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Nucleophilic Displacements of Imidazoles. I Oxygen, Nitrogen and Carbon Nucleophiles

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Abstract

4(5)-Bromo- and -iodo-imidazoles, activated by an adjacent nitro substituent, undergo nucleophilic displacement with methoxide, phenoxide, cyclic secondary amines and cyanide. The regiochemistry of the reactions of 5-iodo-4-nitroimidazole with methoxide has been confirmed by spectroscopic and X-ray methods, and a number of erroneous structures from the literature have been revised. Some apparently anomalous reactions of methoxide with 5-halo-1,2-dimethyl-4-nitroimidazoles, and of cyanide with 4-halo-1-methyl-5-nitroimidazole have been noted. The crystal and molecular structure of 5-methoxy-1-methyl-4-nitroimidazole has been determined by direct methods. Crystals are monoclinic, $P2_1/c$, a 10·929(3), b 8·899(2), c 7·290(2) Å; β 92·87(2)°; Z 4. The structure was refined to $R = 0{\cdot}095$ for 818 reflections ($I > 2\sigma I$).

Introduction

Nitro-substituted imidazoles have found important applications, particularly as antibacterial agents and in cancer chemotherapy.[1,2] As part of a project aimed at the preparation of a variety of nitroimidazoles for agricultural and pharmacological testing, we have embarked on a survey of the nucleophilic displacements of halogen-substituted imidazoles in which an iodo or bromo group is activated by an adjacent nitro function.

A survey of the literature showed that very little systematic work has been done. It is known that imidazole is resistant to the Chichibabin reaction, and if there is no electron-withdrawing group present, nucleophilic displacement is not at all facile.[3] Whereas 5-chloro-1-methylimidazole does not react with piperidine even at elevated temperatures, a stronger nucleophile (lithium piperidide) will achieve some displacement of the chlorine, but yields are low and some of the attack results in *cine*-substitution at C2. A halogen at C2 is similarly labile, but 4-bromo-(or 4-chloro-)1-methylimidazole would not react.[4] With potassium amide in liquid

[1] Breccia, A., Cavalleri, R., and Adams, G. E., (Eds) 'Nitroimidazoles: Chemistry, Pharmacology and Clinical Application' NATO Advanced Study Institutes Series A, Life Sciences: Vol. 42 (Plenum Press: New York 1982).
[2] Grimmett, M. R., in 'Comprehensive Heterocyclic Chemistry' (Eds A. R. Katritzky and C. W. Rees) Vol. 4, p. 498 (Pergamon Press: Oxford 1984).
[3] Grimmett, M. R., *Adv. Heterocycl. Chem.*, 1980 **27**, 241.
[4] De Bie, D. A., van der Plas, H. C., and Guertsen, G., *Recl Trav. Chim. Pays-Bas*, 1971, **90B**, 594.

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ammonia 5-bromo-1-methylimidazole gave only a mixture of 1-methylimidazole and 4-bromo-1-methylimidazole through halogen elimination and migration.[5]

There have, however, been a number of reports of displacements of nitro-activated halogens by cyclic secondary amines,[6–9] cyanide,[8–11] hydroxy, alkoxy and aryloxy,[6,9,12] thiols,[9] and other halogens.[13–15] Activated 4-bromo and -iodo groups are, however, not replaced in reaction with metal fluorides,[16,17] and 4-fluoro (but not 2-fluoro) groups resist displacement by other nucleophiles.[18] Groups other than halogen are sometimes displaced. Hydroxylamine reacts with 1,2-dimethyl-4- and -5-nitroimidazoles to give the amino derivatives,[8] and a recent paper has listed substitutions of 4,5-dinitroimidazole and 4-nitroimidazole-5-sulfonic acid.[19]

It seems that an activated halogen substituent at C2 is displaced more readily than one at C4 or C5,[7] while it is also apparent that a 5-halogen is easier to replace than one at the 4-position. A contrary report[8] was based on substitutions of 1,2-dimethylimidazoles which are atypical in their reactions (see below). In the presence of copper(I) salts a 2-chloro substituent even in an unactivated imidazole can be displaced by secondary amines.[20]

The present paper describes reactions of 4(5)-nitro-5(4)-bromo- (or -iodo-) imidazoles with methoxide, phenoxide, some secondary amines and cyanide. Reactions with sulfur nucleophiles and displacements of methylsulfonyl groups are discussed in Part II.

One of the reasons for the confused and often contradictory natures of past reports of nucleophilic substitutions of (especially) iodonitroimidazoles is a consequence of incorrect structure assignments of 4-iodo- and 4,5-diiodo-imidazoles nearly sixty years ago. Pauly[21] believed these compounds to be the 2- and 2,4-isomers respectively, and in spite of doubts raised by Naidu,[22] it was left to Dickens[15] to redefine the structures unequivocally, rendering many earlier publications erroneous.

Because of the need to revise many reported structures, this present study has concentrated in the first instance on repeating earlier work with the aid of modern

[5] De Bie, D. A., and van der Plas, H. C., *Recl Trav. Chim. Pays-Bas*, 1969, **88B**, 1246.
[6] Kochergin, P. M., Tsyganova, A. M., Shlikhunova, V. S., and Klykov, A. M., *Chem. Heterocycl. Compd.* (Engl. Transl.), 1971, **6**, 648.
[7] Barlin, G. B., *J. Chem. Soc. B*, 1967, 641.
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[9] Winkelmann, E., Raether, W., Gebert, V., and Sinharay, A., *Arzneim.-Forsch.*, 1977, **27**(II), 2251.
[10] Sarasin, J., and Wegmann, E., *Helv. Chim. Acta*, 1924, **7**, 713.
[11] Baddiley, J., Buchanan, J. G., Hardy, F. E., and Stewart, J., *J. Chem. Soc.*, 1959, 2893.
[12] Hoffer, M., Toome, V., and Brossi, A., *J. Heterocycl. Chem.*, 1966, **3**, 454.
[13] Sharnin, G. P., Fassakhov, R. Kh., Eneikina, T. A., and Orlov, P. P., *Chem. Heterocycl. Compd.* (Engl. Transl.), 1977, **13**, 529.
[14] Sharnin, G. P., Fassakhov, R. K., and Eneikina, T. A., *Chem. Heterocycl. Compd.* (Engl. Transl.), 1977, **13**, 1332.
[15] Dickens, J. P., Dyer, R. L., Hamill, B. J., Harrow, T. A., Bible, R. H., Finnegan, P. M., Henrick, K., and Owston, P. G., *J. Org. Chem.*, 1981, **46**, 1781.
[16] Kirk, K. L., and Cohen, L. A., *J. Am. Chem. Soc.*, 1971, **93**, 3060.
[17] Kirk, K. L., and Cohen, L. A., *J. Am. Chem. Soc.*, 1973, **95**, 4619.
[18] Kirk, K. L., Nagai, W., and Cohen, L. A., *J. Am. Chem. Soc.*, 1973, **95**, 8389.
[19] Mokrushin, V. S., Belyaev, N. A., Kolobov, M. Yu., and Fedotov, A. N., *Chem. Heterocycl. Compd.* (Engl. Transl.), 1983, **19**, 650.
[20] Whittle, C. P., *Aust. J. Chem.*, 1980, **33**, 1545.
[21] Pauly, H., and Arauner, E., *J. Prakt. Chem.*, 1928, **118**, 33.
[22] Naidu, M. S. R., and Bensusan, H. B., *J. Org. Chem.*, 1968, **33**, 1307.

