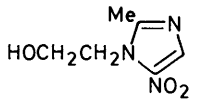
Cyclic Meso-ionic Compounds. Part 21.[1] The Examination of Nitro-derivatives of Meso-ionic Heterocycles as Potential Pharmaceuticals

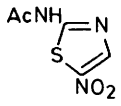
Christopher G. Newton and W. David Ollis *
Department of Chemistry, The University, Sheffield S3 7HF
Michael L. Podmore and Derek E. Wright
The Research Laboratories, May and Baker Ltd., Dagenham, Essex RM10 7XS

The synthesis of nitro-substituted meso-ionic compounds has been examined in an attempt to obtain analogues of the biologically active heterocycles (1)—(3). The synthesis of the compounds (4) and (5) has been achieved but their instability precluded biological evaluation. The synthesis of the type-B meso-ionic heterocycle (6) was not successfully completed, but unusual nucleophilic displacement reactions of the pyrazole (13) ⟶ (16) + (17) and the pyrazolium salt (14) ⟶ (15) are reported.

Considerable interest has developed recently in the synthesis and biological evaluation of nitro-derivatives of five-membered heterocycles. These investigations have been prompted by the discovery that several of these compounds possess a broad spectrum of biological properties including antibacterial, anti-protozoal, and herbicidal activities. The nitroimidazole, metronidazole (1),[2,3] is now widely used in human medicine and important biological activities have been demonstrated for the nitrothiazole, acinitrazole (2),[3] and the 3-nitropyrazoles (3).[4]



(1) Metronidazole



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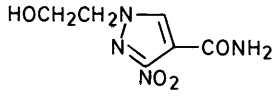

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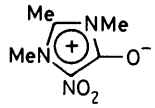

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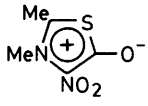

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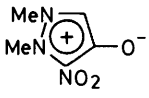

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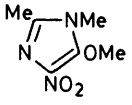

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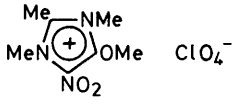

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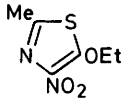

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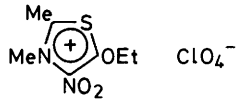


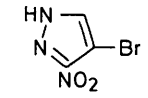
(10)

These results encouraged our attempted synthesis of nitro-derivatives of meso-ionic heterocycles which could be regarded as structural analogues of the biologically active compounds (1)—(3). Meso-ionic heterocycles have already been shown to exhibit a wide range of biological activities,[5-7] but only two nitro-derivatives of meso-ionic heterocycles have been previously described. Nitration of *N*-phenylsydnone (3-phenyl-1,2,3-oxadiazolium-5-olate) yields the 4-nitro-derivative [8] and similarly 3-*p*-tolyl-1,2,3-thiadiazolium-4-olate yields the 5-nitro-derivative.[9] The nitro-derivatives (4)—(6) were initially chosen as synthetic objectives: the strategy for their synthesis was based upon the view that it would be more efficient to try to generate their meso-ionic systems from appropriately substituted nitro-heterocycles which were known compounds.

The synthesis of the 5-nitro-1,3-diazolium-4-olate (4) from the known 5-bromo-1,2-dimethyl-4-nitroimidazole [10] was achieved by the following route. Nucleophilic displacement of 5-bromo-1,2-dimethyl-4-nitroimidazole [10] was easily achieved by boiling with methanol in the presence of anhydrous sodium carbonate. This yielded 5-methoxy-1,2-dimethyl-4-nitroimidazole (7),[11] which with methyl fluorosulphonate in chloroform gave the *N*-methylimidazolium fluorosulphonate isolated as 4-methoxy-1,2,3-trimethyl-5-nitroimidazolium perchlorate (8). Selective *O*-demethylation of the perchlorate (8) was achieved using pyridine at room temperature yielding the required meso-ionic heterocycle (4). Unfortunately this compound could not be subjected to biological evaluation because it was unstable to storage at room temperature.

