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Nitroimidazoles: Part IX—Addition of Diazomethane to 1-Methyl-5-nitro-2-acylamino- & 2-Sulphonamidoimidazoles & to 2-Dichloracetamido-5-nitrothiazole†‡

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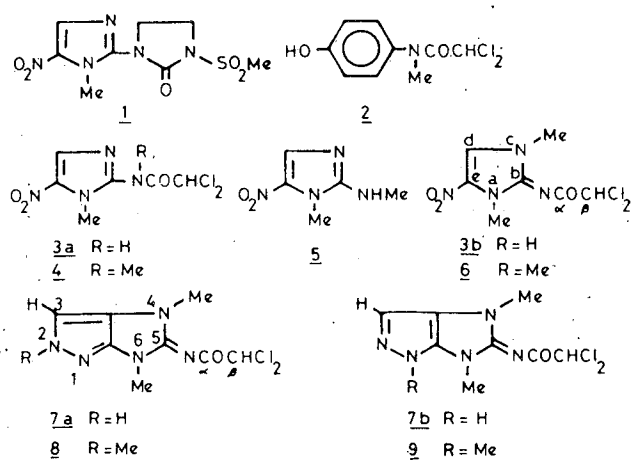
1-Methyl-2-dichloracetamido-5-nitroimidazole (**3**) undergoes an anomalous reaction with diazomethane to give imidazo(4,5-*c*)pyrazoles (**8**) and (**9**), the reaction proceeding by the initial formation of 2-dichloracetylimino-1,3-dimethyl-4-nitroimidazoline (**6**), cycloaddition of diazomethane to the nitroethylene bond in (**6**), elimination of nitrous acid from the adduct leading to imidazopyrazole (**7**) and subsequent alkylation of **7** at either of the two pyrazole nitrogen centres. Two less frequently encountered byproducts are **5** arising from the expected N-methyldichloracetamide (**4**) and the ring-opened amidine (**12**). The formation of **12** from **6** is rationalized. 1-Methyl-2-*p*-toluenesulphonamido-5-nitroimidazole (**14**) undergoes a similar reaction with diazomethane to form in addition to the *exo* (**15**)-and *endo* (**16**)-N-methyl derivatives, imidazopyrazoles (**17**, **18** and **20**) by cycloaddition of diazomethane to **16**. Two N-methyl carbamoyl derivatives (**19**) and (**21**) of **17** are byproducts of the reaction, arising from **17** by interaction with methyl isocyanate contaminating diazomethane, and have been prepared from it by deliberate treatment with methyl isocyanate. Two further byproducts, the imidazoline (**22**) and the related amidoxime (**23**) resulted from addition of methanol to nitroimidazoline (**16**) to form **24** followed by standard transformations. The cycloaddition reaction is shown to be a general one, by isolation of thiazolopyrazoles (**27** and **28**) by treating 2-dichloracetylamino-5-nitrothiazole (**26**) with diazomethane. Extensive use of ^{13}C NMR spectroscopy has helped structural assignments, in particular, in differentiating isometric pairs, **8**, **9**; **15**, **16**; **18**, **20**; and **27**, **28**. Further, it is of diagnostic value in providing insight into the tautomeric nature of **3** (as **3a**), **7** (as **7a**), **14** (as **14b**) and **17** as (**17a**).

The well-known antiamoebic activity of dioxanide (**2**)[1] and our interest in the area of 5-nitroimidazoles which culminated in the clinical development of **1** spurred us to synthesise 1-methyl-2-(N-methyl-N-dichloracetyl)-amino-5-nitroimidazole (**4**) by the action of diazomethane on the desmethyl derivative (**3**)[3] of the latter. Although this was realized, albiet, in very poor yield, we encountered an anomalous and interesting cycloaddition of diazomethane to the C-4, C-5 double bond of **3**[4]. We present in this paper full details of these observations and extensions to other nitroimidazoles and nitrothiazoles.

Reaction of **3** in methanol with an ethereal solution of diazomethane afforded a complex mixture of products from which **4**, 1-methyl-2-methylamino-5-nitroimidazole (**5**), 1,3-dimethyl-2-dichloracetylimino-4-nitroimidazoline (**6**) and imidazopyrazoles (**7**, **8** and **9**) were isolated by silica gel chromatography in varying yields depending upon the amount of diazomethane employed. In one experiment when a large excess of the reagent was used only **8** and **9** could be obtained. Structural assignments utilised extensively, analytical and mass, ^1H (Tables 1 and 2) and ^{13}C NMR spectral (Tables 3 and 4) data. Arguments for assignment of structures (**6-9**) have been already presented in the earlier communication[4] and will be only briefly mentioned in the ensuing discussion.



The PMR spectrum of **4**, $C_7H_8Cl_2N_4O_3$, M^+ 266**, was generally consistent except that the singlet due to $CHCOCl_2$ appeared at very low field (7.83, Table 1). Although this could be explained on the basis of a preferred geometry of the C = O group, placing the CH in the deshielding region of the lone pair of electrons on, we consider structure (**4**) as tentative.

5, $C_5H_8N_4O_2$, M^+ 156, was identical with an authentic sample prepared by an independent method[3]. It was also obtained by acid hydrolysis of the N-methyl toluenesulphonamide derivative (**15**). Obviously, **4** had hydrolysed (methanolysis?) to give **5**.

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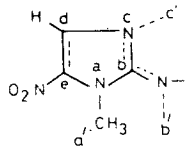
**Mass peaks due to only ^{35}Cl are quoted for all the dichloroacetyl derivatives.