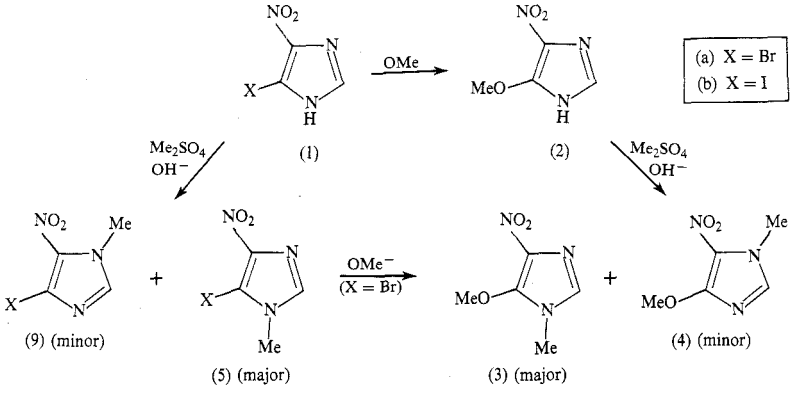
physical methods for defining regiochemistry. In particular, the regiochemistry of the key compound, 5-methoxy-1-methyl-4-nitroimidazole, has been confirmed by X-ray methods. At the same time, we have taken the opportunity to gather together spectroscopic data for these imperfectly described compounds, and for a number of previously undescribed products isolated during this study. Some assignments, particularly in the ^{13}C n.m.r. spectra, must be considered as tentative until we are able to study a wider range of these compounds.

Results and Discussion

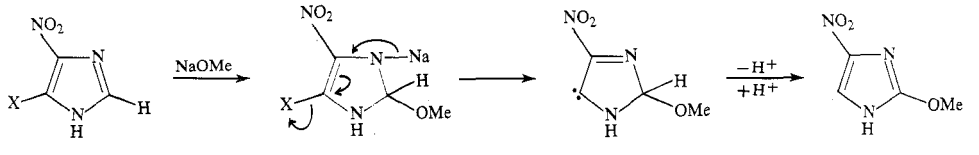
Displacements by Methoxy

Hoffer *et al.*[12] reported the formation of 2-methoxy-4-nitroimidazole by reaction of sodium methoxide with what he believed to be 2-iodo-4-nitroimidazole. As demonstrated recently,[15] the substrate was in fact 5-iodo-4-nitroimidazole (1b). We found that both 5-bromo- and 5-iodo-4-nitroimidazoles reacted smoothly with methoxide to give a product which had the same melting point as Hoffer's product, and as the compound recently designated[19] as 5-methoxy-4-nitroimidazole (2) (Scheme 1). The ^1H n.m.r. spectrum in trifluoroacetic acid showed a three-proton singlet for methoxy and a one-proton singlet at 8·56 ppm. While this, with hindsight, can be assigned to H2, it could equally well be accounted for in terms of H5 adjacent to a nitro group. The ^{13}C n.m.r. spectrum exhibited four signals assigned as follows: 58·4 (methoxy), 135·4 (C2), 140·3 (C5), 154·6 (C4). In the proton-undecoupled spectrum the highest intensity peak at 135·4 ppm appeared as a doublet with $^1J_{CH}$ = 217 Hz, comparable with the one-bond CH-coupling constant (215 Hz) for C2 of 5-iodo-4-nitroimidazole. *C*-Nitro signals, where present, are frequently assigned to the often broad, lowest intensity signal in the spectrum.

There remains the possibility, though, that nucleophilic attack by methoxide could have occurred at C2[4] (Scheme 2). This means that the structural assignment of 5-methoxy-4-nitroimidazole[19] is not unequivocal.



Scheme 1



Scheme 2

Methylation of (2) in basic medium gave two *N*-methyl isomers (3), (4), with the major isomer, as expected in an S_E2cB process,[3] being assigned the structure 5-methoxy-1-methyl-4-nitroimidazole (3). The same compound was isolated when 5-bromo-1-methyl-4-nitroimidazole (5a) reacted with methanolic sodium methoxide. A crystal structure of (3) (Figs 1, 2) finally demonstrated that the methoxy function was at C 5, confirming the n.m.r. assignments for (2) and its *N*-methyl derivatives (3), (4).

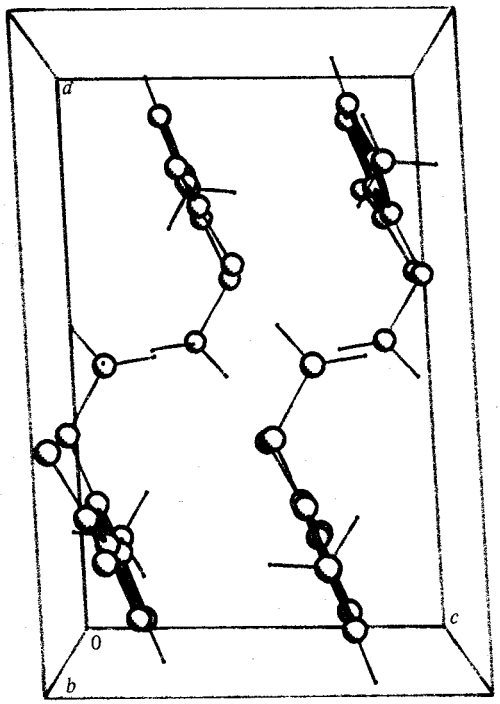


Fig. 1. Packing diagram for compound (3).

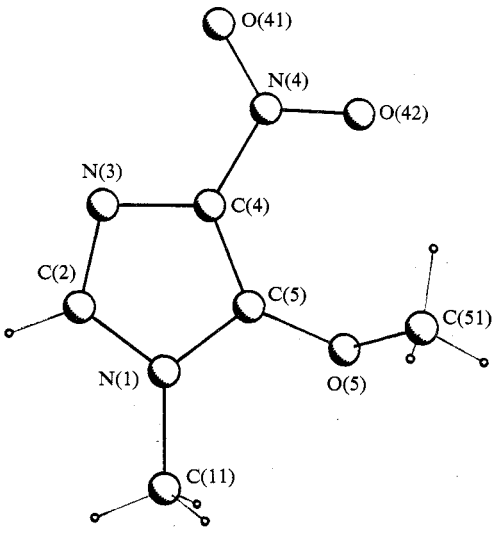


Fig. 2. Molecular structure of compound (3) viewed perpendicular to the plane of the imidazole ring, showing the atom numbering scheme.

In no instance did we detect any products resulting from nucleophilic attack at C 2 of imidazole, though it must be admitted that yields were only in the range 65–70%, and no gas chromatographic analysis was attempted. The substrates studied by van der Plas[4] were, however, probably not sufficiently activated for an S_NAr process, in contrast to the halonitroimidazoles in the present study.

The structure of (3) consists of well separated molecules with the closest intermolecular contact not involving hydrogen atoms being 3·04 Å between C(11) and O(41). The arrangement of molecules in layers parallel to the *ab* plane of the monoclinic unit cell is shown in Fig. 1. Fig. 2 shows a perspective view of the molecule, perpendicular to the plane of the imidazole ring, and details the crystallographic numbering scheme. Bond lengths, angles, and selected meanplane data are given in Tables 1–3.