A similar sequence was used for the synthesis of the 4-nitro-1,3-thiazolium-5-olate (5). 5-Ethoxy-2-methyl-4-nitrothiazole (9) [12] and methyl fluorosulphonate gave the corresponding *N*-methylthiazolium fluorosulphonate which was isolated as 5-ethoxy-2,3-dimethyl-4-nitrothiazolium perchlorate (10). Attempts to convert the perchlorate (10) into the meso-ionic heterocycle (5) using a variety of standard methods for *O*-dealkylation were unsuccessful. Eventually it was established that these failures could be attributed to the instability of the product. The reaction between 5-ethoxy-2,3-dimethyl-4-nitrothiazolium perchlorate (10) and sodium iodide in hexadeuterioacetone was monitored by ^{1}H n.m.r. spectrometry. At room temperature, during a period of 25 min, signals appeared which could be assigned to the expected product (5) and to ethyl iodide. However, the product (5) was clearly unstable and all attempts to isolate the required 2,3-dimethyl-4-nitro-1,3-thiazolium-5-olate (5) failed.

The transformation of 4-bromo-3-nitropyrazole (11) into the meso-ionic analogue (6) of the biologically active 3-nitropyrazoles (3) [4] could not be achieved but results of interest in relation to the chemistry of nitropyrazoles are reported. Bromination of 3-nitropyrazole [13] gave 4-bromo-3-nitropyrazole (11) which, by methylation with dimethyl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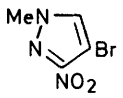
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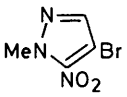
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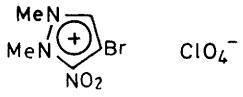
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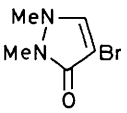
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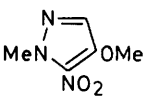
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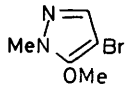
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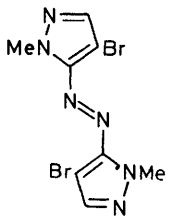
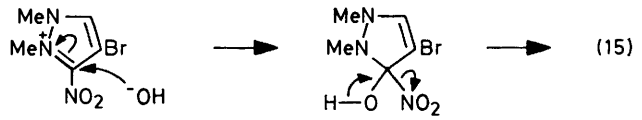

(18)

sulphate and aqueous potassium hydroxide, gave a mixture of two products which were clearly the isomeric *N*-methyl derivatives (12) and (13). The assignment of constitutions to these two *N*-methyl isomers posed an interesting problem. Although both isomers showed differences in their ^1H and ^{13}C n.m.r. spectra, we did not consider that the observed differences in chemical shifts for corresponding atoms or groups were of structural significance. However, an informative difference was observed in the mass spectral fragmentation patterns of the two *N*-methyl isomers. The compound, m.p. 158—160 °C, showed a strong molecular ion ($M^{+\cdot}$ 205; ^{79}Br), but no sign of a fragment ion (*m/z* 188). In contrast, the compound, m.p. 54—55 °C, not only showed a strong molecular ion ($M^{+\cdot}$ 205; ^{79}Br) but also a fragment ion (*m/z* 188) corresponding to the process (M − OH). This fragmentation suggests that the *N*-methyl and *C*-nitro groups are adjacent and this observation supports the formulation of the isomer, m.p. 54—55 °C, as 4-bromo-1-methyl-5-nitropyrazole (13). By exclusion, the constitution, 4-bromo-1-methyl-3-nitropyrazole (12) could be allocated to the isomer, m.p. 158—160 °C. These assignments were supported by the measurement of spin-lattice relaxation times (T_1) and the nuclear Overhauser effects from which dipolar relaxation times (T_1^{DD}) can be calculated for the four carbon atoms in the natural abundance ^{13}C n.m.r. spectra of the two isomers. This method (see Experimental section) which provides estimates of the average distance between the C–NO_2 carbon atoms and the protons of the *N*-methyl groups ultimately confirmed the formulation of the isomers (12) (m.p. 158—160 °C) and (13) (m.p. 54—55 °C).

The problem of determining the constitution of pairs of isomers produced by methylation of 3-nitropyrazoles has also been examined by others. Dumanović, Maksimović, Ćirić, and Jeremić [14] distinguished between 1-methyl-3-nitropyrazole and 1-methyl-5-nitropyrazole by n.m.r. spectrometry, mass spectrometry, and polarography. A comprehensive review of the *N*-alkylation of unsymmetrical pyrazoles has been reported,[15] but the structural differentiation between pairs of isomers was made by comparison of n.m.r. spectral assignments.