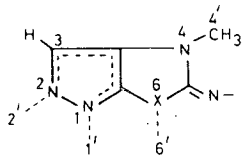
Table 1—PMR Data of Compounds Having the Following General Structure



Compd	Chemical shifts (multiplicity) of protons at positions				
	d	a'	b'	c'	Others
3[g]	8.10(*s*)	3.78(*s*)	—	—	C*H*Cl$_2$, 6.62; N*H*, 8.00
4[f]	7.96(*s*)	4.12(*s*)	—	3.96(*s*)	C*H*Cl$_2$, 7.83(*s*)(!)
5[f]	7.90(*s*)	3.69(*s*)	3.11(*d*)	-	N*H*, 4.2 (*bs*)
6[f]	8.03(*s*)	3.88(*s*)	-	3.66(*s*)	C*H*Cl$_2$ 6.11(*s*)
14[h]	7.70(*s*)	3.60(*s*)	-	—	Ar*H*, 7.15 (2H, *m*), 7.73 (2H, *m*); ArC*H*$_3$, 2.33(*s*); N*H* 7.60 (*bs*)
15[f]	7.7 (*s*)	4.00(*s*)	3.03(*s*)	-	Ar*H*, 7.27 (2H, *m*); 7.53(2H, *m*); ArCH$_3$, 2.40(*s*)
16[f]	7.69(*s*)	3.78(*s*)		3.72(*s*)	Ar*H*, 7.27 (2H, *m*); 7.83 (2H, *m*); ArC*H*$_3$, 2.41(*s*)

For Tables 1-4: f in $CDCl_3$
g in DMSO-d_6
h in a mixture of above solvents.

Table 2—PMR Data of Compounds Having the Following General Structure



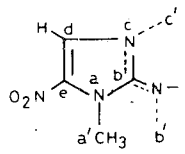
Compd	Chemical shifts (multiplicity) of protons at positions					
	3	1'	2'	4'	6'	Others
7[h]	7.50(*s*)	—	—	3.60(*s*)	3.60(*s*)	C*H*Cl$_2$, 6.25(*s*)
8[f]	7.30(*s*)	—	4.00(*s*)	3.53(*s*)	3.60(*s*)	C*H*Cl$_2$, 6.20(*s*)
9[f]	7.35(*s*)	4.07(*s*)	—	3.53(*s*)	3.72(*s*)	C*H*Cl$_2$, 6.15(*s*)
17[h]	7.40(*s*)	—	—	3.55(*s*)	3.55(*s*)	Ar *H*, 7.20 (2H, *m*), 7.77 (2H, *m*); Ar C*H*$_3$, 2.40(*s*); N*H*, 12.4 (*bs*)
18[f]	7.29(*s*)	—	3.95(*s*)	3.58(*s*)	3.63(*s*)	Ar*H*, 7.25 (2H, *m*), 7.87 (2H, *m*) ArC*H*$_3$, 2.40(*s*)
19[f]	7.86(*s*)	—	—	3.63(*s*)	3.64(*s*)	Ar*H*, 7.29 (2H, *m*), 7.90 (2H, *m*); ArC*H*$_3$, 2.42 (*s*); C*H*$_3$NHCO-3.04 (3H, *d*, J = 5.1 Hz collapsing into *s* with D_2O); N*H*, 6.90 (*bs* disappearing with D_2O)
20[f]	7.25(*s*)	4.01(*s*)	—	3.54(*s*)	3.77(*s*)	Ar*H*, 7.24 (2H, *m*), 7.81 (2H, *m*); ArC*H*$_3$, 2.40 (*s*)
21[f]	7.40(*s*)	—	—	3.79(*s*)	3.81(*s*)	Ar*H*, 7.25 (2H, *m*), 7.85 (2H, *m*); ArC*H*$_3$, 2.40 (*s*); C*H*$_3$NHCO-3.02 (3H, *d*, J = 5.1 Hz, collapsing into *s* with D_2O); N*H*, 7.00 (*bs* disappearing with D_2O)
27[f]	7.54(*s*)	4.00(*s*)	—	3.85(*s*)	—	C*H*Cl$_2$, 6.18(*s*)
28[f]	7.42(*s*)	4.07(*s*)	—	3.81(*s*)	—	C*H*Cl$_2$, 6.19(*s*)

The structure of **6**, $C_7H_8Cl_2N_4O_3$, M^+ 266, rested largely upon ^{13}C NMR data, especially upon the observation of three-bond CH couplings for C—d with the protons of the methyl group on N—c and for the latter methyl C atom with the proton at d. This was reinforced by the absence of such a coupling for the C=O group which the isomer **4** would have required and which was seen prominently for diloxanide (**2**).

7, $C_8H_9Cl_2N_5O$, M^+ 261, had again dichloracetyl carbonyl carbon exhibiting no multiplicity due to a three-bond coupling with a N-methyl group.

The major clue to the structures of the isomeric imidazopyrazoles (**8**) and (**9**), $C_9H_{11}Cl_2N_5O$ (M^+ 275) came from the observation that they were formed by addition of diazomethane to **6**, the nitro group being lost in the process. **8** was easily differentiated from **9**

Table 3—Carbon-13 NMR Data of Compounds Having the Following General Structure



Compd	Chemical shifts (multiplicity) and J = values for						
	C-b	C-d	C-e	C-a'	C-b'	C-c'	Others
3[h]	144.3(*m*) $^3J_{CH}=14$; $^3J_{CH}=4$	127.1(*d*) $^1J_{CH}=204.2$	136.8(*m*) $^2J_{CH}=9.5$; $^3J_{CH}$ not resolved	32.9(*q*) $^1J_{CH}=144.6$	—	—	C-α 166.3 (*d*) $^2J_{CH}=1.7$ C-β 67.3 (*d*) $^1J_{CH}=181.5$
6[h]	—	122.8(*dxq*) $^1J_{CH}=208$; $^3J_{CH}=3.5$	—	33.2(*q*) $^1J_{CH}=145$	—	34.6(*qxd*) $^1J_{CH}=143$; $^3J_{CH}=2$	C-α 168.1 (*d*) $^2J_{CH}=2$ C-β 70.4 (*d*) $^1J_{CH}=181$
14[h]	146.0(*m*)	119.2(*d*) $^1J_{CH}=207.1$	134.1(*m*)	31.2(*q*) $^1J_{CH}=143.6$	—	—	Ar: C-1 141.9; C-4 140.9; C-3, C-5 129.2; C-2, C-6 125.8; CH_3 21.1
15[h]	145.3(*m*)	130.3(*d*) $^1J_{CH}=201.8$	—	34.4(*q*) $^1J_{CH}=144.6$	—	37.7(*q*) $^1J_{CH}=142.2$	Ar: C-1 132.8; C-4 129.2; C-3, C-5 129.9; C-2, C-6 128.9; CH_3 21.6
16[h]	145.6(*m*)	122.7(*dxq*) $^1J_{CH}=211.2$; $^3J_{CH}=1.8$	—	33.9(*q*) $^1J_{CH}=144.5$	—	35.0(*qxd*) $^1J_{CH}=142.8$; $^3J_{CH}=1.8$	Ar: C-1 143.0; C-4 141.4; C-3, C-5 129.1; C-2, C-6 125.4; CH_3 21.1