Table 1. Selected bond lengths (Å)

Atoms	Length	Atoms	Length
N(1)–C(2)	1·357(5)	N(1)–C(11)	1·465(5)
N(1)–C(5)	1·358(4)	C(4)–N(4)	1·419(5)
C(2)–N(3)	1·312(5)	N(4)–O(41)	1·222(4)
N(3)–C(4)	1·373(4)	N(4)–O(42)	1·234(4)
C(4)–C(5)	1·366(5)	C(5)–O(5)	1·344(4)
C(5)–N(1)	1·358(4)	O(5)–C(51)	1·441(5)

Table 2. Selected bond angles (degrees)

Atoms	Angle	Atoms	Angle
C(2)–N(1)–C(5)	106·7(3)	N(3)–C(4)–N(4)	120·6(3)
N(1)–C(2)–N(3)	113·3(3)	N(4)–C(4)–C(5)	127·5(3)
C(2)–N(3)–C(4)	103·1(3)	C(4)–N(4)–O(41)	119·1(3)
N(3)–C(4)–C(5)	111·8(3)	C(4)–N(4)–O(42)	118·2(3)
N(1)–C(5)–C(4)	105·0(3)	O(42)–N(4)–O(41)	122·6(3)
C(11)–N(1)–C(2)	126·9(3)	N(1)–C(5)–O(5)	119·4(3)
C(11)–N(1)–C(5)	126·4(3)	C(4)–C(5)–O(5)	135·5(3)
		C(5)–O(5)–C(51)	116·6(3)

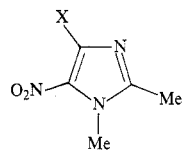
Table 3. Least-squares planes and distances (Å) of atoms from the planes

Atom	Distance	Atom	Distance	Atom	Distance
Plane through N(1), C(2), N(3), C(4), C(5)					
$(-0·3365)X+(0·0159)Y+(-0·9416)Z-(-1·6106)=0$					
N(1)	0·000(4)	C(2)	0·003(4)	N(3)	−0·005(4)
C(4)	0·005(4)	C(5)	−0·003(4)	C(11)	−0·016(5)
N(4)	0·060(4)	O(41)	−0·030(4)	O(42)	0·235(3)
O(5)	0·052(3)	C(51)	−1·042(5)		
Plane through N(4), O(41), O(42)[A]					
$(-0·4663)X+(0·0021)Y+(-0·8846)Z-(-1·9838)=0$					
N(1)	0·119(3)	C(2)	0·278(4)	N(3)	0·231(3)
C(4)	0·046(4)	C(5)	−0·037(4)		

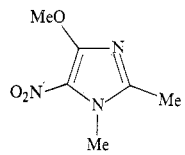
[A] The equation of each plane is defined as $AX+BY+CZ=0$. Angles between normals to planes, 8·2°.

Bond lengths and angles within the planar imidazole ring do not differ significantly from those found in the parent heterocycle.[23] The C(2)–N(3) bond is particularly short [1·312(5) Å], consistent with a localized double bond between these atoms, but similarities in the remaining bond distances within the ring point to additional delocalization in the heterocyclic system. The ring-bound atoms of the methyl, C(11), methoxy, O(5), and nitro, N(4), substituents lie close to the ring plane. Molecular parameters for the methyl[24] and methoxy[25] substituents are unremarkable.

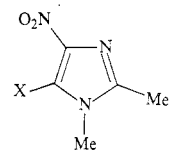
The angle between the least-squares plane of the imidazole ring and its nitro substituent is 8·2°, somewhat greater than those observed in less congested nitroimidazoles.[26,27] This may result from the minimization of steric interactions between the adjacent nitro and methoxy substituents; comparable interactions have been reported previously in imidazole systems.[28–30] Despite this displacement, the C(4)–N(4) bond is short [1·419(5) Å] offering further evidence for extended exocyclic conjugation in nitroimidazole systems.[31–33] Such conjugation seems a necessary prerequisite for effective delocalization of the negative charge of the Meisenheimer intermediate in the addition–elimination processes assumed to be involved in the nucleophilic displacements under study.



(6a) X = Br
(6b) X = I



(7)



(8a) X = Br
(8b) X = I

4-Bromo-(or 4-iodo-)1,2-dimethyl-5-nitroimidazoles (6) reacted similarly with methoxide to give the 4-methoxy product (7), while phenoxy, too, displaced the halogen functions of (1). However, one anomaly remains: both 5-halogeno-1,2-dimethyl-4-nitroimidazoles (8) failed to react under the usual conditions with either methoxide or phenoxide. Only unchanged starting material was isolated, and increasing the reaction time or the nucleophile : substrate ratio gave rise to tars. A similar phenomenon had been reported earlier,[8] but later disclaimed.[6] We were not able to confirm the latter reports, perhaps surprisingly in view of the usual greater ease

[23] McMullan, R. K., Epstein, J., Ruble, J. R., and Craven, B. M., *Acta Crystallogr., Sect. B*, 1979, **35**, 688.
[24] Dupont, L., Dideberg, O., and Jamoulle, J. C., *Acta Crystallogr., Sect. C*, 1984, **40**, 1269.
[25] Barlin, G. B., Brown, I. L., Golic, L., and Kaucic, V., *Aust. J. Chem.*, 1982, **35**, 423.
[26] Brown, J. N., Rist, P. E., and Agarwal, K. C., *Cryst. Struct. Commun.*, 1975, **8**, 761.
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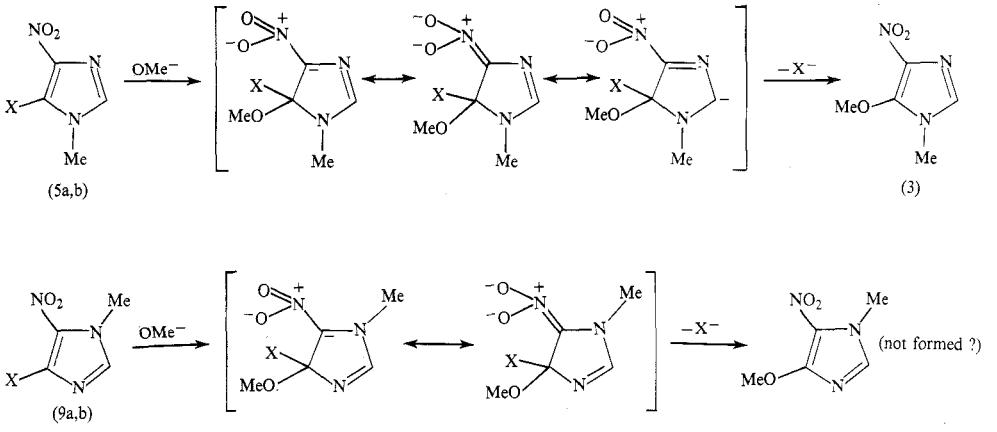
[28] Glass, R. S., Blount, J. F., Butler, D., Perrotta, A., and Oliveto, E. P., *Can. J. Chem.*, 1972, **50**, 3472.
[29] Destro, R., *Acta Crystallogr., Sect. B*, 1979, **35**, 1714.
[30] Teulade, J. C., Escale, R., Rossi, J. C., Chapat, J. P., Grassy, G., and Payard, M., *Aust. J. Chem.*, 1982, **35**, 1761.
[31] Germain, G., Declercq, J. P., van Meerssche, M., and Koch, M. H. J., *Acta Crystallogr., Sect. B*, 1977, **33**, 2269.
[32] Blaton, N. M., Peeters, O. M., and De Ranter, C. J., *Acta Crystallogr., Sect. C*, 1979, **35**, 753; 2465.
[33] Kalman, A., van Meurs, F., and Toth, J., *Cryst. Struct. Commun.*, 1980, **9**, 709.

of substitution of 5-halogeno groups in which the anionic intermediate should be more delocalized (Scheme 3). There was no evidence of competing attack by the nucleophile at the 2-methyl group, and from the ^{13}C n.m.r. evidence[34] which places 2-methyl carbon signals of 2-methyl-4-nitroimidazoles upfield of those in the 5-nitro isomers, base-catalysed deprotonation would appear to be less likely in (8) than in (6). A more attractive proposition might be that when there are methyl groups at both the 1- and 2-positions (5-chloro-2-methyl-4-nitroimidazole is reported to react normally by displacement of the chlorine atom by alkoxide[6]), they may sterically hinder reaction at C 5. The observation[8] that in isomeric 1,2-dimethyl-4(5)-bromo-5(4)-nitroimidazoles it was harder to displace a 5-bromo group by piperidine is in line with this behaviour toward alkoxide.