Methylation of 4-bromo-1-methyl-3-nitropyrazole (12) with methyl fluorosulphonate followed by treatment with perchloric acid gave the pyrazolium perchlorate (14). All attempts to transform 4-bromo-1,2-dimethyl-3-nitropyrazolium perchlorate (14) into the required type B meso-ionic [5,6] heterocycle (6) failed. For example, mild alkaline hydrolysis of 4-bromo-1,2-dimethyl-3-nitropyrazolium perchlorate (14) gave 4-bromo-1,2-dimethylpyrazol-3(2*H*)-one [16] (15) (yield 74%) presumably by the following mechanism.



This result may be compared with the similar mild hydrolysis of 1,2-dimethyl-3,4-dibromopyrazolium tosylate which yielded three products including 4-bromo-1,2-dimethylpyrazol-3(2*H*)-one (15) (yield 22%).[16]

As the formation of the type B meso-ionic heterocycle (6) could not be successfully achieved by alkaline hydrolysis of the pyrazolium perchlorate (14), an alternative route from 4-bromo-1-methyl-5-nitropyrazole (13) was explored. This was based upon the belief that nucleophilic displacement of the 4-bromo-substituent by methoxide anion might be achieved yielding 4-methoxy-1-methyl-5-nitropyrazole (16). Unfortunately the 4-methoxy-derivative (16) could be isolated only in low yield by careful fractionation. Reaction between 4-bromo-1-methyl-5-nitropyrazole (13) with sodium methoxide in boiling methanol yielded 4-methoxy-1-methyl-5-nitropyrazole (16) (2 parts) and 4-bromo-5-methoxy-1-methylpyrazole (17) (5 parts). The formation of these two products by competition between two very different nucleophilic displacement reactions is surprising, particularly in view of the very smooth conversion of 5-bromo-1,2-dimethyl-4-nitroimidazole into the corresponding 5-methoxy-derivative (7). However, a good analogy for the nucleophilic displacement of the nitro-group is provided by an interesting study of the reaction between nitroimidazoles and thiolate anions.[17] 4-Bromo-1-methyl-5-nitropyrazole (13) with sodium ethoxide in ethanol was reductively coupled yielding the azo-pyrazole derivative (18).

Experimental

Melting points are uncorrected and were determined using a Kofler hot-stage apparatus. Evaporation refers to evaporation under diminished pressure. Light petroleum refers to the fraction (b.p. 60—80 °C) unless otherwise stated.

Hopkin and Williams aluminium oxide was used for ordinary column chromatography. Merck Kieselgel-H (type 60) was used for medium-pressure column chromatography. Merck Kieselgel-G coated on glass plates was used for analytical (thin layer) and preparative (thick layer) chromatography. During fractionation by column chromatography, appropriate fractions were combined on the basis of their t.l.c. behaviour.

Low resolution mass spectra were determined with an A.E.I. MS-12 mass spectrometer. High resolution mass spectra and fragmentation patterns were determined using an A.E.I. MS-9 mass spectrometer.

Unless otherwise stated, i.r. spectra were measured for solutions in chloroform, u.v. spectra in ethanol, and n.m.r. spectra in deuteriochloroform. Only significant bands from i.r. spectra are quoted.

Unless otherwise stated, ^{1}H n.m.r. spectra (220 MHz) were recorded on a Perkin-Elmer R-34 spectrometer. ^{1}H n.m.r. spectra (100 MHz) were recorded on a JEOL PFT-100 spectrometer equipped with an EC-100 computer. All chemical shifts (δ) are related to tetramethylsilane as internal standard and spectral details are reported as follows: δ (solvent); δ values in p.p.m. (number of protons, multiplicity, coupling constant Hz, and assignments). The multiplicity of signals is expressed by the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, dm = double multiplet, br s = broad singlet, br t = broad triplet, br q = broad quartet.

^{13}C N.m.r. spectra (25 MHz) were recorded using a JEOL PFT-100 spectrometer with an EC-100 computer. Chemical shifts were initially determined from proton decoupled spectra and multiplicities due to C–H coupling were determined from off-centre resonance decoupled spectra. Spectral details are reported as follows: δ (solvent), δ values in p.p.m. (multiplicity and assignments).

