IR spectrum.

5-Nitro- and 5-chloroindazoles upon reaction with the sulphone (**2**) gave high yields of products formulated as **17a** and **17b** respectively. Structures **18a** and **18b** although not completely ruled out are considered unlikely since these are partially deprived of aromaticity.

Condensation of *s*-triazole with **2** afforded a product in 42% yield which could be **19** or **20**. The PMR spectrum of the product exhibiting three singlets one-proton each in the aromatic region at 8.0 (C-4H), 8.25 (C-3′H) and 9.0 (C-5′H) decidedly favoured **19** over **20**; the latter having a symmetrically substituted triazole ring would show one singlet for both C-2′H and C-5′H. Products were also obtained from benzotriazole (53%) and 5-nitrobenzotriazole (80%) which are somewhat arbitrarily formulated as **21a** and **21b** respectively. The product obtained in 9% yield from tetrazole can be formulated in two ways, **22** being one of them.

Homologues **23a** and **23b** of the active preparation **7a** were obtained by the condensation of 1-methyl-2-chloromethyl-5-nitroimidazole with the sodium salts of imidazole and its 2-methyl derivative respectively, while with pyrazole, **24** was obtained. Similar condensation of appropriate halides with imidazole led to the thiazole **25** and pyridine **26**.



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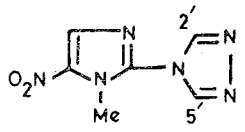

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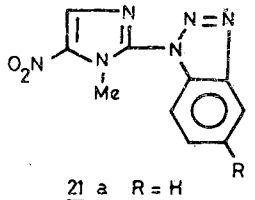
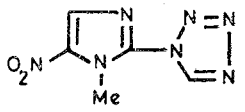


21 a R = H
b R = NO_2



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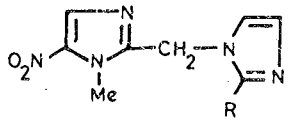
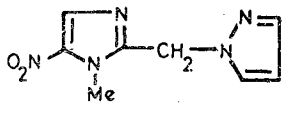


23 a R = H
b R = Me



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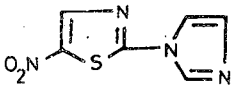

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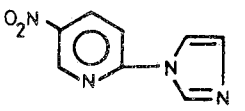

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The physical data of the compounds synthesised are listed in Table 2.

Experimental Procedure

Syntheses of 1-methyl-2-methylsulphonyl-5-nitroimidazole (**2**) and its 1-(*n*-butyl) and 1-(2-methoxy ethyl) analogues are described in our earlier paper[1].

1-*Methylimidazol-2-yl*)-5-*nitroimidazole* **7a**)—To a solution of imidazole (1.7 g) in dimethylformamide (20 ml) was added 50% NaH (1.2 g) under stirring at 5-10°. The reaction mixture was stirred at 10-15° for 30 min more after which a solution of **2** (5.1 g) in dimethylformamide (20 ml) was added dropwise keeping the temperature of the reaction mixture between 15 and 20°. The reaction mixture was stirred at room temperature for 4 hr more, the solvent removed under reduced pressure, the residue dissolved in chloroform and filtered. The filtrate was evaporated *in vacuo* and the gummy residue obtained converted into nitrate salt.

Other compounds prepared by similar method are listed in table 1.

In the reaction of **2** with the sodium salt of 3, 5-dimethyl-4-nitropyrazole a mixture of **12f** and **14** was obtained. These were separated by chromatography on silica gel using $CHCl_3$-MeOH (99 : 1) as the eluent.

Acetylation of **16a**—A mixture of **12g** (0.3 g) and acetic anhydride (1.5 ml) was heated under reflux for 30 min. The residue was cooled, ice added and left at