Scheme 3

Mokrushin[19] reported that in reactions of methoxide and ethoxide with 4,5-dinitroimidazole, there was evidence of considerable ring cleavage and reductive denitration (~ 10%) both at elevated temperatures and with excess nucleophile, while similar effects were evident with hydrazines and amines. An anion–radical mechanism has been suggested for these substitutions. Harder anionic nucleophiles such as azide, acetate and phenoxide in water, alcohols, or dimethylformamide did not displace a nitro group, even at elevated temperatures.[19]

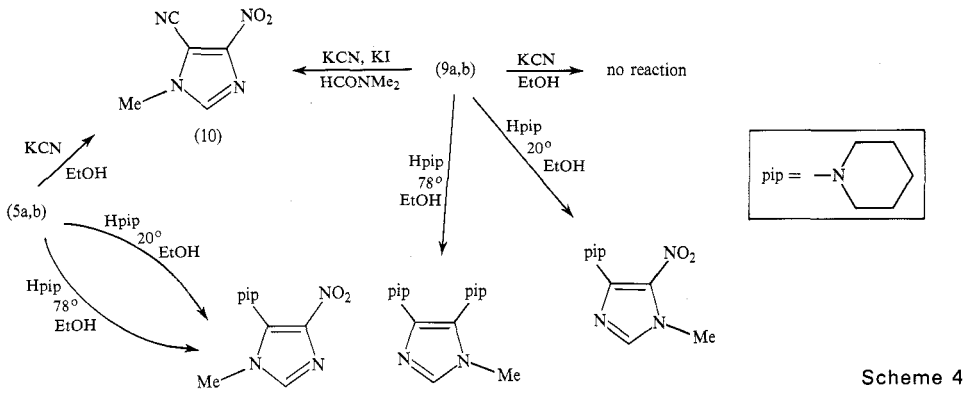
Nitrogen Nucleophiles: Reactions with Secondary Amines

Previous workers have studied the reactions mainly of 4(or 5)-chloro-5(or 4)-nitroimidazoles with piperidine[6–9] along with a few displacements of the bromo analogues.[7,8] Piperidine is reported to react at room temperature with 4-chloro-1-methyl-5-nitroimidazole[6] displacing the halogen. At higher temperatures (reflux in ethanol) both chloro and nitro groups are replaced by the amine.[6] A kinetic study[7] has demonstrated that the activating effect of a 4- or 5-nitro group is greater than an extra annular nitrogen. Thus, 2-bromo-1-methyl-5-nitro- and 5-bromo-1-methyl-4-nitro-imidazoles reacted more quickly with piperidine than did 5-bromo-1-methyl-(1*H*)-1,2,4-triazole and 3-bromo-4-methyl-(4*H*)-1,2,4-triazole respectively.

[34] McKillop, A., Wright, D. E., Podmore, M. L., and Chambers, R. K., *Tetrahedron*, 1983, **39**, 3797.

Both 4,5-dinitroimidazole and 4-nitroimidazole-5-sulfonic acid reacted readily at low temperatures with methylamine and diethylamine, but ammonia and aniline required heating.[19]

When 4-bromo(or iodo)-1-methyl-5-nitroimidazole (9) were treated at 20°C with ethanolic piperidine, the 4-piperidino compounds were formed readily in high yield; under reflux conditions both halogen and nitro were replaced (Scheme 4). The alternative isomers (5) gave only the monosubstitution products even at elevated temperatures. As one might expect, it is usually easier to displace a nitro group from C 5 than from C 4. If the transition states for such displacements resemble the anionic intermediates, then it should require rather less activation energy to displace a 5-nitro group. When there are methyl groups in both the 1- and 2-positions, however, as in (8), only the halogen is replaced, and even that occurs more readily when it is at C 4. Steric factors may again be involved.



Scheme 4

A survey of the reactions of a series of 4(5)-nitro-5(4)-halogenoimidazoles with piperidine, pyrrolidine and morpholine has produced a number of previously undescribed substitution products all with satisfactory analytical and spectroscopic data (see Experimental section). Diphenylamine, a poor nucleophile, failed to react with 5-iodo-4-nitroimidazole under mild conditions.

Carbon Nucleophiles

Cyanide

Reaction of 5-chloro-1-methyl-4-nitroimidazole with KCN and KI in ethanol gives 5-cyano-1-methyl-4-nitroimidazole (10).[10,11,35] The other isomer, 4-chloro-1-methyl-5-nitroimidazole, failed to react under the same conditions[11,35] (Scheme 4), although in refluxing dimethylformamide, the isolated reaction product proved to be again (10), perhaps resulting from a methyl migration induced by the solvent methylating the imidazole substrate to form the quaternary salt which subsequently decomposes.[11] Certainly the known orientation of dequaternization of such a salt would be expected to give rise to 5-chloro-1-methyl-4-nitroimidazole,[36] and this would

[35] Taylor, E. C., and Loeffler, P. K., *J. Am. Chem. Soc.*, 1960, **82**, 3147.
[36] Chan, B. K. M., Chan, N.-H., and Grimmett, M. R., *Aust. J. Chem.*, 1977, **30**, 2005.

be converted into the 5-cyano product. A similar phenomenon has been described for isomeric 4(5)-bromo-1,2-dimethyl-5(4)-nitroimidazoles[8] (the 5-bromo substituent was displaced by cyanide, but the 4-bromo isomer decomposed when heated with KCN in a variety of solvents), and in the pyrazole series.[37] Although 5-chloro-1,3-dimethyl-4-nitropyrazole reacts smoothly with KCN in dimethylformamide to replace the chlorine atom, the 4-chloro-1,5-dimethyl-4-nitro isomer failed to react.

The present study confirms that both the 5-iodo- and 5-bromo-4-nitroimidazoles react like the chloro derivative, and that the 4-halogeno compounds are equally resistant to cyanide displacement unless boiled in dimethylformamide solution. The products from all reactions were identical (10). That the dimethylformamide is not entirely necessary for the process was demonstrated by heating a melt of 4-iodo-1-methyl-5-nitroimidazole and KCN in the absence of any solvent; a low yield of (10) was detected. While the KI may assist the reaction, it too is not absolutely necessary. The proposed action of dimethylformamide as a methylating agent is not a compelling proposition and the mechanism of the transmethylation remains obscure.

Some comment on an earlier report of the synthesis of 2-cyano-1-methyl-5-nitroimidazole needs to be made here. Winkelmann[9] claimed to have prepared this compound from what he thought to be 2-iodo-1-methyl-5-nitroimidazole (now known to be the 4-iodo isomer). His product (m.p. 83°), though, corresponds neither with authentic 5-cyano-1-methyl-4-nitroimidazole (m.p. 140°[11]), nor can it conceivably correspond with the authentic 2-cyano compound (m.p. 91–92°[38]) prepared from 1-methyl-2-methylsulfonyl-5-nitroimidazole. Some other derivatives reported in the same paper,[9] and purporting to have sulfur substituents at C2, are more likely to be 4- or 5-substituted.

Alkyl Radicals

Homolytic alkylation by nucleophilic radicals generated from silver-catalysed oxidative decarboxylation of carboxylic acids has been shown to give 2-substituted imidazoles, albeit in low yields.[39,40] 4-Bromo-, 4-iodo- and 4-nitro-imidazoles and their 1-methyl derivatives proved to be resistant to such alkylations with methyl and trifluoromethyl radicals. It is possible that the very weakly basic natures of these imidazole substrates may be the problem, since it has been reported[41] that the reactions proceed at an appreciable rate only with protonated nitrogen heterocycles.