because C-3 in the former exhibited in addition to a one-bond coupling with a proton, a three-bond coupling with the three protons of the methyl group on N-2, which was absent in **9**. The chemical shift difference of C-3 in the two molecules (**8**-111.6; **9**-120.0) corresponded to that in model pyrazoles[5].

A plausible scheme for the formation of **5**-**9** from **3** by the action of diazomethane is depicted in Chart 1. It is worth reiterating that unlike nitroimidazoles like **1**, 1-methyl-2-dimethylamino-5-nitroimidazole, 1-methyl-5-nitroimidazole, 1-methyl-2-methanesulphonyl-5-nitroimidazole (**13**) and the N-methyltoluenesulphonamide (**15**) which are inert towards diazomethane, **3** undergoes anomalous reactions because of the intervention of nitroimidazoline (**6**).

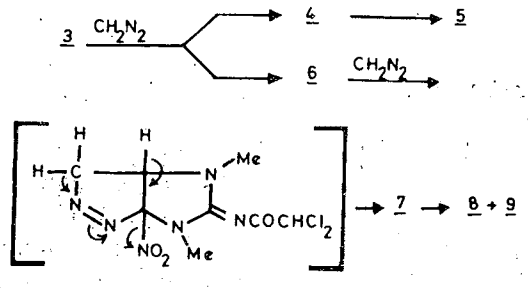


Chart 1

Lacking the aromaticity of **4** and molecules cited earlier, **6** exhibits an understandable dipolarophilic predilection towards diazomethane[6].

Yet another product, $C_9H_{14}Cl_2N_4O_4$, M^+ 312, m.p. 140°, occasionally encountered in the reaction of **3** with diazomethane and possessing dichloroacetyl group was assigned structure (**12**) on the basis of its PMR spectrum which exhbited signals at δ 3.45 (6H, *s*, 2N-Me), 3.77 (3H, *s*, 1N-Me), 4.10 (2H, doublet collapsing to a singlet with D_2O, $-CH_2-O$), 4.85 (1H, *bs* disappearing with D_2O, OH), 5.91 (1H, *s*,

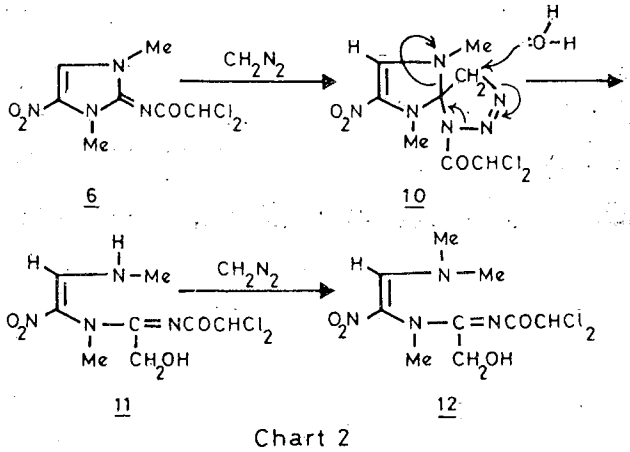
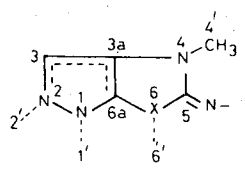


Chart 2

Table 4 — Carbon-13 NMR Data of Compounds Having the Following General Structure



Compd	Chemical shifts (multiplicity) and J values for					
	C-3	C-1′	C-2′	C-4′	C-6′	Others
7[h]	110.4(*d*) $^1J_{CH}$ = 195.6		—	32.4(*q*) $^1J_{CH}$ = 141.2	30.4(*q*) $^1J_{CH}$ = 141.9	C-α 167.4; C-β 70.8(*d*), $^1J_{CH}$ = 180.9; C-3a 117.0; C-5 156.8; C-6a 146.2
8[h]	111.6(*dxq*) $^1J_{CH}$ = 194 $^3J_{CH}$ = 1.5	—	40.0(*q*) $^1J_{CH}$ = 140.6	32.9(*q*) $^1J_{CH}$ = 142.6	30.7(*q*) $^1J_{CH}$ = 142.6	C-α 169.0; C-β 70.6 (*d*), $^1J_{CH}$ = 179.7
9[f]	120.0(*d*) $^1J_{CH}$ = 195.3	36.7(*q*) $^1J_{CH}$ = 140.6	—	32.7(*q*) $^1J_{CH}$ = 141.6	31.2(*q*) $^1J_{CH}$ = 142.6	C-α 169.4; C-β 70.6 (*d*), $^1J_{CH}$ = 179.7
17[g]	110.8(*d*) $^1J_{CH}$ = 201.0		—	32.8(*q*) $^1J_{CH}$ = 141.9	30.7(*q*) $^1J_{CH}$ = 142.0	Ar: C-1 143.3; C-4 140.7; C-3, C-5 129.0; C-2, C-6 125.2; ArCH_3 20.6
18[h]	113.4(*dxq*) $^1J_{CH}$ = 198.3; $^3J_{CH}$ = 3.5		39.6(*qxd*) $^1J_{CH}$ = 132.0 $^3J_{CH}$ = 2.7	33.0(*q*) $^1J_{CH}$ = 141.9	31.0(*q*) $^1J_{CH}$ = 141.9	Ar: C-3, C-5 129.2; C-2, C-6 125.7; CH_3 20.9
19[g]	110.0(*d*)	—	—	—	—	
20[f]	120.0(*d*) $^1J_{CH}$ = 145.1	36.7(*q*) $^1J_{CH}$ = 140.2	—	33.1(*q*) $^1J_{CH}$ = 142.0	31.6(*q*) $^1J_{CH}$ = 142.0	Ar: C-1 143.6; C-4 141.2; C-3, C-5 129.2; C-2, C-6 126.0; CH_3 21.3
21[g]	119.1(*d*)					
27[h]	122.3(*d*) $^1J_{CH}$ = 196.1	38.2(*q*)	—	34.2(*q*)		C-α 170.9 (*d*), $^2J_{CH}$ = 1.6; C-β 69.70(*d*), $^1J_{CH}$ = 196.1; C-3a 127.9; C-5 169.0; C-6a 129.9
28[g]	115.4(*dxq*) $^1J_{CH}$ = 198.6 $^3J_{CH}$ = 2.5	—	40.0(*q*) $^1J_{CH}$ = 139.7	34.4(*q*) $^1J_{CH}$ = 142.7	—	C-α 171.2; C-β 69.8(*d*); $^1J_{CH}$ = 182.4; C-3a 126.1; C-5 169.9; C-6a 138.9

