Imidazol-5-yl Radicals as Reactive Intermediates

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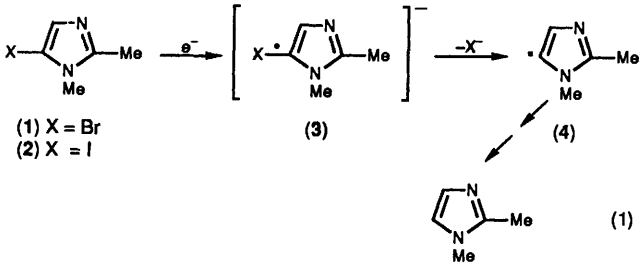
Imidazol-5-yl radicals have been generated as reactive intermediates in reduction reactions *e.g.* the reduction of 5-bromo-1,2-dimethylimidazole with $Na/NH_3/Bu^tOH$ and the reduction of 5-iodo- and 5-bromo-imidazole with Bu_3SnH, to yield 1,2-dimethylimidazole. The imidazol-5-yl radical resulting from the $Na/NH_3/Bu^tOH$ and Bu_3SnH reduction of 5-bromo-1-(but-3-en-1-yl)-2-methylimidazole has been trapped by *exo*-radical cyclisation to yield the bicyclic imidazole (**7**). Attempted $S_{RN}1$ substitution reactions between nucleophiles and 5-bromo- and 5-iodo-1,2-dimethylimidazole were unsuccessful. The radical anions of 5-nitroimidazoles were shown not to dissociate to nitrite anions and the corresponding imidazol-5-yl radicals, thereby disproving a putative explanation for the generation of nitrite anions in the antimicrobial mode of action of 5-nitroimidazoles. A mechanism has been proposed to explain the release of nitrite in the mode of action of nitroimidazoles. ^{13}C NMR spectroscopy has been used to distinguish between 4- and 5-bromo- and -iodo-imidazoles.

Many aryl and heteroaryl σ-radicals are well known and have been observed using electron spin resonance (ESR) spectroscopy and shown to participate in a wide variety of reactions. We report our studies on the investigation of reactions proceeding *via* imidazol-5-yl radicals, previously unreported species. The aim of this study was to obtain evidence for imidazol-5-yl radicals as reactive intermediates and to obtain knowledge of their formation and reactivity.

The reduction of 5-halogenoimidazoles to the corresponding radical anions followed by dissociation of these species to imidazol-5-yl radicals and halide ions [*e.g.* reaction (1)] appeared to provide the most accessible route to the radicals.



With this general aim we prepared a range of 5-bromo- and 5-iodo-imidazoles, which were subjected to reactions that are predicted to proceed *via* aromatic σ-radicals, *e.g.* reduction with sodium in liquid ammonia (NH_3) and t-butanol (Bu^tOH),[1] reduction with tributyltin hydride (Bu_3SnH),[2] and $S_{RN}1$ substitution reactions.[3] Preliminary results have been reported.[4]

Electron addition to the halogenoimidazoles, (**1**) and (**2**), to yield the corresponding σ* radical anions, with the SOMO delocalised in the C-halogen bonds [*e.g.* (**3**)] has been observed using ESR spectroscopy at low temperature.[4,5] Attempts to observe dissociation of these radical anions to the corresponding imidazol-5-yl radicals [*e.g.* (**4**)] and halide ions [*e.g.* reaction (1)] using ESR spectroscopy were less successful. On annealing the solid matrices of the trapped radical anions of 4- and 5-bromoimidazoles from 77 K to *ca.* 120 K, new species were indicated by poorly resolved broad singlets in the ESR spectra. These species could not be clearly identified and were tentatively assigned to the respective imidazolyl radicals suggesting that dissociation of the radical anions to bromide anions and imidazolyl radicals is possible. The studies using ESR spectroscopy clearly indicate that electron capture by halogenoimidazoles is feasible.

Results and Discussion

Preparation of 5-Bromo- and 5-Iodo-1,2-dimethylimidazole.—Methylation of 4(5)-bromo- and 4(5)-iodo-2-methylimidazole with dimethyl sulphate in ethanolic sodium hydroxide[6] gave mixtures of 4- and 5-halogeno-1,2-dimethylimidazoles which could not be separated by crystallisation or chromatography. Methylation with diazomethane of 2-methyl-4(5)-nitroimidazole gives predominantly the 5-nitro isomer.[7] However, use of diazomethane also gave a roughly equal mixture of 4- and 5-halogeno-1,2-dimethylimidazoles. Methylation with methyl *p*-toluenesulphonate gave only the respective 5-halogeno isomers. Both of these compounds have also been prepared by bromination, (Br_2)[8,9] or iodination, (I_2)[8,9] of lithio-1,2-dimethylimidazole, prepared by reaction between 1,2-dimethylimidazole and butyl-lithium.