Experimental

(*a*) General

Microanalyses were performed by Professor A. D. Campbell and staff at the University of Otago. ^{1}H n.m.r. spectra were recorded on a Varian EM-390 spectrometer operating at 90 MHz. ^{13}C n.m.r. spectra were obtained by using a JEOL FX-60 Fourier-transform n.m.r. spectrometer operating at 15·04 MHz in the FT mode. Chemical shifts (δ) are quoted in ppm downfield from tetramethylsilane. In some instances not all carbon signals could be detected in the ^{13}C n.m.r.

[37] Townsend, L. B., Long, R. A., McGraw, J. P., Miles, D. W., Robins, R. K., and Eyring, H. E., *J. Org. Chem.*, 1974, **39**, 2023.
[38] Henry, H. D., U.S. Pat. 3,341,549 (*Chem. Abstr.*, 1968, **68**, 105195).
[39] Bertini, F., Galli, R., Minisci, F., and Porta, O., *Chim. Ind. (Milan)*, 1972, **54**, 223.
[40] Begg, C. G., Grimmett, M. R., and Lee, Y.-M., *Aust. J. Chem.*, 1973, **26**, 415.
[41] Citterio, A., Minisci, F., Porta, O., and Sesana, G., *J. Am. Chem. Soc.*, 1977, **99**, 7960.

signals. Mass spectra were obtained on a Varian MAT CH-7 instrument, while ultraviolet spectra in ethanol were recorded on a Shimadzu UV-240 double-beam spectrophotometer. Infrared spectra, examined as KBr discs, were obtained on a Perkin–Elmer 357 spectrophotometer. Analytical thin-layer chromatography routinely used commercially available aluminium roll precoated with silica gel $60F_{254}$.

(*b*) Synthesis of Starting Compounds

The following compounds were prepared by published procedures or adaptations of these. Purity was proved by microanalysis, melting point, and the usual spectroscopic and chromatographic techniques. Where there was considerable variation from the literature values, or where some physical data has not been recorded previously, it is now included. Mass spectral data are listed, but not interpreted in detail. Fragmentation patterns were typical of nitroimidazoles.[42]

5-Bromo-4-nitroimidazole (1a)

M.p. 280–281° (lit.[43] 279°). ^{1}H n.m.r. δ (CF_3CO_2D): 8·76, H 2. ^{13}C n.m.r.: δ [$(CD_3)_2SO$]: 106·8, C 5; 139·0, C 2; 145·4, C 4. Mass spectrum *m/z*: 193, 191 (100%), 163, 161 (100), 147, 145 (100). λ_{max} (log ε) 312 (4·62) nm.

4-Bromo-1-methyl-5-nitroimidazole (9a)

M.p. 104–105° (lit.[44] 105–106°). ^{1}H n.m.r. δ (CF_3CO_2D): 4·33, s, 3H, 1-CH_3; 8·94, s, 1H, H 2. ^{13}C n.m.r.: δ ($CDCl_3$): 33·5, 1-CH_3; 120·4, C 4; 139·8, C 2. Mass spectrum *m/z*: 207, 205 (100%), 191, 189 (54), 177, 175 (61), 161, 159 (78). ν_{max} 1530, 1500, 1350 cm^{-1}. λ_{max} (log ε) 308 (4·12) nm.

5-Bromo-1-methyl-4-nitroimidazole (5a)

M.p. 178° (lit.[7,44] 178–179°). ^{1}H n.m.r. δ (CF_3CO_2D): 3·97, s, 3H, 1-CH_3; 8·37, s, 1H, H 2. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 34·8, 1-CH_3, 108·0, C 5; 139·0, C 2; 145·0, C 4. Mass spectrum *m/z* 207, 205 (100%), 191, 189 (44), 177, 175 (52), 161, 159 (100). λ_{max} (log ε) 309 (4·13) nm.

5-Bromo-2-methyl-4-nitroimidazole

M.p. 270–271° (lit.[45] 271–273°). ^{1}H n.m.r. δ (CF_3CO_2D): 2·90, s, 2-CH_3. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 14·7, 2-CH_3; 107·5, C 5; 141·6, C 2; 146·9, C 4.

4-Bromo-1,2-dimethyl-5-nitroimidazole (6a)

M.p. 107–108° (lit.[8] 108–109°). ^{1}H n.m.r. δ (CF_3CO_2D): 2·80, s, 2-CH_3; 4·13, s, 1-CH_3. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 14·6, 2-CH_3; 34·4, 1-CH_3; 119·9, C 4; 148·9, C 5. Mass spectrum *m/z*: 221, 219 (100%), 191, 189 (71), 175, 173 (100).

5-Bromo-1,2-dimethyl-4-nitroimidazole (8a)

M.p. 158–159° (lit.[8] 161–162°). ^{1}H n.m.r. δ (CF_3CO_2D): 2·83, s, 2-CH_3; 3·83, s, 1-CH_3. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 14·0, 2-CH_3; 32·6, 1-CH_3; 105·3, C 5; 143·2, C 2; 144·8, C 4. Mass spectrum *m/z*: 221, 219 (100%), 205, 203 (18), 191, 189 (11), 175, 173 (52).

5-Iodo-4-nitroimidazole (1b)

M.p. 287–288° (lit.[12] quotes 2-iodo-4-nitroimidazole, m.p. 281°). ^{1}H n.m.r. δ (CF_3CO_2D): 8·90, s, H 2. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 75·8, C 5; 140·3, d, $^1J_{CH}$ 215 Hz, C 2; 150·4, C 4. Mass spectrum *m/z*: 239 (100%), 212 (47), 209 (40), 193 (40). ν_{max} 1710, 1540 cm^{-1}. λ_{max} (log ε) 336 (4·45) nm.

[42] Luitjen, W. C. M. M., and van Thuijl, J., *Org. Mass Spectrom.*, 1981, **16**, 199.
[43] Balaban, I. E., and Pyman, F. L., *J. Chem. Soc.*, 1922, **121**, 947.
[44] Balaban, I. E., and Pyman, F. L., *J. Chem. Soc.*, 1924, **125**, 1564.
[45] Light, L., and Pyman, F. L., *J. Chem. Soc.*, 1922, **121**, 2626.

4-Iodo-1-methyl-5-nitroimidazole (9b)

M.p. 152–153° (lit.[12] quotes 150–151° for 2-iodo-1-methyl-5-nitroimidazole). ^{1}H n.m.r. δ [$(CD_3)_2SO$]: 3·93, s, 3H, 1-CH_3; 8·05, s, 1H, H2. δ (CF_3CO_2D) 4·30, 8·87. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 93·6, C4; 140·3, d, $^1J_{CH}$ 217 Hz, C2; 143·5, C5. Mass spectrum *m/z*: 253 (100%), 237 (67), 223 (100). ν_{max} 1525, 1360, 1235 cm^{-1}. λ_{max} (log ε) 302 (3·52) nm.

5-Iodo-1-methyl-4-nitroimidazole (5b)

M.p. 240–241° (lit.[12] quotes 240° for 2-iodo-1-methyl-4-nitroimidazole). ^{1}H n.m.r. δ [$(CD_3)_2SO$]: 3·75, s, 3H, 1-CH_3; 8·12, s, 1H, H2. δ (CD_3CO_2D) 3·97, 8·43. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 83·5, C5; 140·3, C2; 145·3, C4. Mass spectrum *m/z*: 253 (100%), 238 (100), 223 (100), 207 (100). ν_{max} 1520, 1490, 1370, 1340, 1310 cm^{-1}. λ_{max} (log ε) 336 (3·51) nm.