When substances are stated to be identical, their identity has been established by comparison of, where appropriate, m.p. and mixed m.p. determinations, i.r. spectra, ^{1}H n.m.r. spectra, and t.l.c. behaviour.

5-*Methoxy*-1,2-*dimethyl*-4-*nitroimidazole* (7).—A mixture of 5-bromo-1,2-dimethyl-4-nitroimidazole [10] (2 g), anhydrous sodium carbonate (6 g), and methanol (50 ml) was heated under reflux for 12 min, added to water, and continuously extracted with chloroform for 18 h. The chloroform extract was evaporated and the residue was crystallised from di-isopropyl ether yielding 5-methoxy-1,2-dimethyl-4-nitroimidazole (1 g, 65%) as colourless crystals, m.p. 102—103 °C (lit.,[11] m.p. 180—181 °C) (Found: C, 42.2; H, 5.1; N, 24.5%; $M^{+\cdot}$, 171. Calc. for $C_6H_9N_3O_3$: C, 42.1; H, 5.3; N, 24.6%; *M*, 171); δ 2.34 (3 H, s, CCH_3), 3.42 (3 H, s, NCH_3), and 4.20 (3 H, s, OCH_3).

4-*Methoxy*-1,2,3-*trimethyl*-5-*nitroimidazolium Perchlorate* (8).—A solution of 5-methoxy-1,2-dimethyl-4-nitroimidazole (0.4 g) in chloroform (10 ml) was treated with methyl fluorosulphonate (1 ml) and kept at room temperature for 12 min. The oil which separated was isolated by decantation of the liquors, washed twice with chloroform, and then dissolved in a mixture of acetic acid (2 ml) and aqueous perchloric acid solution (1 ml; 60% w/v). Addition of ether to the solution gave the *imidazolium perchlorate* as colourless crystals (0.42 g, 63%), m.p. 103—106 °C (decomp.) (Found: C, 29.2; H, 4.2; Cl, 12.5; N, 14.6. $C_7H_{12}ClN_3O_7$ requires C, 29.5; H, 4.3; Cl, 12.4; N, 14.7%); $\nu_{max.}$ (KBr) 1 640 and 1 120—1 050 cm^{-1}; δ (CF_3CO_2H) 2.78 (3 H, s, CCH_3), 3.80 (3 H, s, NCH_3), 4.15 (3 H, s, NCH_3), and 4.45 (3 H, s, OCH_3).

1,2,3-*Trimethyl*-5-*nitro*-1,3-*diazolium*-4-*olate* (4).—A solution of 4-methoxy-1,2,3-trimethyl-5-nitroimidazolium perchlorate (0.151 g) in pyridine (1.3 ml) was stirred at room temperature until the initial yellow solution acquired a purple coloration. The solid which separated (69 mg, 76%) was crystallised from acetonitrile–ether giving the *diazolium*-4-*olate* as pale yellow crystals, m.p. 173—174 °C (Found: C, 42.0; H, 5.1; N, 24.4%; $M^{+\cdot}$, 171. $C_6H_9N_3O_3$ requires C, 42.1; H, 5.3; N, 24.6%; *M*, 171); $\lambda_{max.}$ (MeCN) 248sh and 362 nm (ε 4 900 and 16 000); $\nu_{max.}$ (KBr) 1 710 cm^{-1}; δ CD_3NO_2 2.52 (3 H, s, CCH_3), 3.30 (3 H, s, 3-CH_3), and 3.90 (3 H, s, 1-CH_3). This compound was unstable on storage at room temperature.