^{13}C *NMR Spectroscopy of Halogenoimidazoles.*—The differences in chemical shift in the ^1H NMR spectra between 4-and 5-halogenoimidazoles are not sufficiently large to allow positive assignment of the structures. The same problem has also been found for 4- and 5-nitroimidazoles. However, ^{13}C NMR spectroscopy was found to give sufficiently different chemical shifts for 4- and 5-nitroimidazoles allowing clear identification.[10,11]

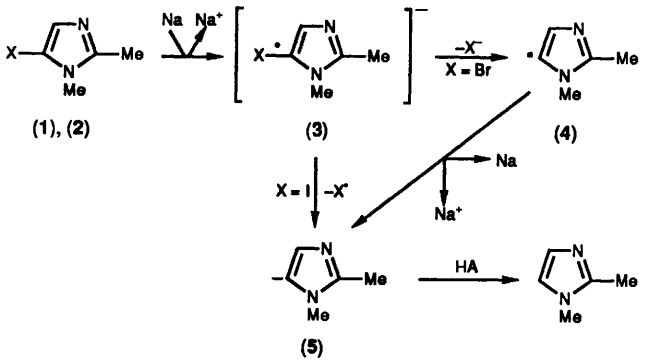
We therefore measured the ^{13}C NMR spectra of a range of halogenoimidazoles and non-halogenoimidazole (for comparison) (see the Table), which allowed unambiguous assignment of 4- and 5-halogeno isomers. The expected heavy atom effect of iodine, and to a lesser extent, bromine, were particularly noticeable, *e.g.*, for the 1,2-dimethylimidazoles, the C-5 atom in the 5-bromo isomer is shifted *ca.* 18 ppm upfield and the C-4 in the 4-bromo isomer is shifted upfield by *ca.* 14.5 ppm. Unfortunately some of the iodoimidazoles gave solubility problems.

$Na/NH_3/Bu^tOH$ *Reduction of 1,2-Dimethyl-5-halogenoimidazoles,* (**1**) *and* (**2**).—5-Bromo- and 5-iodo-1,2-dimethylimidazole were reduced to 1,2-dimethylimidazole in 48% and

Table. ^{13}C NMR spectroscopic chemical shift (δ/ppm) data for halogenoimidazoles.

Imidazole	C-2	C-4	C-5	C-2(Me)	Other
Imidazole	138.3	129.6	120.3		
2,4-Dimethylimidazole	144.1	131.6	117.3	13.8	11.8 [C-4(Me)]
1,2-Dimethylimidazole	144.9	126.8	120.4	12.6	32.63 (*N*-Me)
4-Bromo-2-methylimidazole	144.5	112.1	114.9	13.6	
4-Bromo-1,2-dimethylimidazole[a]	144.7	112.3	118.8	12.1	32.4 (*N*-Me)
5-Bromo-1,2-dimethylimidazole	145.5	126.5	11.6	13.5	30.9 (*N*-Me)
1-Allyl-5-bromo-2-methylimidazole	145.8	127.7	102.1	13.9	46.7, 117.2, 131.7 ($CH_2CH{=}CH_2$)
4-Iodo-2-methylimidazole	146.4	78.8	122.6	13.7	
4,5-Dibromo-2-methylimidazole	145.8	106.2	105.9	14.0	
4,5-Dibromo-1,2-dimethylimidazole	146.0	113.8	102.8	13.8	32.8 (*N*-Me)
4,5-Di-iodo-2-methylimidazole	150.0	84.7	84.7	13.8	
4,5-Di-iodo-1,2-dimethylimidazole	149.1	93.1	83.4	14.0	35.5 (*N*-Me)

[a] Calculated by subtraction of signals for the 5-bromo isomer in a mixture of the 4- and 5-bromo isomers.



Scheme 1. $Na/NH_3/Bu^tOH$ reduction of 5-halogeno-1,2-dimethylimidazoles.

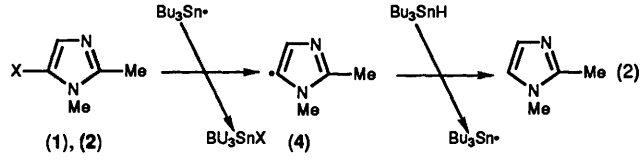
15% yields, respectively, using Na in liquid ammonia and Bu^tOH. This method has been extensively investigated.[1] The lower yield from the iodo derivative was thought to be due to poor solubility in liquid ammonia and Bu^tOH.