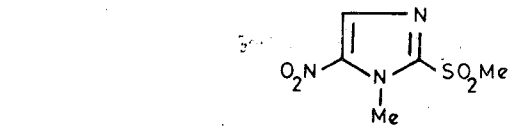
$COCHCl_2$) and 7.95 (1H, *s*, O_2N ⟨ ⟩ H). The formation of **12** from **6** can be visualised as shown in Chart 2, with diazomethane adding to the azomethine linkage to form species **10**. Scission of the triazoline ring by attack of a water molecule (moisture?) is followed by fission of one of the two adjacent C-NMe bonds. The option leading to **11** is chosen for the reason that the negative charge generated can be delocalised into the nitroethylene group. Subsequent methylation of the nitrogen atom leads to **12**.

The dichloracetamide (**3**) and imidazopyrazole (**7**) are capable of exhibiting tautomerism involving a proton, leading to possibilities: **3a**, **3b** and **7a**, **7b** respectively.

C-4 in **3** has a chemical shift of 127.1, which is much closer to those of aromatic 5-nitroimidazoles[7] (also compound **15** in this study) than to that in the dichloroacetyliminoimidazoline (**6**; C-4, 122.8), suggesting that **3** exists more as the amidoimidazole tautomer (**3a**). The formulation is supported further by UV data[7]. The imidazopyrazole (**7**) likewise can exist as a 2-H (**7a**) or 1-H (**7b**) formulation. ^{13}C NMR shift data for **7**, **8** and **9** (110.4, 111.6 and 120.0 respectively) clearly favour structure (**7a**) for this imidazopyrazole.

1-Methyl-2-(*p*-nitrobenzamido)-5-nitroimidazole and diazomethane also afforded an imidazopyrazole derivative, m.p. 235°, M^+ 314, analogous to **8** or **9**. Insufficient material precluded a firm assignment.

The cycloaddition reaction of diazomethane was then extended to 1-methyl-2-(*p*-toluenesulphonamido)-5-nitroimidazole (**14**) which was readily synthesised from the sulphone (**13**) and sodium *p*-



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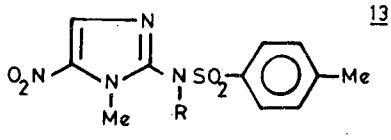
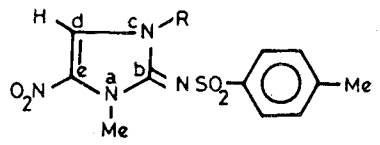
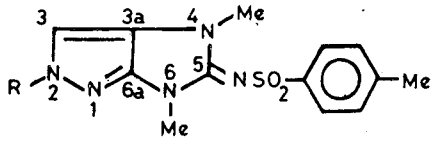


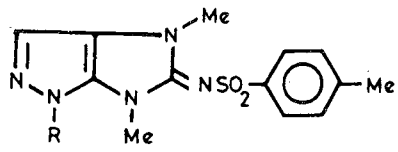
14a R = H
15 R = Me



14b R = H
16 R = Me



17a R = H
18 R = Me
19 R = MeNHCO



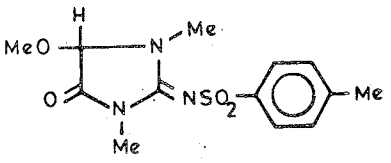
17b R = H
20 R = Me
21 R = MeNHCO

toluenesulphonamide. Reaction of **14** with a limited quantity of diazomethane gave the iminoimidazoline (**16**) in 30% yield and some of imidazopyrazole (**17**); while with excess diazomethane in methanol a bewildering plethora of compounds **15-23** were obtained which were separated by silica gel chromatography. Some of these corresponded to products **5-9** encountered in our earlier reaction, while others were new. The structures were elucidated as before, resorting heavily to analytical and mass, ^{1}H NMR (Tables 1 and 2) and ^{13}C NMR (Tables 3 and 4) spectral data.

16, $C_{12}H_{14}N_4O_4S$ (M^+ 310) was easily identified as an iminoimidazoline, vital supportive structural evidence coming from ^{13}C NMR data (Table 3). Thus C-d was seen at 122.8 as a doublet ($^1J_{CH}=211$ Hz), split further into a quartet ($^3J_{CH}=3.3$ Hz) by the adjacent N-c methyl protons. The signal of the latter carbon atom seen at 35.0 had its expected quartet split further by three-bond coupling (1.8 Hz) with the proton at C-d. **16** was isomeric with and different from the *exo*-N-methyltoluenesulphonamide (**15**) ($C_{12}H_{14}N_4O_4S$, M^+ 310) in whose ^{13}C NMR specrum, the signal due to C-d at 130.3 was a doublet ($^1J_{CH}=201.8$ Hz) with no further fine structure. The structure of **15** was further confirmed by unambiguous synthesis from the sulphone (**13**) and the sodium salt of N-methyl-*p*-toluenesulphonamide. Comparison of the chemical shifts of C-d, in **14**, **15** and **16** (Table 3) reveals that unlike **3**, **14** prefers to exist in solution at least as the imine (**14b**).