5-Iodo-2-methyl-4-nitroimidazole

M.p. 270–271° (lit.[12] 271–273°). ^{1}H n.m.r. δ (CF_3CO_2D): 2·88, s, 3H, 2-CH_3. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 14·1, 2-CH_3; 73·8, C5; 148·4, C2; 152·4, C4. Mass spectrum *m/z*: 253 (100%), 223 (100), 207 (59). ν_{max} 1800, 1650 cm^{-1}. λ_{max} (log ε) 330 (3·35) nm.

4-Iodo-1,2-dimethyl-5-nitroimidazole (6b)

M.p. 144–146° (lit.[12] 150–151°). ^{1}H n.m.r. δ (CF_3CO_2D): 2·87, s, 2-CH_3; 4·21, s, 1-CH_3. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 14·3, 2-CH_3; 92·6, C4; 140·2, C2; 152·6, C5. Mass spectrum *m/z*: 267 (100%), 251 (30), 237 (66), 221 (100). ν_{max} 1540, 1390 cm^{-1}. λ_{max} (log ε) 335 (3·92), 263 (3·67) nm.

5-Iodo-1,2-dimethyl-4-nitroimidazole (8b)

M.p. 208–209° (lit.[12] 204–205°). ^{1}H n.m.r. δ (CF_3CO_2D): 2·92, s, 2-CH_3; 3·97, s, 1-CH_3. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 13·7, 2-CH_3; 81·5, C5; 147·5, C2; 148·0, C4. ν_{max} 1570, 1490, 1370 cm^{-1}.

(*c*) Nucleophilic Displacement Reactions: (i) Displacement by Methoxy and Phenoxy

5-Methoxy-4-nitroimidazole (2)

A mixture of 5-iodo-4-nitroimidazole (1b) (0·24 g, 0·001 mol), sodium methoxide (0·004 g-atoms of sodium) and methanol (6 cm^3) was boiled under reflux for 2 h. Removal of the solvent gave a red, gelatinous sodium salt which was dissolved in warm water (2 cm^3), neutralized to pH 7 with acetic acid, and allowed to cool whereupon yellow needles separated. Recrystallization from 50% aqueous dimethylformamide gave (2) in 64% yield, m.p. 216–217° (lit.[12] quotes 2-methoxy-4-nitroimidazole m.p. 219°; lit.[19] m.p. 212–213°) (Found: C, 33·4; H, 3·3; N, 29·2. Calc. for $C_4H_5N_3O_3$: C, 33·6; H, 3·5; N, 29·4%). ^{1}H n.m.r. δ (CF_3CO_2D): 4·50, s, 3H, OCH_3; 8·56, s, 1H, H2. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 58·4, OCH_3; 135·4, d, $^1J_{CH}$ 217 Hz, C2; 140·3, C5; 154·6, C4. Mass spectrum *m/z*: 143 (100%), 113 (65), 97 (79). ν_{max} 1590, 1380 cm^{-1}. λ_{max} (log ε) 339 (3·69) [lit.[12] λ_{max} (MeOH) 233, 330 nm; lit.[19] λ_{max} (H_2O) 225 (3·75), 387 (4·11) nm].

The same compound was obtained in 72% yield when the bromo analogue (1a) was similarly heated with methoxide for 1 h.

5-Methoxy-1-methyl-4-nitroimidazole (3)

By using the same general method as above, a 67% yield of (3) was obtained from (5b). M.p. 138–139° (lit.[12] quotes 2-methoxy-1-methyl-4-nitroimidazole, m.p. 134–135°) (Found: C, 38·2; H, 4·5; N, 26·7. Calc. for $C_5H_7N_3O_3$: C, 38·2; H, 4·5; N, 26·7%). ^{1}H n.m.r. δ (CF_3CO_2D): 4·23, s, 3H, OCH_3; 5·35, s, 3H, 1-CH_3; 8·12, s, 1H, H2. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 31·3, 1-CH_3; 63·9, OCH_3; 131·6, d, C2; 146·7, C4. Mass spectrum *m/z*: 157 (100%), 156 (67), 139 (75), 127 (54), 111 (56). λ_{max} (log ε) 336 (3·45) nm.

The same compound was formed in similar yield from the 5-bromo compound (5a) heated for 0·5 h, and in 53% yield by methylation of (2) in basic medium.

4-Methoxy-1,2-dimethyl-5-nitroimidazole (7)

This compound was prepared in 64% yield from (6b) heated with methoxide for 0·5 h. It was recrystallized from ethanol, m.p. 124–125° (lit.[8] 127–128°) (Found: C, 42·3; H, 5·6; N, 24·7. Calc. for $C_4H_3N_3O_3$: C, 42·1; H, 5·3; N, 24·6%). ^{1}H n.m.r. δ (CF_3CO_2D): 2·70, s, 2-CH_3; 4·03, s, OCH_3; 4·30, s, 1-CH_3. ν_{max} 1550, 1380, 1189 cm^{-1}. λ_{max} (log ε) 330 (3·55) nm.

4-Nitro-5-phenoxyimidazole

A solution of (1b) (0·24 g, 0·001 mol) and sodium phenoxide (prepared from 0·004 g-atom of sodium and 0·004 mol of phenol) was refluxed for 7 h in toluene (6 cm^3). Removal of the solvent gave a yellow gelatinous salt which was dissolved in water (2 cm^3) and neutralized with acetic acid. The yellow needles which separated on cooling were recrystallized from 50% aqueous dimethylformamide in 56% yield, m.p. 207–208° (lit.[46] incorrectly quotes 4-nitro-2-phenoxyimidazole m.p. 209–210°) (Found: C, 52·6; H, 3·4; N, 20·4. Calc. for $C_9H_7N_3O_3$: C, 52·7; H, 3·4; N, 20·5%). ^{1}H n.m.r. δ (CF_3CO_2D): 7·14, 7·50, m, 5H, phenyl; 8·56, s, 1H, H2. Mass spectrum *m/z*: 205 (100%), 188 (54), 175 (69), 159 (75), 132 (31).

The same product was prepared in 75% yield from (1a).

(ii) Displacement by Secondary Amine Nucleophiles

1-Methyl-5-nitro-4-piperidinoimidazole

To a stirred solution of (9b) (0·25 g, 0·001 mol) in ethanol (6 cm^3) at 20° piperidine (0·43 g, 0·005 mol) was added, and the mixture was stirred for 5 h (monitored by t.l.c.), then poured into ice-water (30 cm^3) and extracted with chloroform (3×50 cm^3). The dried extracts were concentrated and subjected to alumina column chromatography with chloroform as the solvent. From the initial yellow band eluted from the column, orange-yellow needles (0·14 g, 67%) were isolated and recrystallized from light petroleum (b.p. 30–40°), m.p. 71–72° (lit.[6] 70–71°) (Found: C, 51·4; H, 7·0; N, 26·7. Calc. for $C_9H_{14}N_4O_2$: C, 51·4; H, 6·7; N, 26·6%). ^{1}H n.m.r. δ ($CDCl_3$): 1·80, 3·58, m, (6H, 4H), piperidine-H; 3·90, s, 3H, 1-CH_3; 7·30, s, 1H, H2. Mass spectrum *m/z*: 210 (100%), 195 (56), 194 (51), 193 (71), 180 (67). ν_{max} 1590, 1530 cm^{-1}.

The same compound was obtained in 73% yield from (9a).

The following compounds were prepared similarly from the iodo and bromo precursors. No attempts have been made to resolve the proton signals of the secondary amine substituents, although the expected patterns and integrals were obtained in all cases.