We propose the mechanism shown in Scheme 1 for the reduction. Electron capture of the solvated electron by the 5-halogenoimidazoles yields the corresponding σ* radical anions (**3**; X = I and Br). In the case of the bromo radical anion, dissociation takes place to yield the imidazol-5-yl radical (**4**) which is further reduced to the corresponding anion (**5**). However, the results from the studies using ESR spectroscopy[4,5] suggest that the iodo radical anion (**3**; X = I) probably dissociates with loss of iodine ($I^•$) to yield the anion (**5**) directly. The tendency for the dissociation of C-hal σ* radical anions, $(R^•X)^-$, to dissociate to R^-, and $X^•$, rather than $R^•$ and X^-, is favoured in the order: I > Br > Cl.[12] Therefore it is quite possible that the iodo radical anion dissociates with loss of $X^•$ ($I^•$) whereas the bromo radical anion dissociates with loss of X^- (Br^-).

The reaction is completed by protonation of the 5-anion of 1,2-dimethylimidazole (**5**). The lithio 5-anion of 1,2-dimethylimidazole with butyl-lithium and treated with a wide variety of electrophiles, including D_2O.[8,13] The 5-anion is therefore a feasible intermediate.

A point of interest is that sodium sulphite reduces 4,5-dibromo-and 4,5-di-iodo-2-methylimidazole to the respective 4(5)-halogenoimidazole, but no further, and does not reduce 4,5-dibromo- and 4,5-di-iodo-1,2-dimethylimidazole. Therefore, the reduction of the monohalogenoimidazoles takes place with the strongly reducing sodium but not with sulphite.

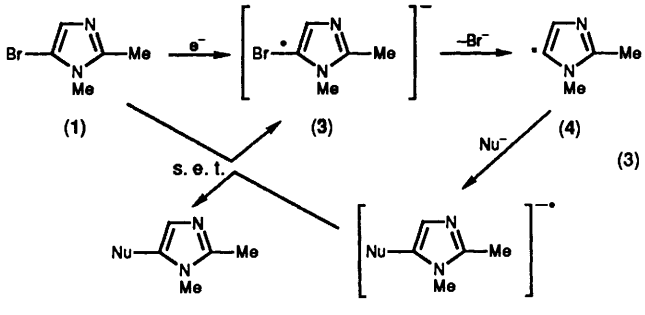
Bu_3SnH *Reduction of* 1,2-*Dimethyl-5-halogenoimidazoles.*—5- Iodo- and 5-bromo-1,2-dimethylimidazole were reduced with Bu_3SnH[2] in 50% and 53% yield, respectively. Azobisisobutyronitrile (AIBN) was used as the initiator for the chain reaction. Similar results were obtained using either toluene or benzene as solvent. We propose that the mechanism[4,14] proceeds as shown in reaction (2), *i.e.* abstraction of halogen by $Bu_3Sn^•$ to yield 1,2-dimethylimidazol-5-yl radicals wihich subsequently abstract hydrogen from Bu_3SnH. Inhibition studies with 50 mol% of

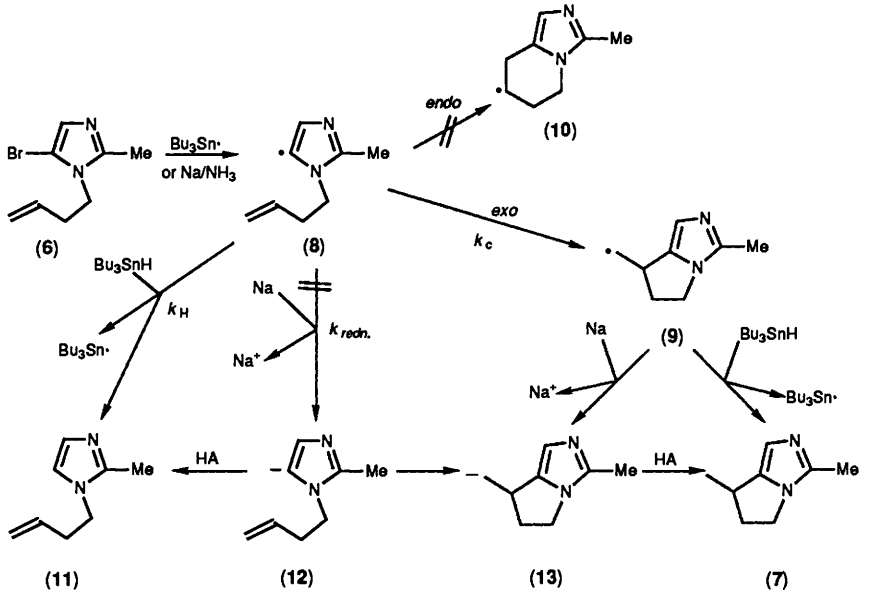


added di-t-butylnitroxide, a commonly used radical scavenger, gave high, but not complete, inhibition. Even when the inhibitor was used in an atmosphere of oxygen (O_2) in place of nitrogen, inhibition was not 100%. These studies clearly suggest the imidazol-5-yl radical to be an intermediate.