Table 2 —Nitroimidazolylazoles

Compd	Yield %	Crystallised from	m.p. (°C)	Mol. formula	M^+ m/z	Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
5	26	CH_2Cl_2 + MeOH – hexane	94	$C_8H_8N_4O_2$	192	49.99	4.20	29.16	50.36	4.47	29.40
6	45	CH_2Cl_2-hexane	179	$C_{12}H_{10}N_4O_2$	242	59.50	4.16	23.13	59.38	4.38	23.40
7a	66	CH_2Cl_2-hexane	99-100	$C_7H_7N_5O_2$	—	43.52	3.65	36.26	43.74	3.90	36.53
7a*		MeOH	155-6(d)	$C_7H_7N_5O_2.HNO_3$	—	32.82	3.15	32.81	33.08	3.32	33.09
7a†		—	1550-55	$C_7H_7N_5O_2$ $C_{11}H_8O_3$	—	56.69	3.96	18.37	56.88	4.19	18.33
7b*	55	MeOH-EtOAc	200	$C_8H_9N_5O_2.HNO_3$	—	35.56	3.73	31.10	35.84	4.00	31.45
7c*	35	MeOH-EtOAc	180	$C_9H_{11}N_5O_2.HNO_3$	—	38.03	4.26	29.57	38.14	4.41	29.47
7d*	40	MeOH-EtOAc	149-50	$C_{10}H_{13}N_5O_2.HNO_3$	—	40.27	4.73	28.18	40.53	4.98	28.48
7e*	49	EtOH	144-5	$C_8H_9N_5O_2S.HNO_3$	—	31.79	3.34	27.81	31.89	3.59	28.13
7f	72	Benzene	146-7	$C_8H_9N_5O_4S$	—	35.43	3.35	25.83	35.76	3.44	25.95
7g	42	DMF	225-6	$C_7H_6N_6O_4$	238	35.30	2.54	35.29	35.60	2.80	35.67
7h	35	CH_2Cl_2 + MeOH – Hexane	188-90	$C_8H_8N_6O_4$	252	38.10	3.20	33.33	38.43	3.59	33.49
7i*	46	CH_3OH-EtOAc	159-60	$C_9H_{11}N_5O_2.HNO_3$	—	38.03	4.26	29.57	37.54	4.50	29.42
7j*	45	MeOH-EtOAc	178-80	$C_{10}H_{13}N_5O_2.HNO_3$	—	40.27	4.73	28.18	40.37	4.96	28.38
7k*	67	CH_2Cl_2-MeOH -Hexane	170	$C_{13}H_{11}N_5O_2$	269	57.98	4.12	26.01	57.80	4.38	26.27
9a*	20	MeOH-EtOAc	82-3	$C_{10}H_{13}N_5O_2.HNO_3$	—	40.27	4.73	26.82	40.55	4.51	26.71
9b*	40	MeOH-Et_2O	152-3	$C_9H_{11}N_5O_3.HNO_3$	—	36.00	4.03	27.99	35.94	4.28	28.36
10	80	CH_2Cl_2 + MeOH --Et_2O	190	$C_{11}H_9N_5O_2$	243	54.32	3.73	28.80	54.57	4.00	29.09
11	36	H_2O	122-4	$C_{11}H_{13}N_5O_2$	—	53.43	5.30	28.33	53.70	5.61	28.56
12a	34	CH_2Cl_2-Hexane	139	$C_7H_7N_5O_2$	193	43.52	3.65	36.26	43.50	3.90	36.42
12b	20	CH_2Cl_2-Et_2O	138-40	$C_9H_{11}N_5O_2$	—	48.86	5.01	31.66	48.98	5.31	31.50
12c	54	$CHCl_3$ – Pet. ether	131-2	$C_7H_6N_6O_4$	—	35.30	2.54	35.29	35.39	2.80	35.08
12d	48	$CHCl_3$-Et_2O	120-21	$C_7H_6N_6O_4$	—	35.30	2.54	35.29	35.51	2.70	35.60
12f	60	CH_2Cl_2-Hexane	132-36	$C_9H_{10}N_6O_4$	266	40.60	3.79	31.57	40.81	3.83	31.31
14	20	CH_2Cl_2-Et_2O	190-93	$C_{13}H_{13}N_9O_6$	391	39.90	3.35	32.22	39.98	3.69	32.24
16a	24	CH_2Cl_2-Et_2O	143-4	$C_8H_9N_5O_3$	223	43.05	4.06	31.38	43.07	4.40	31.59
16b	40	CH_2Cl_2-Et_2O	110-11	$C_{10}H_{11}N_5O_4$	—	45.28	4.18	26.41	45.45	4.40	26.09
17a	69	DMF-Et_2O	205-6	$C_{11}H_8N_6O_4$	—	45.84	2.80	29.16	46.20	3.08	28.78
17b	65	DMF	196-7	$C_{11}H_8ClN_5O_2$	—	47.58	2.90	25.22	47.90	3.14	24.95
19	48	CH_2Cl_2-Et_2O	149-50	$C_6H_6N_6O_2$	194	37.11	3.11	43.29	37.12	3.35	43.61
21a	53	CH_2Cl_2-hexane	122	$C_8H_8N_6O_2$	244	49.18	3.30	34.42	48.98	3.57	34.14
21b	80	MeOH	148-9	$C_{10}H_7N_7O_4$	289	41.53	2.44	33.90	41.64	2.76	33.42
22	9	CH_2Cl_2-Et_2O	80-81	$C_5H_5N_7O_2$	—	30.77	2.58	50.25	30.42	2.61	49.82
23a	28	MeOH	183	$C_8H_9N_5O_2.HNO_3$	—	35.56	3.73	31.10	35.81	3.97	31.16
23b	55	EtOAc	210	$C_9H_{11}N_5O_2$	221	48.86	5.01	31.66	48.96	5.29	31.99
24	26	CH_2Cl_2-Hexane	83	$C_8H_9N_5O_2$	207	46.37	4.38	33.80	46.63	4.70	33.84
25	12	MeOH	139-40	$C_6H_4N_4O_2S$	196	36.74	2.06	28.57	36.52	2.42	28.15
26	70	Dioxane	225-7	$C_8H_6N_4O_2$	—	50.53	3.18	29.47	50.93	3.50	29.33

*As salts of HNO_3.

†As 2-hydroxy-3-naphthoate.

room temperature for 30 min. The solid obtained was filtered off, washed with water and recrystallized from methylene chloride-ether to afford **16b** (150 mg), m.p. 110-11°.

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