5-*Ethoxy*-2,3-*dimethyl*-4-*nitrothiazolium Perchlorate* (10).—A solution of 5-ethoxy-2-methyl-4-nitrothiazole [12] (1 g) in chloroform (30 ml) was treated with methyl fluorosulphonate (4 ml), and the mixture was heated under reflux for 30 min. The oil which separated was isolated by decantation of the liquors, washed with chloroform, and dissolved in a mixture of acetic acid (2 ml) and aqueous perchloric acid (2 ml; 60% w/v). Addition of ether to the solution gave the *thiazolium perchlorate* (1.05 g, 65%) as colourless crystals, m.p. 110—112 °C (Found: C, 27.9; H, 3.4; Cl, 11.4; N, 9.3; S, 10.8. $C_7H_{11}ClN_2O_7S$ requires C, 27.8; H, 3.7; Cl, 11.7; N, 9.3; S, 10.6%); $\nu_{max.}$ (Nujol) 1 150—1 080 cm^{-1}; δ (CF_3CO_2H) 1.68 (3 H, t, J_{AX} 7.5 Hz, OCH_2CH_3), 3.05 (3 H, s, 2-CH_3), 4.35 (3 H, s, 3-CH_3), and 4.64 (2 H, q, J_{AX} 7.5 Hz, OCH_2CH_3).

2,3-*Dimethyl*-4-*nitro*-1,3-*thiazolium*-5-*olate* (5).—Several attempts to convert 5-ethoxy-2,3-dimethyl-4-nitrothiazolium perchlorate (10) into the corresponding thiazolium-5-olate (5) by standard procedures failed to yield the required (5) as an isolable product. This failure is probably related to the inherent instability of the latter compound (5). However, its formation from the former compound (10) was established *in situ* in the following manner.

The ^{1}H n.m.r. spectrum of a solution of 5-ethoxy-2,3-dimethyl-4-nitrothiazolium perchlorate (30 mg) in [$^2H_6$]acetone was recorded, and the solution was then treated with sodium iodide (20 mg). The ^{1}H n.m.r. spectrum of the mixture was recorded immediately and subsequently at 5 min intervals during 25 min. These spectra indicated the gradual appearance of ethyl iodide [δ 1.88 (3 H, t, J_{AX} 6 Hz, CH_2CH_3) and 3.32 (2 H, q, J_{AX} 6 Hz, CH_2CH_3)] and the formation of the desired *thiazolium-5-olate* [δ 2.95 (3 H, s, 2-CH_3) and 4.27 (3 H, s, 3-CH_3)]. After 24 h at room temperature, signals due to decomposition products dominated the ^{1}H n.m.r. spectrum of the mixture.

4-*Bromo*-3-*nitropyrazole* (11).—A mixture of 3-nitropyrazole [13] (15 g), bromine (8.4 ml), sodium acetate (11.04 g), and acetic acid (150 ml) was heated at 100 °C for 3 h. The mixture was cooled and added to ice, and the colourless solid which separated was filtered off and crystallised from aqueous ethanol (50% v/v) giving 4-*bromo*-3-*nitropyrazole* (11.3 g, 44%) as colourless crystals, m.p. 197—198 °C (Found: C, 19.0; H, 1.0; Br, 41.4; N, 22.0%; $M^{+\cdot}$, 191. $C_3H_2BrN_3O_2$ requires C, 18.8; H, 1.1; Br, 41.6; N, 21.9%; *M*, 191); $\nu_{max.}$ 3 250—3 100, 1 555, 1 375, and 1 335 cm^{-1}; δ [$(CD_3)_2SO$] 8.19 (1 H, s, 5-H) and 14.28 (1 H, br s, NH).

Methylation of 4-*Bromo*-3-*nitropyrazole* (11): *Formation of* 4-*Bromo*-1-*methyl*-3-*nitropyrazole* (12) *and* 4-*Bromo*-1-*methyl*-5-*nitropyrazole* (13).—A solution of 4-bromo-3-nitropyrazole (10.24 g) and potassium hydroxide (2.95 g) in water (100 ml) was treated with dimethyl sulphate (3.34 g) and the mixture was stirred at room temperature for 1 h. The solid which separated was filtered off, and the yellow filtrate was treated with a further portion of dimethyl sulphate (2.66 g), kept at room temperature for 18 h, and filtered. The combined solids were washed with water and crystallised from aqueous ethanol (50% v/v) yielding 4-*bromo*-1-*methyl*-3-*nitropyrazole* (5.5 g, 50%) as colourless crystals, m.p. 158—160 °C (Found: C, 23.0; H, 1.9; Br, 38.9; N, 20.6%; $M^{+\cdot}$, 205. $C_4H_4BrN_3O_2$ requires C, 23.3; H, 2.0; Br, 38.8; N, 20.4%; *M*, 205); $\nu_{max.}$ (KBr) 3 100, 1 550, 1 510, and 1 370 cm^{-1}; δ 4.02 (3 H, s, NCH_3) and 7.58 (1 H, s, 5-*H*); δ_C [$(CD_3)_2SO$ + Cr(acac)$_3$] 40.7 (CH_3), 88.8 (C-4), 136.0 (C-5), and 150.9 (C-3).