Interestingly, the ^1H NMR spectra of crude reaction mixtures indicated that the imidazol-5-yl radicals had added to the toluene or benzene solvents by some sort of homolytic aromatic substitution mechanism. The products were not isolated and characterised.

Attempted $S_{RN}1$ *Substitution Reactions.*—The success of Na/NH_3 and Bu_3SnH reduction in generating imidazol-5-yl radicals as intermediates encouraged us to investigate $S_{RN}1$ substitutions. The expected mechanism of these substitutions is shown in reaction (3). $S_{RN}1$ reactions have been reported for a wide variety of halogenoheterocycles.[3,15] We chose phenylthiolate and the anion of diethylphosphite, two of the most commonly used anions for our studies.





Scheme 2. Cyclisation of *N*-(but-3-en-1-yl)-imidazol-5-yl radicals.

Reaction between phenylthiolate and 5-bromo-1,2-dimethylimidazole under conditions favouring $S_{RN}1$ substitution [dimethylformamide (DMF) or liquid ammonia as solvent, irradiation at 350 nm] failed to yield any of the expected 1,2-dimethyl-5-(phenylthio)imidazole. After prolonged forcing conditions and with large excesses of thiolate an increasing amount of diphenyl disulphide and decomposed material was isolated. The results suggest that the initiating single electron transfer between thiolate and bromoimidazole is not favourable but does slowly take place yielding thiyl radicals which dimerise to yield the disulphide in a non-chain redox reaction. The fate of the bromoimidazole radical anion (**3**) is unclear, but it does not appear to dissociate to yield imidazol-5-yl radicals, or if this does take place, the nucleophile does not add to yield the second radical anion intermediate required to carry the chain reaction. A possible explanation is that radical anions in which the unpaired electron resides in the σ* SOMO are not favoured in $S_{RN}1$ reactions. However, the assumption that has normally been made is that the π* radical anion ($^{\cdot-}$Ar–X) somehow changes to the σ* radical anion, $(Ar^{\cdot}X)^-$ prior to dissociation.[3]

The lack of reaction is surprising, particularly as phenylthiolate has been reported to undergo $S_{RN}1$ reactions with iodobenzene, 2-chloropyridine, -quinoline, and -pyrimidine, and with 4-bromoquinoline.[3,15,16] Iddon and co-workers[17] also reported that phenylthiolate does not react with 5-bromo-1,2-dimethylimidazole in dioxane or dimethyl sulphoxide, but irradiation was not used. Reaction[17] between phenylthiolate and 2,4,5-tribromo-1-alkylimidazoles gave substitution at the 2-position, but presumably by an S_NAr mechanism.

Reactions between the anion of diethylphosphate and 5-bromo-1,2-dimethylimidazole in DMF with light catalysis (4, 48, 96 h) also failed and *ca.* 70% of the starting imidazole was isolated in each case.

Reductive Cyclisation of 5-*Bromo*-1-(*but*-3-*en*-1-*yl*)-2-*methylimidazole.*—Cyclisation of *o*-alkenyl aryl radicals [*e.g. o*-(but-3-en-1-yl)-phenyl radicals] to give *exo*-radicals has been widely used as a diagnostic test[1,2,18] for the intermediacy of aryl σ-radicals. Although these cyclisations had not previously been applied to five-membered ring σ radicals, there appeared to be no reason why cyclisation should not be successful. 5-Bromo-1-(but-3-en-1-yl)-2-methylimidazole (**6**) was prepared and reduced with Bu_3SnH and $Na/NH_3/Bu^tOH$ under the same conditions as for the 1-methyl analogue (**1**). The *exo*-cyclised product (**7**) was isolated in quantitative yield in both reactions.

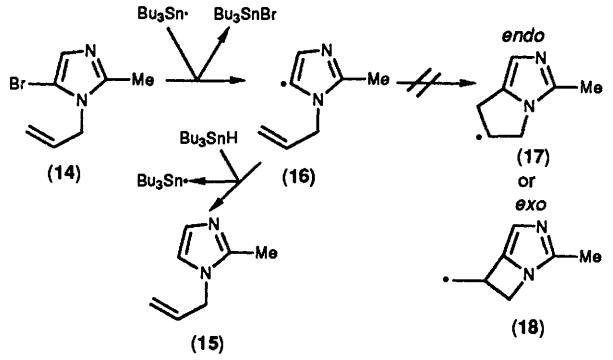
We propose that the mechanisms are as shown in Scheme 2. The yield of reduced material (**7**) was considerably higher than that for the *N*-methyl analogue (50%), suggesting that the intermediate imidazol-5-yl radical (**8**) is rapidly trapped by cyclisation and subsequent reduction whereas the imidazolyl radical (**4**) also undergoes other reactions not leading to the reduced product (1,2-dimethylimidazole).