17, $C_{13}H_{15}N_5O_2S$ (M^+ 305), **18**, $C_{14}H_{17}N_5O_2S$ (M^+ 319) and its isomer **20** were easily recognised as imidazopyrazoles, arising from **16** by cycloaddition to diazomethane and subsequent transformations. ^{1}H and ^{13}C NMR data (Tables 1-4) proved of diagnostic value: **18** with C-3 (113.4) as a doublet ($^1J_{CH}=198.3$) split further into a quartet ($^3J_{CH}=3.5$ Hz) and C-2′ (39.6) as a quartet ($^1J_{CH}=132.0$ Hz) subsplit into a doublet ($^3J_{CH}=2.7$ Hz) had to be necessarily methylated on N-2, while **20** not exhibiting such fine structure for relevent C-atoms was methylated at N-1. These assignments also helped to depict **17** with δ C-2 at 110.8 as the 2-H isomer (**17a**) rather than as the 1-H isomer (**17b**).

19, $C_{15}H_{18}N_6O_3S$ (M^+ 362), initially presented an enigma, but was eventually amenable to structural unravelment. Bands in the IR at 3400 (NH) and 1720 cm^{-1} (CO), significant signals in the ^{1}PMR spectrum (full data in Table 2) at 3.04 ($N-CH_3$, *d*, $J=5.1$ Hz collapsing to a singlet with D_2O) and 6.90 (NH, *bs*, disappearing with D_2O) and a prominent fragment (100%) in the mass spectrum at *m/z* 305 reckoned as being due to $M^+ -$ MeNCO allowed us to realise that it was a methylcarbamoyl derivative of **17**. A careful chromatographic analysis of the complex mixture arising from the reaction of **14** with diazomethane revealed that an isomer (**21**) of **19** had also been formed. Its isolation and characterization became imperative since we expected that this would help us differentiate between **19** and **21**. Deliberate treatment of **17** with methyl isocyanate helped us to achieve the twin goals of gross structural assignment and subtle differentiation by providing a separable mixture of **19** and **21**. **19** as expected had the proton at C-3 at a lower field in the (7.86) compared to **21** (7.40). The ^{13}C NMR spectra of **19** (δ C-3 110.0) and **21** (δ C-3 119.1) provided additional confirmation, the observed difference matching that found in model pyrazoles[5] (cf. C-3 in **18** and **20**).



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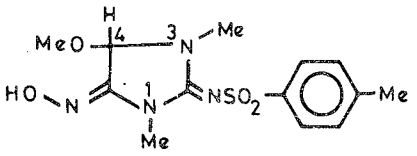

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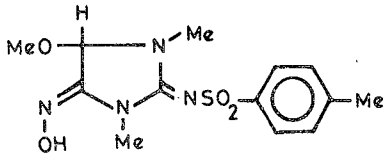

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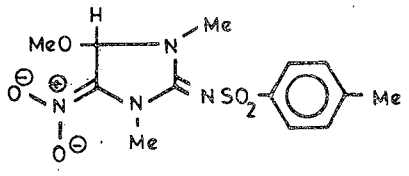

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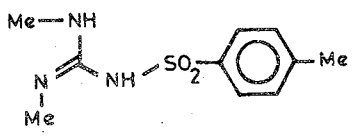

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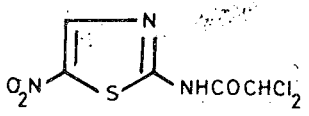
Treatment of **16** or **17** with excess diazomethane afforded the two methylated derivatives (**18**) and (**20**) as the major and **19** and **21** as the minor products, indicating the intermediacy of **16** and **17** in the course of reactions of diazomethane with **14**. The formation of **19** and **21**, while even more unexpected than that of **16**, **17**, **18** and **20**, is not inexplicable, since methyl isocyanate is known to be a significant contaminant in crude ethereal diazomethane (used aqueous alkali on nitrosomethyl urea[8].

The last two products **22** and **23** from the reaction of **14** with diazomethane were characterised as follows. The elemental compositions of **22**, $C_{13}H_{17}N_3O_4S$ (M^+ 311) and **23**, $C_{13}H_{18}N_4O_4S$ (M^+ 326) suggested immediately that these were formed from **14** without the intervention of diazomethane. It further appeared that **22** unlike **23** had lost one nitrogen atom, most probably the one from the NO_2 group which **23** had retained. The mass spectrum of **22** showed besides the molecular ion peak at *m/z* 311, other peaks at *m/z* 294 ($M-OH$), 283 ($M-CO$), 280 ($M-OCH_3$), 247 ($M-SO_2$) and 155 (*p*-Tos). The IR spectrum exhibited νCO at 1710 cm^{-1}. The PMR spectrum displayed in addition to the signals due to the *p*-toluenesulphonyl group, signals at 3.06 (3H, *s*, NMe), 3.39 (3H, *s*, NMe), 3.45 (3H, *s*, OMe) and 5.0 (1H, *s*, $HC\langle^{O-}_{O-}$). The structural support was provided by the ^{13}C NMR spectrum which exhibited signals at 21.4 ($Ar-CH_3$), 26.58 [$N(4)-CH_3$], 32.3 [$N(6)-CH_3$], 53.6 (OCH_3), 87.3 ($O-CH-N$) and 168.2 ($C=O$), besides aromatic signals, displaying the expected multiplicity. Most importantly, the signal due to *CH* at 87.3 was a doublet. It thus appears that **22** exists in the 'keto' form, with no perceptible enolisation. These data are best accommodated by structure (**22**). Analytical and spectral data of **23** indicated it to be an oxime corresponding to **22**: ν OH at 3360 cm^{-1}. The ^{1}PMR spectrum displayed interestingly two sets of signals for many protons: 2.42 (3H, *s*, Ar – Me), 3.10 (3H, *s*, N – Me), two singlets at 3.3 (70%) and 3.4 (30%) together accounting for 3H (NMe), two singlets at 3.34 (70%) and 3.48 (30%) integrating together for 3H (OMe), two singlets at 5.19 (30%) and 5.68 (70%) accounting for 1H (*H*C – OMe), two singlets at 6.86 and 6.88 integrating likewise for 1H (OH, disappearing with D_2O) and two multiplets centred at 7.25 and 7.86 for the tosyl aromatic protons. The phenomenon could be best explained by postulating that **23** had its oxime both in the *E* (**23a**) and *Z* forms (**23b**). Making the reasonable assumption that the methine proton (at C-4) in **23a** would be more deshielded than in **23b**, it is concluded that **23** exists as **23a** to about 70% and **23b** for the rest. The formation of **22** and **23** can be best visualised by addition [base-catalysed (?); trace alkali (?) in ethereal diazomethane] of methanol to the reactive nitroethylene bond in **16** to give the nitronic acid (**24**). A Nef reaction on **24** would lead to **22** and nitrous acid which can reduce a second molecule of **24** to the oxime **23**[9]. Confirmatory chemical evidence for the above postulation was obtained by heating a solution of **16** in methanol with a trace of alkali, when reaction occurred very rapidly to produce **22** as the major and **23** as the minor products. A third compound obtained in very low yield was tentatively identified as the amidine (**25**), m.p. ~ 180° (M^+ 241) arising by fission of the imidazole ring in **22**.