The filtrate was concentrated and the solid (2.15 g) which separated was purified by column chromatography [$CHCl_3$–EtOAc (1 : 1) as eluant] when 4-*bromo*-1-*methyl*-5-*nitro*-

pyrazole was obtained (1.0 g, 9%) as colourless crystals, m.p. 54—55 °C, from aqueous ethanol (Found: C, 23.1; H, 1.9; Br, 38.8; N, 20.1%; $M^{+\cdot}$, 205. $C_4H_4BrN_3O_2$ requires C, 23.3; H, 2.0; Br, 38.8; N, 20.4%; *M*, 205); $\nu_{max.}$ (KBr) 3 100, 1 555, 1 505, and 1 350 cm^{-1}; δ 4.26 (3 H, s, NCH_3) and 7.60 (1 H, s, 3-H); δ_C [$(CD_3)_2SO$ + $Cr(acac)_3$] 42.0 (NCH_3), 93.7 (C-4), 139.4 (C-3), and 142.9 (C-5).

A second fraction from the column chromatography gave 4-bromo-1-methyl-3-nitropyrazole (1.1 g, 10%), m.p. 158—160 °C, identical with an authentic sample obtained above.

Assignment of the Constitutions 4-*Bromo*-1-*methyl*-3-*nitropyrazole* (12) *and* 4-*Bromo*-1-*methyl*-5-*nitropyrazole* (13) *to the Methylation Products from* 4-*Bromo*-3-*nitropyrazole* (11).—The method adopted was (i) the measurement of the spin-lattice relaxation time, T_1, for the carbon atom bearing the nitro-group, (ii) the derivation of the dipolar relaxation time, T_1^{DD}, making use of observed nuclear Overhauser enhancement, (iii) calculation of the correlation times, τ_c, of the molecules assuming isotropic molecular motion from appropriate dipolar relaxation times similarly obtained from spin-lattice relaxation times, and (iv) from the dipolar relaxation times, T_1^{DD}, and the correlation times, τ_c, the average distances between the protons of the *N*-methyl group and the carbon atom of the $C-NO_2$ group were determined. Comparison of calculated values of these C–H distances with those measured from Dreiding models enabled structures to be assigned to the two *N*-methylation products (12) and (13).

Relaxation times and n.O.e.s for the carbon atoms of 4-bromo-1-methyl-3-nitropyrazole (12) [a]

Assignment	Chemical shift (p.p.m.)	T_1 (observed) (s)	N.O.e.	T_1^{DD} (s) [c]
$N-CH_3$	40.6	4 [b]	—	—
C-3	151.5	70 ± 10	0.23	620 ± 100
C-4	89.5	9.5	0	—
C-5	136.5	1.8	1.7	2.1

Relaxation times and n.O.e.s for the carbon atoms of 4-bromo-1-methyl-5-nitropyrazole (13) [a]

Assignment	Chemical shift (p.p.m.)	T_1 (obs.) (s)	N.O.e.	T_1^{DD} (s) [c]
$N-CH_3$	41.7	4 [b]	2	4
C-3	139.5	1.8	1.7	2.1
C-4	93.6	8.7	0.1	174
C-5	142.5	98	0.9 ± 0.2	220 ± 30

[a] ^{13}C N.m.r. spectra were measured for solutions in $(CD_3)_2SO$. [b] The *N*-methyl carbon signal of both isomers was overlapped by the $(CD_3)_2SO$ signal. It was therefore difficult to obtain reliable values for T_1 and n.O.e. for this carbon atom, but T_1 = 4 s is an acceptable compromise. [c] Calculated from the equation $T_1^{DD} = 2T_1/\text{n.O.e.}$

The observed relaxation rate, $1/T_1$, is dependent upon the combined contributions from several relaxation mechanisms. The dipolar relaxation time, T_1^{DD}, is dependent upon the internuclear distances. For small molecules in solution, the equation relating T_1^{DD} to internuclear C–H distances reduces to

$$\frac{1}{T_1^{DD}} = \frac{h^2}{4\pi^2}\gamma_H^2\gamma_C^2\sum\frac{N\tau_c}{r_{CH}^6} \quad (1)$$

γ_H = proton gyromagnetic ratio, γ_C = carbon-13 gyromagnetic ratio, *N* = number of protons, τ_c = correlation time, and r_{CH} = distance between carbon and proton.