The intermediate imidazolyl radical (**8**) cyclises to yield the *exo*-radical (**9**) selectively with no observable traces of products resulting from cyclisation to the *endo*-radical (**10**). The observed regioselectivity of *exo*-cyclisation over *endo*-cyclisation is in keeping with analogous aryl radicals.[1,2,18] The results also indicate that the rate of cyclisation of (**8**) to (**9**) (k_C) is considerably faster than the rate of reduction of (**8**) by Bu_3SnH (k_H) because no non-cyclised product (**11**) resulting from reduction was detected.

Cyclisation in the $Na/NH_3/Bu^tOH$ reduction could possibly proceed *via* the anion (**12**) rather than the radical (**8**) (see Scheme 2). However, Bunnett and co-workers[1] have reported that the rate of protonation of the *o*-butenyl phenyl anion analogous to (**12**) is far more rapid than its rate of cyclisation in the same reduction system. Therefore, by analogy we suggest that the imidazol-5-yl anion (**12**) is also likely to protonate to yield the non-cyclised imidazole (**10**) faster than cyclisation to (**13**). Cyclisation *via* an anionic route therefore appears unlikely. Reduction of the cyclised radical (**9**) to the anion (**13**) followed by protonation is therefore the most likely route to explain the overall mechanism. Study of the analogous iodoimidazole, in which the radical anion may dissociate directly to the anion (**12**) by loss of I^-, was precluded because the required *N*-butenyl-5-iodoimidazole could not be synthesised due to rapid decomposition during the butenylation.

Reduction of 1-allyl-5-bromo-2-methylimidazole (**14**) with Bu_3SnH only gave the non-cyclised reduction product (**15**) (Scheme 3). The rate of reduction of the intermediate imidazolyl radical (**16**) is obviously much faster than the rate of cyclisation to either the *endo*-radical (**17**) or the *exo*-radical (**18**). These results are in accord with the lack of cyclisation reported for analogous *o*-allyl-phenyl radicals.[2,18]

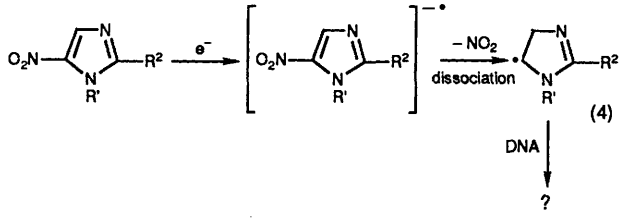
The cyclisation reaction is to our knowledge the first to use an



Scheme 3. Reduction of 1-allyl-5-bromo-2-methylimidazole.

N-alkenyl chain on a five-membered ring azole and indicates a potentially useful synthetic route.

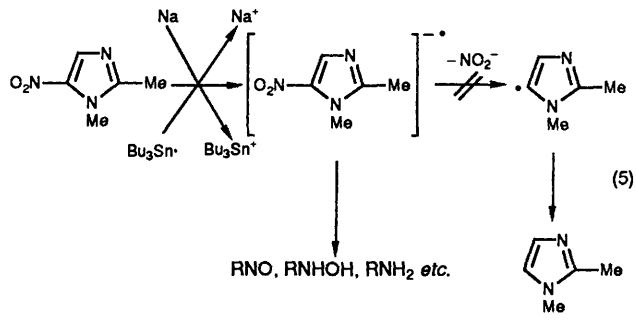
Imidazol-5-yl Radicals as Intermediates in the Mode of Action of 5-Nitroimidazoles.—2- and 5-Nitroimidazoles are the most commonly used antibiotics for the treatment of anaerobic bacterial and protozoal diseases.[19,20] Evidence suggests that the mode of action of nitroimidazoles is due to interaction between DNA and reactive intermediates resulting from reduction of the nitroimidazoles within the cell. Nitrite anion (up to 30%) has been measured in several *in vitro* and *in vivo* studies on the mode of action of 5-nitroimidazoles,[19,21,22] leading to the proposal[21,22] that dissociation of the initially formed nitroimidazole radical anions to imidazol-5-yl radicals may be important (reaction (4)].