The generality of the cycloaddition of diazomethane to nitro heterocycles of disorganised aromaticity was



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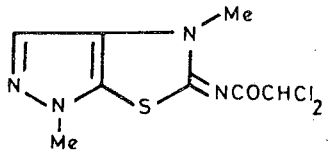

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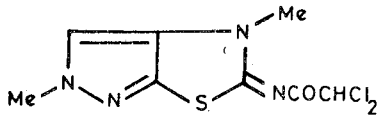

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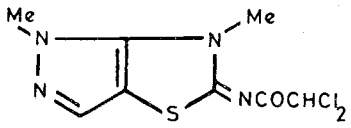

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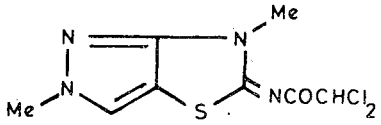

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further demonstrated by treating 2-dichloroacetamido-5-nitrothiazole (**26**)[10] with diazomethane. Two products corresponding to alkylated thiazolopyrazoles were also obtained in this instance. 1,3-Dipoles are known to display interchangeability of formal charges[11] which in the case of diazomethane would generate $-CH_2-N=N^+$ (a) and $H_2C^+-N=N^-$ (b) in the sextet formulation. Attack of either species on the imidazoline (**6**) would produce the same imidazopyrazole (**7**), because of its 'symmetrical' character. But with the thiazoline formed initially from **26**, two different thiazolopyrazoles corresponding to **7** would arise which would finally, after N-methylation, lead to two sets of products; **27** and **28** would result from attack by the dipole (a) and **29** and **30** through dipole (b). In view of the experimental[11,12] and theoretical[13] evidence pointing to the carbon atom of diazomethane being more strongly nucleophilic than the outer nitrogen, we favour structures (**27**) and (**28**) for the products. As in the earlier cases, the structures of **27**, $C_8H_8Cl_2N_4OS$, M^+ 278 and the isomer **28**, are supported by analytical and spectral (Tables 2 and 4) features. **27** was routinely differentiated from **28** using ^{13}C NMR data, with C-3 in the latter (but not in **27**) exhibiting three-bond coupling with the protons on the 2'-methyl group.

Experimental Procedure

Reaction of diazomethane with 2-dichloracetamido-1-methyl-5-nitroimidazole (**3**)—An ice-cold solution of diazomethane [prepared from nitrosomethyl urea (125 g) and potassium hydroxide solution (50%, 625 ml) in ether (800 ml)] was added to an ice-cold solution of **3** (10 g) in methanol (1000 ml) and the solution left at room temperature for 2 days. The solvent was removed under reduced pressure and the residue carefully chromatographed on silica gel (250 g) using solvents of increasing polarity: toluene, methylene chloride and methylene chloride-methanol mixture.

Fractions with toluene gave a solid which was recrystallised from hexane to yield **4** (150 mg), m.p. 92-93°; M^+ 266 (Found: C, 32.1; H, 3.3; N, 20.2. $C_7H_8Cl_2N_4O_3$ requires C, 31.5; H, 3.0; N, 21.0%).

The solid obtained from 0.5% methanolic methylene chloride was recrystallised from methylene chloride-ether to give **12**, (50 mg), m.p. 138-40° (Found: C, 34.3; H, 4.6; N, 18.0; Cl, 22.8. $C_9H_{14}Cl_2N_4O_4$ requires C, 34.5; H, 4.5; N, 17.8; Cl, 2.7%).

Fractions with 1% methanolic methylene chloride gave **6** which recrystallised from methylene chloride-ether (3 g) m.p. 119-20° (Found: C, 31.7; H, 3.3; N, 21.0. $C_7H_8Cl_2N_4O_3$ requires C, 31.5; H, 3.0; N, 21.0%). Further fractions with 1% methanolic methylene chloride gave a solid which was recrystallised from methylene chloride-ether to yield **5** (150 mg), m.p. 172-73° (Found: C, 38.2; H, 5.5; N, 36.2. $C_5H_8N_4O_2$ requires C, 38.5; H, 5.2; N, 35.9%).