The correlation time of each molecule was calculated using equation (1), from the T_1^{DD} of the protonated ring carbon atoms assuming (i) a C–H bond length of 1.084 Å and (ii) that only the directly attached hydrogen atom causes relaxation of this carbon atom. The dipole–dipole relaxation of the carbon atom bearing the nitro-group is brought about by the four protons in the molecule. For the *C*-nitro carbon atom, equation (1) becomes

$$\frac{1}{T_1^{DD}} = \frac{h^2}{4\pi^2}\gamma_H^2\gamma_C^2\left\{\frac{3\tau_c}{r^6(C_{NO_2}-CH_3)} + \frac{\tau_c}{r^6(C_{NO_2}-CH)}\right\} \quad (2)$$

where $r(C_{NO_2}-CH_3)$ is the average distance between the *C*-nitro-carbon atom and the methyl protons. The distance $r(C_{NO_2}-CH)$ in both isomers is measured to be 3.25 Å from molecular models. Thus, $r(C_{NO_2}-CH_3)$ is calculable for both isomers and the values are recorded below.

Structure	$r(C_{NO_2}-CH_3)$ [a] (Å)	$r(C_{NO_2}-CH_3)$ [b] (Å)
(12)	3.7	4.0
(13)	2.9	2.9

[a] Experimental result from equation (2). [b] Measured from molecular models.

Considering the assumptions made in the calculation and the difficulties encountered in extracting data from the spectra, the calculated and measured distances agree satisfactorily and distinguish between the isomers (12) and (13). This is an application of the measurement of ^{13}C spin-lattice relaxation times leading to the assignment of constitutions to a pair of isomers. The method corresponds with similar measurements used to determine the position of a proton in an intramolecular hydrogen bond.[18]

These measurements were made using a Varian CFT 20 spectrometer.

4-*Bromo*-1,2-*dimethyl*-3-*nitropyrazolium Perchlorate* (14).—A mixture of 4-bromo-1-methyl-3-nitropyrazole (2 g), chloroform (50 ml), and methyl fluorosulphonate (5 ml) was heated under reflux for 36 h. The solid which separated was washed with chloroform and dissolved in acetic acid (4 ml). Addition of aqueous perchloric acid solution (4 ml; 60% w/v) to the acetic acid solution, followed by ether (60 ml) gave the *perchlorate* (2.78 g, 89%) as colourless crystals, m.p. 178—180 °C (Found: C, 18.5; H, 2.1; Br, 25.0; Cl, 11.1; N, 12.9. $C_5H_7BrClN_3O_6$ requires C, 18.7; H, 2.2; Br, 24.9; Cl, 11.1; N, 13.1%); $\nu_{max.}$ (Nujol) 3 140 and 1 575 cm^{-1}; δ (CF_3CO_2H) 4.41 (3 H, s, 1-CH_3), 4.52 (3 H, s, 2-CH_3), and 8.49 (1 H, s, 5-H).

4-*Bromo*-1,2-*dimethylpyrazol*-3(2H)-*one* (15).—A mixture of 4-bromo-1,2-dimethyl-3-nitropyrazolium perchlorate (1 g), potassium hydroxide (0.6 g), and water (10 ml) was stirred at room temperature for 18 h and concentrated by evaporation. The solid which separated was purified by column chromatography (methanol as eluant) when the pyrazolone was obtained as a pale yellow solid (0.44 g, 74%), m.p. 108—110 °C (after recrystallisation from ethyl acetate–light petroleum, b.p. 40—60 °C) (lit.,[16] m.p. 100—102 °C) (Found: C, 31.6; H, 3.4; Br, 41.9; N, 14.8%; $M^{+\cdot}$, 190. Calc. for $C_5H_7BrN_2O$: C, 31.4; H, 3.7; Br, 41.8; N, 14.7%; *M*, 190; $\nu_{max.}$ 1 655 cm^{-1}; δ 3.46 (3 H, s, $N-CH_3$), 3.48 (3 H, s, $N-CH_3$), and 7.42 (1 H, s, 5-H); δ_C 29.0 (q, $N-CH_3$), 36.7 (q, $N-CH_3$), 86.3 (s, C-4), 139.9 (d, C-5), and 162.2 (s, C-3).