Considerable evidence has been reported to show that the 5-nitroimidazoles are reduced by the pyruvate:ferrodoxin oxidoreductase complex and NADPH:ferrodoxin oxidoreductase in the hydrogenosomes of trichomonads, and by NADPH-linked reductases in bacteria to the corresponding radical anions.[20] The radical anions but not the imidazolyl radicals have been detected using ESR spectroscopy.[21,23]

Studies using ESR spectroscopy[21–25] have shown that the radical anions of 5-nitroimidazoles are surprisingly stable. The radical anions of 4-and 5-nitro-1,2-dimethylimidazole can be clearly observed in solid matrices at 77 K and even when warmed to room temperature and refrozen, no dissociation to imidazolyl radicals was observed.[24,25] To our knowledge there are no reported examples of dissociation of aromatic nitro radical anions to nitrite anions and the corresponding aromatic σ-radicals. This lack of dissociation is to be expected because the σ-radical will have a higher energy than the nitro radical anion. However, as we were studying the reactivity of 5-nitroimidazole radical anions as part of our research into the mode of action of nitroimidazoles, we therefore also searched for evidence of imidazolyl radical formation [see reaction (5)].

1,2-Dimethyl-5-nitroimidazole was reduced with Na/NH_3/-Bu^tOH and Bu_3SnH under the same conditions as for the bromo- and iodo-analogues, (**1**) and (**2**). No signs of 1,2-dimethylimidazole could be detected by TLC or ^1H NMR spectroscopy and only a multitude of intractable brightly

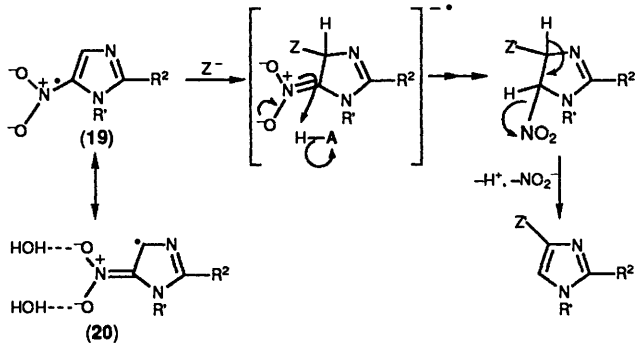


coloured products arising from the reduction were observed. The radical anion is almost certainly generated in these reactions but does not dissociate under the same conditions which give dissociation to imidazol-5-yl radicals for the halogeno analogues. An initial red colour observed in these reactions, and in the studies[23] using ESR spectroscopy, is likely to be the nitro radical anion. 1,2-Dimethylimidazole was subjected to the same conditions with 100% recovery to prove that if formed in the above reactions it would not be degraded.

The use of sodium dithionite as reductant or electrochemical reduction gave similar results, *i.e.* no 1,2-dimethylimidazole was observed. Dithionite or electrochemical reduction of 1-(but-3-en-1-yl)-2-methyl-5-nitroimidazole also yielded only coloured products and none of the cyclised imidazole (**7**) was detected by TLC or ^1H NMR spectroscopy.

We therefore conclude that the radical anions of 5-nitroimidazoles do not dissociate to nitrite anions and imidazol-5-yl radicals. The antimicrobial mode of action of 5-nitroimidazoles is therefore very unlikely to involve the dissociation of nitroimidazole radical anions, or imidazol-5-yl radicals as reactive intermediates. The formation of nitrite observed[21,22] must therefore derive from some other process which may include the formation of an intermediate species resulting from reaction between the nitro radical anion and some biological substrate such as DNA.

A possible mechanism for the release of nitrite anions has been postulated by Crozet and co-workers[26] for the single electron transfer reaction between 1,2-dimethyl-5-nitroimidazole and the anion of 2-nitropropane. The reaction involves the formation of the nitro radical anion followed by *cine*-substitution, thereby releasing nitrite anion. Based on this reaction, a possible mechanism for the mode of action for release of nitrite is shown in Scheme 4. Calculations[24,25] of spin densities of the unpaired electron on the radical anions of 5-nitroimidazole indicate *ca.* 50% on the nitro nitrogen atom [canonical form (**19**)] and *ca.* 20% on C-4 [canonical form (**20**)]. The nitronate anion at C-5 would be strongly solvated in aqueous medium, thereby partly neutralising the negative charge and favouring addition reactions involving a C-4 radical centre.



Scheme 4. Putative mechanism for the loss of nitrite anions in the mode of action of 5-nitroimidazoles. Z = A biological molecule such as DNA or EnzymeSH.

Experimental

General.—IR spectra were determined as Nujol mulls for solids and as thin films for liquids on a Pye Unicam PU9516 IR spectrophotometer. ^{1}H NMR spectra were determined at 60 MHz on a Varian EM360A instrument and ^{13}C NMR spectra on a Bruker WP-80 spectrometer using $SiMe_4$ as internal standard. ^{1}H NMR analyses of reaction mixtures were carried out using a known amount of *p*-dinitrobenzene as an internal standard.