Fractions with 2% methanolic methylene chloride yielded 5-dichloroacetylimino-2,4,6-trimethyl-2,4,5,6-tetrahydroimidazo[4,5-*c*]pyrazole (**8**) which crystallised from methylene chloride-ether (100 mg), m.p. 155-57° (Found: C, 39.4; H, 4.3; N, 25.7. $C_9H_{11}Cl_2N_5O$ requires C, 39.1; H, 4.0; N, 25.4%). Further fractions with 2% methanolic methylene chloride yielded 5-dichloroacetylimino-1,4,6-trimethyl-1,4,5,6-tetrahydroimidazo[4,5-*c*]pyrazole (**9**) which crystallised from methylene chloride-ether (50 mg), m.p. 98-100°. (Found: C, 39.2; H, 4.4; N, 25.7. $C_9H_{11}Cl_2N_5O$ requires C, 39.1; H, 4.0; N, 25.4%).

Fractions with 4% methanolic methylene chloride yielded 5-dichloroacetylimino-4,6-dimethyl-1,4,5,6-

tetrahydroimidazo [4,5-*c*]pyrazole (7), which crystallised from CH_2Cl_2-ether (500 mg), m.p. 155-56° (Found: C, 36.5; H, 4.0; N, 26.4. $C_8H_9Cl_2N_5O$ requires C, 36.7; H, 3.5; N, 26.7%).

Reaction of diazomethane with **6**—To a cooled solution of **6** (1 g) in methanol (100 ml), was added an ice-cold solution of diazomethane in ether (300 ml) [prepared from nitrosomethylurea (30 g) and potassium hydroxide (50%, 100 ml)] and left overnight at room temperature. The solvent was removed under reduced pressure and the residue chromatographed over silica gel (50 g) and eluted with 1% methanolic methylene chloride to yield **8** (150 mg), m.p. 156-57°, identical (m.p. and m.m.p.) with that prepared in the previous experiment. Later fractions contained **9**.

1-*Methyl*-5-*nitro*-2-(*p*-*toluenesulphonamido*)*imidazole* (**14**)—A solution of 2-methanesulphonyl-1-methyl-5-nitroimidazole (**13**)[2] (6.15 g) in dimethylformamide (DMF, 25 ml) was mixed with a solution of *p*-toluenesulphonamide (5.2 g) in DMF (10 ml). The solution was added dropwise to a suspension of sodium hydride (100%, 1 g) in DMF (10 ml) at 15-20°, stirred at 15-20° for 2 hr and at room temperature for 15 hr. The solvent was removed under reduced pressure, the residue was treated with ice and water and acidified with acetic acid. The solid was filtered, washed with cold water, dried and crystallised from methanol-methylene chloride-ether to yield **14** (4 g), m.p. 168-72; M^+ 296 (Found: C, 44.4; H, 4.4; N, 18.5. $C_{11}H_{12}N_4O_4S$ requires C, 44.6; H, 4.1; N, 18.9%).

1-*Methyl*-2-[*N*-*methyl*-(*p*-*toluenesulphonamido*]-5-*nitroimidazole* (**15**)—A solution of **13** (4 g) in DMF (20 ml) was mixed with a solution of N-methyl-*p*-toluenesulphonamide (3.7 g) in DMF (10 ml). The solution was added dropwise with stirring at 15-20° to a suspension of sodium hydride (50%) (1.1 g) in DMF (10 ml). The mixture was stirred at 15° for 2 hr and at room temperature, overnight. The solvent was removed under reduced pressure, and the residue treated with ice and water, the solid obtained filtered, washed with cold water, dried and crystallised from methylene chloride-ether to yield **15** (1.8 g), m.p. 176-80°; M^+ 310 (Found: C, 46.6; H, 4.8; N, 18.1. $C_{12}H_{14}N_4O_4S$ requires C, 46.5; H, 4.6; N, 18.1%).

Reaction of **14** *with limited amounts of diazomethane*—(a) To a solution of **14** (4.5 g) in methylene chloride (45 ml)—methanol (10 ml) cooled in ice was added a solution of diazomethane (prepared from 8 g of nitrosomethyl urea) in ether (100 ml). The mixture was left overnight at room temperature, the pale yellow precipitate obtained filtered off and the filtrate evaporated under reduced pressure. Both the residue and the above yellow solid were a mixture of **16** and the starting material **14** from which **14** was removed by slurrying with 5% aq. sodium hydroxide. The insoluble solid was filtered, washed with water and recrystallised from methylene chloride-ether to obtain **16** (1.2 g), m.p. 152-54° (Found: C, 46.6; H, 4.8; N, 18.2. $C_{12}H_{14}N_4O_4S$ requires C, 46.5; H, 4.6; N, 18.1%).

(b) An ice cold solution of **14** (4.5 g) in methylene chloride (45 ml)—methanol (10 ml) was added to diazomethane solution (prepared from 30 g of nitrosomethyl urea) in ether (400 ml) cooled under ice. The mixture was kept under ice for 2-3 hr and left at room temperature overnight. The pale yellow precipitate was filtered, washed with ether and recrystallised from methylene chloride-ether to afford **16**, (1.2 g), m.p. and m.m.p. 152-54°.

The above filtrate was evaporated *in vacuo*. The residue which showed 2 spots on TLC was boiled with methylene chloride and filtered hot. The insoluble solid was recrystallised from methanolic methylene chloride-ether to obtain **17** (0.5 g), m.p. 184-88° (Found: C, 50.9; H, 5.3; N, 22.6. $C_{13}H_{15}N_5O_2S$ requires C, 51.1; H, 5.0; N, 22.9%).

Careful chromatography of the mother liquor over silica gel using acetone-hexane (1:1) gave 2 compounds. Recrystallisation of the faster moving compound from methylene chloride-hexane afforded **19** (200 mg), m.p. 222-26° (Found: C, 49.8; H, 5.6; N, 23.4. $C_{15}H_{18}N_6O_3S$ requires C, 49.7; H, 5.0; N, 23.2%).

The slower moving compound was recrystallised from methanolic methylene chloride-ether to get 0.5 g of **17**, m.p. and m.m.p. 184-88°.