1-Methyl-4-nitro-5-piperidinoimidazole

Compounds (5a) and (5b) were heated under reflux in ethanol for 9 and 12 h respectively giving yields of 70 and 66%, m.p. 184–185° (lit.[7] 178–180°) (Found: C, 51·2; H, 6·7; N, 26·6. Calc. for $C_9H_{14}N_4O_2$: C, 51·4; H, 6·7; N, 26·6%). ^{1}H n.m.r. δ ($CDCl_3$): 1·67, 3·10, m (6H, 4H), piperidine; 3·58, s, 3H, 1-CH_3; 7·20, s, 1H, H2. Mass spectrum *m/z*: 210 (100%), 193, 192, 164. ν_{max} 2940, 2880, 1565, 1325 cm^{-1}. λ_{max} (log ε) 285 (3·63) nm.

1-Methyl-5-morpholino-4-nitroimidazole

Compounds (5a) and (5b) were refluxed in ethanol for 12 and 9 h respectively giving yields of 75 and 88%, m.p. 114–115° (Found: C, 45·5; H, 6·0; N, 26·3. $C_8H_{12}N_4O_3$ requires C, 45·3; H, 5·7; N, 26·4%). ^{1}H n.m.r. δ ($CDCl_3$): 2·68, 3·87, m (4H, 4H), morpholine; 3·63, s, 3H, 1-CH_3; 7·38, s, 1H, H2. Mass spectrum *m/z*: 212 (100%), 195, 182, 166. ν_{max} 2860, 1570 cm^{-1}.

1-Methyl-4-nitro-5-pyrrolidinoimidazole

Compounds (5a) and (5b) were refluxed for 6 and 9 h respectively. The product was recrystallized from aqueous ethanol (2 : 1) in yields of 87 and 69%, m.p. 90–91° (Found: C, 49·0; H, 6·4; N, 28·3. $C_8H_{12}N_4O_2$ requires C, 49·0; H, 6·2; N, 28·6%). ^{1}H n.m.r. δ ($CDCl_3$): 2·01, 3·28, m (4H, 4H), pyrrolidine; 3·56, s, 3H, 1-CH_3, 7·27, s, 1H, H2. ^{13}C n.m.r. δ ($CDCl_3$): 26·3, 51·2, pyrrolidine; 31·4, CH_3; 131·7, C2; 139·8, C5; 140·8, C4. Mass spectrum *m/z*: 196 (100%), 180 (76), 166 (52), 123 (100). λ_{max} (log ε) 365 (3·54), 310 (3·46), 205 (3·92) nm.

[46] Hoffer, M., U.S. Pat. 3,341,548 (*Chem. Abstr.*, 1968, **68**, 198c).

1,2-Dimethyl-5-nitro-4-piperidinoimidazole

Compounds (6a) and (6b) were refluxed for 4 and 5 h respectively, the product being recrystallized from ethanol/water (1 : 3) as yellow needles in yields of 89 and 67% respectively, m.p. 107–108° (lit.[8] 109–110°) (Found: C, 53·5; H, 7·2; N, 24·9. Calc. for $C_{10}H_{16}N_4O_2$: C, 53·6; H, 7·2; N, 25·0%). ^{1}H n.m.r. δ ($CDCl_3$): 1·81, 3·59, br s (6H, 4H), piperidine; 2·37, s, 3H, 2-CH_3; 4·00, s, 3H, 1-CH_3. Mass spectrum *m/z*: 224 (100%), 209 (79), 207 (72), 206 (86), 194 (34), 178 (59), 159 (65). ν_{max} 1635, 1530, 1340 cm^{-1}.

1,2-Dimethyl-4-nitro-5-piperidinoimidazole

Compounds (8a) and (8b) were heated under reflux for 5 and 7 h respectively. The products (84%, 69%) were recrystallized from ethanol/water (1 : 3) as yellow needles, m.p. 166–167° (lit.[8] 167–168°) (Found: C, 53·4; H, 7·4; N, 24·8. Calc. for $C_{10}H_{16}N_4O_2$: C, 53·6; H, 7·2; N, 25·0%). ^{1}H n.m.r. δ ($CDCl_3$): 1·67, 3·07, br s (6H, 4H), piperidine; 2·35, s, 3H, 2-CH_3; 3·43, s, 3H, 1-CH_3. ^{13}C n.m.r. δ ($CDCl_3$): 13·9, 2-CH_3; 23·6, 28·4, piperidine; 29·4, 1-CH_3; 139·9, C 5; 140·8, C 4 or C 2. Mass spectrum *m/z*: 224 (100%), 209 (67), 207 (100), 194 (56), 178 (27), 151 (37). ν_{max} 1630, 1395, 1380 cm^{-1}.

1,2-Dimethyl-5-morpholino-4-nitroimidazole

Yields of 83 and 80% were obtained from (8a) and (8b) respectively, m.p. 140–141° (Found: C, 47·6; H, 6·4; N, 24·5. $C_9H_{14}N_4O_3$ requires *C*, 47·8; H, 6·2; N, 24·7%). ^{1}H n.m.r. δ ($CDCl_3$): 2·30, s, 3H, 2-CH_3; 2·60, 3·85, m (4H, 4H), morpholine; 3·42, s, 3H, 1-CH_3. Mass spectrum *m/z*: 226 (100%), 211 (52), 209 (63), 196 (43), 180 (50), 153 (47). ν_{max} 1590, 1370 cm^{-1}.

1,2-Dimethyl-4-nitro-5-pyrrolidinoimidazole

Yields of 84 and 65% were obtained from (8a) and (8b) respectively, m.p. 85–86° (Found: C, 51·2; H, 6·6; N, 26·5. $C_9H_{14}N_4O_2$ requires *C*, 51·4; H, 6·7; N, 26·6%). ^{1}H n.m.r. δ ($CDCl_3$): 2·00, 3·22, m (4H, 4H), pyrrolidine; 2·35, s, 3H, 2-CH_3; 3·42, s, 3H, 1-CH_3. ^{13}C n.m.r. δ ($CDCl_3$): 14·1, 2-CH_3; 26·3, 51·2, pyrrolidine; 30·0, 1-CH_3; 137·5, C 4; 138·9, C 5. Mass spectrum *m/z*: 210 (100%), 194 (19), 193 (100), 180 (21), 164 (46), 137 (100).

1-Methyl-4,5-dipiperidinoimidazole

A solution of (9a) (0·21 g, 0·001 mol) and piperidine (0·43 g, 0·005 mol) was heated under reflux in ethanol during 5 h. The reaction was monitored by t.l.c. on silica chromatoplates with chloroform/hexane/methanol (3 : 1 : 0·5) as solvent. After cooling, the mixture was poured into ice-water (30 cm^3) and extracted with chloroform. Column chromatography of the concentrated extracts gave a yellow oil which was distilled at 96°/3 mm to give the liquid product in 74% yield (lit.[6] gives b.p. 84°/4 mm) (Found: C, 67·6; H, 10·0; N, 22·7. Calc. for $C_{13}H_{24}N_4$: C, 67·7; H, 9·7; N, 22·6%). ^{1}H n.m.r. δ ($CDCl_3$): 1·66, 1·83, 3·51, 3·60, m, 20H, piperidines; 3·50, s, 3H, 1-CH_3; 7·17, s, 1H, H 2.

The same product was obtained from (9b), but even with extended heating times both (5a) and (5b) gave only the 5-monopiperidino product.

Only starting material was isolated from a reaction mixture containing (1b) and diphenylamine even after heating for 5 h.