Materials.—4(5)-Bromo-2-methylimidazole[27] and 4(5)-iodo-2-methylimidazole[28] were prepared by sodium sulphite reduction from the corresponding 4,5-dihalogeno-2-methylimidazoles. 4,5-Dibromo-2-methylimidazole[29] and 4,5-di-iodo-2-methylimidazole[27] were prepared by bromination and iodination, respectively, of 2-methylimidazole. 4,5-Dibromo- and 4,5-di-iodo-1,2-dimethylimidazole[8,30] were prepared by methylation of the respective 4,5-dihalogeno-2-methylimidazoles with dimethyl sulphate in ethanolic sodium hydroxide solution. Allyl *p*-toluene sulphonate was prepared by treatment of allyl alcohol with *p*-tosyl chloride in aq. sodium hydroxide.[31] 1,2-Dimethyl-5-nitroimidazole was prepared by treatment of 2-methyl-4(5)-nitroimidazole with diazomethane.[32]

5-Bromo-1,2-dimethylimidazole.—4(5)-Bromo-2-methylimidazole (10.0 g, 62 mmol) and methyl *p*-toluenesulphonate (12.0 g, 64 mmol) were heated together at *ca.* 140 °C for 90 min under an atmosphere of nitrogen. The reaction mixture was cooled and triturated with saturated aqueous sodium hydrogen carbonate. The resulting solution was basified to pH 11 with aq. sodium hydroxide and extracted with dichloromethane (CH_2Cl_2). The CH_2Cl_2 extracts were dried and evaporated to dryness. Dry column chromatography using acid-washed alumina as absorbent with light petroleum (b.p. 40–60 °C)–chloroform ($CHCl_3$) as eluant yielded colourless crystals of 5-bromo-1,2-dimethylimidazole (5.95 g, 48%), m.p. 91–92 °C (lit.,[9] 88–90 °C); ν_{max} 1 660, 1 528, and 756 cm^{-1}; δ_H 2.30 (3 H, s, Me), 3.49 (3 H, s, NMe), and 6.7 (1 H, s, 4-H).

1,2-Dimethyl-5-iodoimidazole was prepared by the same procedure from 1,2-dimethyl-4(5)-iodoimidazole in 45% yield, m.p. 181–182 °C (lit.,[9] 182–183 °C); ν_{max} 1 664, 1 514, and 730 cm^{-1}; δ_H ($CDCl_3$–[$^2H_6$]DMSO) 2.54 (3 H, s, Me), 3.57 (3 H, s, NMe), and 6.80 (1 H, s, 4-H).

Reductions with $Na/NH_3/Bu^tOH$.—(*a*) *Reduction of 5-bromo-1,2-dimethylimidazole.* Ammonia (*ca.* 60 ml) was distilled from sodium in a 250 ml three-necked flask containing dry Bu^tOH (25 ml) and equipped with a dry-ice condenser and stirrer bar under an atmosphere of dry oxygen-free nitrogen. A three-fold molar excess of sodium was added piecewise whilst the reaction mixture was stirred. A blue colour resulted. 5-Bromo-1,2-dimethylimidazole was added and the reaction refluxed until the blue colour disappeared (*ca.* 5 min). Solid ammonium nitrate was added, the mixture diluted with CH_2Cl_2, and the ammonia allowed to evaporate over several hours. The remaining CH_2Cl_2 solution was washed with water, dried, and evaporated to dryness. The yield of 1,2-dimethylimidazole (48%) in the oily residue was measured using ^{1}H NMR spectroscopy. In a separate experiment the 1,2-dimethylimidazole was fully purified and characterised by comparison with authentic material (IR and ^{1}H NMR spectroscopy, TLC, and m.p. determination).

(*b*) *Reduction of 1,2-dimethyl-5-iodoimidazole.* 1,2-Dimethyl-5-iodoimidazole was reduced by the above procedure to yield only 15% of 1,2-dimethylimidazole. Problems were encountered with poor solubility of the imidazole in the liquid ammonia/Bu^tOH solution.

Reductions with Bu_3SnH.—(*a*) *Reduction of 5-bromo-1,2-dimethylimidazole.* Tributyltin hydride (2.91 g, 100 mmol) was added to a solution of 5-bromo-1,2-dimethylimidazole (0.35 g, 2 mmol) and AIBN (0.164 g, 1 mmol) in dry toluene (25 ml) under an atmosphere of dry oxygen-free nitrogen. The reaction was heated under reflux with irradiation from fluorescent lamps (2 × 100 W, tungsten mercury-blended universal white light lamps) for 48 h. The reaction mixture was cooled and extracted with 2M hydrochloric acid (3 × 50 ml). The hydrochloric acid extracts were basified with 2M aqueous sodium hydroxide solution to pH 11 and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and evaporated to dryness to yield an oily residue which was analysed by ^{1}H NMR spectroscopy using an internal standard. A 50% yield of 1,2-dimethylimidazole was observed. 1,2-Dimethylimidazole was isolated with difficulty in a separate experiment and characterised by comparison with authentic material (IR and ^{1}H NMR spectroscopy, m.p., and TLC).