Reaction of 4-*Bromo*-1-*methyl*-5-*nitropyrazole* (13) *with Methanolic Sodium Methoxide: Formation of* 4-*Methoxy*-1-*methyl*-5-*nitropyrazole* (16) *and* 4-*Bromo*-5-*methoxy*-1-*methylpyrazole* (17).—A solution of sodium (0.26 g) in methanol (10 ml) was treated with 4-bromo-1-methyl-5-nitropyrazole (0.4 g) and the mixture was heated under reflux for 42 h. The solution was added to a mixture of water and chloroform, and the aqueous phase was further extracted with chloroform. The combined chloroform extracts were washed with water, dried, and evaporated. The residual solid (230 mg) was partially purified by preparative t.l.c. [$CHCl_3$–EtOAc (2 : 1) as eluant] when two fractions were obtained: fraction 1 (R_F 0.65) was isolated as a colourless oil (64 mg) which was shown (^1H n.m.r.) to be a mixture of the 5-*methoxypyrazole* and 4-*methoxypyrazole* derivatives (10 : 1) and fraction 2 (R_F 0.7) obtained as a yellow solid (51 mg) was also shown (^1H n.m.r.) to be a mixture of the 5- and 4-methoxy derivatives (0.8 : 1). Final purification of both fractions was carried out by g.l.c. [6ft, 2½% OV 17 on Gas Chrom Q; N_2 at 30 ml/min; 60—150 °C at 5 °C/min; F.I.D. detector; injection temperature 200 °C]. Fraction 1 gave the 5-methoxypyrazole derivative (t_R 1.75 min) as a colourless oil (Found: $M^{+\cdot}$, 189.9749. $C_5H_7BrN_2O$ requires M, 189.9741); $\nu_{max.}$ 1 570 cm^{-1}; δ 3.63 (3 H, s, N–CH_3), 4.06 (3 H, s, O–CH_3), and 7.25 (1 H, s, 3-H); fraction 2 gave the 4-methoxypyrazole derivative (t_R 3.0 min) as a colourless solid, m.p. 132—133 °C (Found: $M^{+\cdot}$, 157.0487. $C_5H_7N_3O_3$ requires M, 157.0487); $\nu_{max.}$ 1 590, 1 450, and 1 345 cm^{-1}; δ 3.95 (3 H, s, N–CH_3), 4.18 (3 H, s, O–CH_3), and 7.29 (1 H, s, 3-H).

4,4′-*Dibromo*-1,1′-*dimethyl*-5,5′-*azopyrazole* (18).—4-Bromo-1-methyl-5-nitropyrazole (0.45 g) was added to a solution of sodium (0.33 g) in ethanol (12 ml) and the mixture was heated under reflux for 1 h. Evaporation gave a residue which was added to a mixture of water and chloroform. The chloroform extract was washed with water, dried, and evaporated. The residual solid (0.225 g) was purified by preparative t.l.c. [$CHCl_3$–EtOAc (3 : 1)] when the *pyrazole* derivative (R_F 0.75) was obtained (53 mg, 14%) as yellow crystals, m.p. 224—226 °C (from ethanol) (Found: $M^{+\cdot}$, 345.9178. $C_8H_8Br_2N_6$ requires M, 345.9179); $\nu_{max.}$ 1315 and 1 310 cm^{-1}; δ 4.18 (6 H, s, 2 × N–CH_3) and 7.60 (2 H, s, 2 × 3-H).

Acknowledgements

We warmly thank the S.E.R.C. and May and Baker Ltd. for the award of a CASE Studentship (to C. G. N.).

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Received 10*th June* 1983; *Paper* 3/971