Reaction of **14** *with excess diazomethane*—A solution of **14** (4.5 g) in methylene chloride (50 ml)-methanol (25 ml) was cooled in ice and treated with diazomethane [prepared from nitrosomethyleneurea (75 g) in ether (700 ml)]. A yellow precipitate formed after 3 hr was dissolved by adding to the above solvent and the solution left at room temperature for 72 hr. The solvent was removed under reduced pressure and the residue chromatographed over silica gel (180 g) using acetone-hexane (1:3). The fractions collected were carefully monitored by TLC and fractions containing each pure compound were combined, evaporated and the residue crystallised. The products isolated were as follows:

15, 0.7 g (from CH_2Cl_2-ether), m.p. and m.m.p., 176-80°.

22, 0.4 g (from CH_2Cl_2-hexane), m.p. 107-10° (Found: C, 50.2; H, 5.8; N, 13.7. $C_{13}H_{17}N_3O_4S$ requires C, 50.2; H, 5.5; N, 13.5%).

23, 0.3 g (from CH_2Cl_2-hexane), m.p. 152-57° (Found: C, 47.8; H, 5.7; N, 17.2. $C_{13}H_{18}N_4O_4S$ requires C, 47.9; H, 5.6; N, 17.2%).

19, 0.1 g (from CH_2Cl_2-hexane), m.p. and m.m.p., 222-26°.

18, 0.45 g (from CH_2Cl_2-hexane), m.p. 196-200° (Found: C, 52.5; H, 5.7; N, 22.0; $C_{14}H_{17}N_5O_7S$

requires C, 52.7; H, 5.4; N, 21.9%).

20, 0.1 g (from CH_2Cl_2-hexane), m.p. 166-70° (Found: C, 52.4; H, 5.6; N, 21.9. $C_{14}H_{17}N_5O_2S$ requires C, 52.7; H, 5.4; N, 21.9%).

Reaction of nitroimidazoline (**16**) *with diazomethane*—An ice-cold solution of diazomethane (prepared from 8 g of nitrosomethyl urea) in ether (100 ml) was added under cooling to a solution of **16** in methylene chloride (40 ml)-methanol (10 ml). The reaction mixture was kept under ice for 2-3 hr and then left overnight at room temperature. The solvent was evaporated *in vacuo*. TLC of the residue showed faint spots corresponding to **19** and **22** and prominent spots corresponding to **17**, **18** and **20**. Crystallisation from methylene chloride-ether gave a mixture of **18** and **20** (mass and TLC) from which **18** was obtained by slow recrystallization from methylene chloride-ether, m.p. ~190° (slight contamination with **20**), m.m.p. with previous sample of **18**, ~190°:M^+ 319.

Reaction of **16** *with methanolic potassium hydroxide*—A solution of **16** (0.4 g) in methylene chloride (25 ml)-methanol (15 ml) was mixed with a drop of 40% aq. potassium hydroxide and left at room temperature for 3 days. The solvent was removed *in vacuo* and the residue carefully chromatographed over silica gel (10 g) using acetone-hexane containing 33% acetone. The products isolated are given below in the same order as they have been eluted.

22, 0.175 g (from CH_2Cl_2-ether), m.p. and m.m.p., 112-14°.

23, ~10 mg (from CH_2Cl_2-hexane), m.p. and m.m.p., 154-58°.

25, ~3 mg, m.p. ~180°, M^+ 241.

A very small amount of an unidentified product corresponding to a two carbon homologue of **23** was obtained from the mother liquor of recrystallisation of **22**, m.p. 110-12°; M^+ 354. (Found: C, 51.0; H, 6.6. $C_{15}H_{22}N_4O_4S$ requires C, 50.8; H, 6.3%).

Reaction of imidazopyrazole (**17**) *with diazomethane*—To a solution of **17** (100 mg) in dioxane (5 ml)-methanol (5 ml) cooled in ice was added diazomethane (from 10 g nitrosomethylurea) in ether (100 ml). The reaction mixture was left overnight at room temperature. The solvent was removed under reduced pressure. HPLC and TLC of the residue showed that it was a mixture of **18**, **19**, **20** and the starting material **17**.

Reaction of **17** *with methyl isocyanate*—To a solution of **17** (100 mg) in anhydrous dioxane (10 ml) was added methyl isocyanate (0.1 ml). The reaction mixture was left at room temperature for 20 min and then warmed on an oil-bath at 50°C for 15 min. The solvent was removed *in vacuo*. The residue which showed 3 spots on TLC was carefully chromatographed over silica gel using acetone-hexane (1:1). The products isolated are given below in the same order as they have been eluted.

19, ~10 mg (from CH_2Cl_2-hexane), m.p. and m.m.p. 224-26°.

21, ~20 mg (from CH_2Cl_2-hexane), m.p. 174-78° (Found: C, 49.2; H, 5.3. $C_{15}H_{18}N_6O_3S$ requires C, 49.7; H, 5.0%).

17, the starting material (eluted with $CHCl_3$ – MeOH 97:3).

Reaction of 2-dichloracetamido-5-nitrothiazole (**26**) *with diazomethane*—A solution of **26** (10 g) in methanol (200 ml) cooled in ice was treated with an ice cold solution diazomethane in ether (700 ml) [prepared from nitrosomethyl urea (100 g)]. The mixture was left at room temperature for 24 hr and the solvent removed under reduced pressure. The residue was chromatographed over silica gel (150 g) and eluted with solvents of increasing polarity starting from toluene. The pure compound eluted with methylene chloride and 0.5% methanolic methylene chloride was recrystallized from methylene chloride-ether to yield 5-dichloracetylimino-1,4-dimethyl-1*H*-pyrazolo[4,3-*d*]thiazole (**27**) (0.25 g), m.p. 202-4°; M^+ 278 (Found: C, 34.6; H, 3.2; N, 19.9. $C_8H_8Cl_2N_4OS$ requires C, 34.4; H, 2.9; N, 20.1%).

The compound which eluted with 1.5% methanolic methylene chloride was recrystallised from methylene chloride-hexane to yield 5-dichloracetylimino-2,4-dimethyl-2*H*-pyrazolo[4,3-*d*]thiazole (**28**) (100 mg), m.p. 202-4; M^+ 278 (Found: C, 34.3; H, 3.2; N, 19.8. $C_8H_8Cl_2N_4OS$ requires C, 34.4; H, 2.9; N, 20.1%).

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