(iii) Displacement by Cyanide

1-Methyl-4-nitroimidazole-5-carbonitrile (10)

(A) A suspension of (5b) (0·24 g, 0·001 mol), KCN (0·13 g, 0·002 mol) and KI (0·023 g, 0·0002 mol) in dimethylformamide (5 cm^3) was boiled under reflux for 4 h with stirring. After cooling, the mixture was poured into ice-water (40 cm^3) and allowed to stand (3 h). The solid which separated was recrystallized from ethanol as colourless cubes (0·09 g, 61%), m.p. 135–137° (lit.[11,35] 141–142°) (Found: C, 39·6; H, 2·7; N, 36·7. Calc. for $C_5H_4N_4O_2$: C, 39·5; H, 2·7; N, 36·8%). ^{1}H n.m.r. δ (CF_3CO_2D): 4·10, s, 3H, 1-CH_3; 8·17, s, 1H, H 2. ^{13}C n.m.r. δ [$(CD_3)_2SO$]: 33·8, 1-CH_3; 105·2, C 5; 109·5, CN; 139·4, C 2; 141·2, C 4. Mass spectrum *m/z*: 152 (100%), 136 (75), 122 (89), 106 (100). λ_{max} (log ε) 291 (3·71) nm.

Heating the iodoimidazole with KCN in ethanol gave the identical 5-cyanoimidazole (10). The same product was also isolated in 68% yield from the 5-bromo analogue (5a) heated for 3 h in dimethylformamide as above.

(B) A mixture of (9b) (0·24 g, 0·001 mol), KCN (0·13 g, 0·002 mol) and KI (0·023 g, 0·0002 mol) in dimethylformamide (5 cm^3) was boiled for 4 h with stirring to give a 63% yield of (10). The 4-bromo compound (9a) gave the same product under the same conditions, but neither halonitroimidazole would react with KCN in ethanol.

It proved possible to detect (t.l.c. and n.m.r.) some (10) when (9b) was heated alone with KCN in the absence of solvent.

(iv) Reaction with Nucleophilic Alkyl Radicals

To a stirred solution of 4-iodoimidazole (1·96 g, 0·01 mol), silver nitrate (0·51 g, 0·003 mol) and acetic acid (6·0 g, 0·1 mol) in sulfuric acid (0·1 M, 10 cm^3) heated at 70°, was added over 10 min a solution of ammonium peroxydisulfate, $(NH_4)_2S_2O_8$ (6·85 g, 0·03 mol) in water (30 cm^3). The temperature was raised to 95–100°. After the evolution of CO_2 had ceased, the mixture was stirred for a further 1 h, then cooled and poured into ice-water (30 cm^3), neutralized with aqueous ammonia, and extracted with chloroform. The extracts were dried and evaporated to yield a solid which was unchanged from the original 4-iodoimidazole.

The same process with trifluoroacetic acid (11·4 g, 0·01 mol) in place of acetic acid was also unsuccessful. Nor did 4-bromo- and 4-nitro-imidazoles and their 1-methyl analogues undergo homolytic alkylation under these reaction conditions.

(v) Methylation Reaction Associated with Structure Determination

5-Methoxy-1-methyl-4-nitroimidazole (3)

A solution of (2) (1·43 g, 0·01 mol) in 3 M aqueous sodium carbonate solution (50 cm^3) was stirred at 60–65° during half an hour with dimethyl sulfate (1·89 g, 0·015 mol). The solid product which separated after cooling and refrigeration was filtered, treated in turn with 5% and 10% NaOH to remove unchanged (2), and then with 10% HCl to remove the more basic 5-nitro isomer (4). The residue was recrystallized from 50% aqueous dimethylformamide in 53% yield, m.p. 138–139°. Other physical characteristics were as quoted above.

Crystallography

X-Ray Structure Determination of (3)

Compound (3) was recrystallized from aqueous dimethylformamide and a needle-shaped crystal with dimensions 0·36 by 0·12 by 0·10 mm was used for the X-ray measurements.

Crystal data.—$C_5H_7N_3O_3$; M 157·13 g mol^{-1}; monoclinic; a 10·929(3), b 8·899(2), c 7·290(2) Å; β 92·87(2)°; V 708·1 $Å^3$; D_m 1·49(2), D_c 1·47 g cm^{-3}, Z 4; $F(000)$ 328; λ 0·71069; μ (Mo Kα) 1·15 cm^{-1}.

Oscillation and Weisenberg photography indicated a monoclinic system and the systematic absences ($h01$, $l = 2n+1$; $0k0$, $k = 2n+1$) uniquely confirmed the space group as $P2_1/c$ (No. 14).[47] . Although the crystals obtained were not of good quality and showed two distinct maxima in ω-scans, the data obtained proved sufficient to allow solution of the structure. Cell dimensions were derived from the angular measurement of 25 strong reflections in the range $26 < 2\theta < 43°$. 926 independent intensities were measured at 20±1°C on a Nicolet four-circle computer controlled diffractometer with Mo Kα radiation, λ 0·71069, and the θ-2θ scan technique ($3 < 2\theta < 43°$). Data were processed using programs from the SHELXTL[48] package. The intensity variation of three standard reflections (013 040 007) monitored throughout the data collection indicated negligible crystal decay. Of the 926 reflections collected, 818 had values of F_o^2 that were greater than twice their estimated standard deviations, and these were used in the final refinement of structural parameters.

[47] 'International Tables for X-Ray Crystallography' Vol. 1 (Kynoch Press: Birmingham 1966).
[48] Sheldrick, G. M., 'SHELXTL. An Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data' University of Gottingen, Federal Republic of Germany, 1980.

Table 4. Final positional and equivalent thermal parameters for compound (3)

Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	x/a	y/b	z/c	U_{eq}
N(1)	0·1794(2)	0·5748(3)	0·1533(5)	0·049
C(11)	0·1937(3)	0·4113(4)	0·1444(7)	0·068
C(2)	0·0804(3)	0·6512(4)	0·2086(6)	0·056
N(3)	0·0945(2)	0·7976(3)	0·2051(5)	0·053
C(4)	0·2097(3)	0·8145(4)	0·1411(6)	0·039
N(4)	0·2579(3)	0·9598(3)	0·1097(5)	0·054
O(41)	0·2006(3)	1·0701(3)	0·1566(5)	0·090
O(42)	0·3549(2)	0·9693(2)	0·0309(4)	0·063
C(5)	0·2638(3)	0·6791(4)	0·1099(5)	0·042
O(5)	0·3701(2)	0·6342(3)	0·0427(4)	0·053
C(51)	0·4807(3)	0·6770(4)	0·1457(7)	0·064

The structure was solved by direct methods using the SOLV and FIND procedures from SHELXTL[48] which revealed the 11 non-hydrogen atoms of the imidazole ring and its substituents. A difference Fourier synthesis, following the application of analytical absorption corrections and least-squares refinement of the non-hydrogen atom positions,[48] showed electron density in reasonable locations for the hydrogen atoms of the methyl and methoxy substituents, and at the 2-position of the imidazole ring. These were input in calculated positions with $d_{C-H} = 0{\cdot}96$ Å. Refinement continued with the non-hydrogen atoms assigned anisotropic temperature factors and a weighting scheme based on counting statistics was introduced. This model converged with $R(\Sigma||F_o| - |F_c||/\Sigma|F_o|) = 0{\cdot}095$ and $R_w(\Sigma w^{1/2}||F_o| - |F_c||/\Sigma w^{1/2}|F_o|) = 0{\cdot}075$. The final difference Fourier map was essentially flat with no peaks higher than $0{\cdot}3$ e A^{-3}. Final atomic coordinates for the molecule are given in Table 4 with other crystallographic data in the deposited material.

Lists of structure factors, thermal parameters, hydrogen atom coordinates and torsion angle data are available on application to the Australian Journal of Chemistry, 314 Albert Street, East Melbourne, Vic. 3002,

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