The use of benzene in place of toluene gave a similar yield.

(*b*) *Reduction of 1,2-dimethyl-5-iodoimidazole.* 1,2-Dimethyl-5-iodoimidazole (2 mmol) was reduced by the above procedure to yield 53% of 1,2-dimethylimidazole.

But-3-en-1-yl p-Toluenesulphonate.—25% Aqueous sodium hydroxide solution (5 ml, 33 mmol) was added dropwise over 60 min to a mixture of but-3-en-1-ol (4.5 g, 62 mmol) and *p*-toluenesulphonyl chloride (5.95 g, 31 mmol) at 0–10 °C and the mixture left overnight at room temperature. The reaction mixture was extracted with diethyl ether. The extracts were dried and evaporated to dryness to yield a pale yellow oil which crystallised on standing to yield but-3-en-1-yl *p*-toluenesulphonate (276 mg, 88%); ν_{max}(neat) 3 076, 2 980, 2 924, 1 640, 1 360, 1 190, and 838 cm^{-1}; δ_H 2.3 (2 H, t, CH_2), 2.48 (3 H, s, Me), 4.00 (2 H, t, CH_2), 4.70–6.05 (3 H, m, $CH{=}CH_2$), and 7.50 (4 H, ABq, aromatic-H).

5-Bromo-1-(but-3-en-1-yl)-2-methylimidazole.—4(5)-Bromo-2-methylimidazole (3.1 g, 19.5 mmol) and but-3-en-1-yl *p*-toluenesulphonate were heated together at 140 °C for 4 h under an atmosphere of nitrogen. The reaction mixture was cooled and saturated aqueous sodium hydrogen carbonate (100 ml) and CH_2Cl_2 (100 ml) were added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (4 × 100 ml). The CH_2Cl_2 extracts were dried and then evaporated to dryness to yield a crystalline residue which was subjected to column chromatography using alumina as absorbent and light petroleum (b.p. 40–60 °C)–$CHCl_3$ (1:1) as eluant to yield 5-bromo-1-(but-3-en-1-yl)-2-methylimidazole (1.53 g, 36%); ν_{max}(neat) 3 076, 2 956, 1 638, and 1 520 cm^{-1}; δ_H 2.38 (3 H, s, Me), 2.45 (2 H, t, CH_2), 4.60–6.10 (3 H, m, $CH{=}CH_2$), and 6.70 (1 H, s, 4-H).

1-Allyl-5-bromo-2-methylimidazole.—Allyl *p*-toluenesulphonate (5.00 g, 31 mmol) and 4(5)-bromo-2-methylimidazole (7.00 g, 38 mmol) were reacted as above for 24 h. Column chromatography yielded a pale yellow oil of 1-allyl-5-bromo-2-methylimidazole (1.12 g, 18%); ν_{max}(neat) 3 120, 3 084, 2 984, 2 928, 1 642, and 1 522 cm^{-1}; δ_H 2.31 (3 H, s, Me), 4.50 (2 H, d, NCH_2), 4.60–6.20 (3 H, m, $CH{-}CH_2$), and 6.75 (1 H, s, 4-H).

1-Allyl-2-methylimidazole.—2-Methylimidazole (2.0 g, 24 mmol) and allyl *p*-toluenesulphonate (5.3 g, 26 mmol) were heated together at 130 °C for 3 h under an atmosphere of nitrogen. The reaction mixture was dissolved in CH_2Cl_2 and aq. sodium hydroxide solution, the layers separated, and the aqueous layer washed with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried, and evporated to dryness to yield an oil which was distilled using a Kugelrohr apparatus to yield 1-allyl-2-methylimidazole, b.p. 80 °C at 1 mmHg (lit.,[33] b.p. 71 °C at 1

mmHg); δ_H 2.35 (3 H, s, Me), 4.40 (2 H, m, NCH_2), 5.10 (2 H, m, CH_2=, *J* 16 Hz, 10 Hz, and 2 Hz), 5.85 (1 H, m, CH=), and 6.82 (2 H, d, 4, 5-H).

Reduction of 5-*Bromo*-1-(*but*-3-*en*-1-*yl*)-2-*methylimidazole*.—(*a*) *Reduction with* Bu_3SnH. 5-Bromo-1-(but-3-en-1-yl)-2-methylimidazole (2.0 g, 9.3 mmol), Bu_3SnH (2.8 g, 9.6 mmol), and AIBN (161 mg) were allowed to react in toluene for 72 h (using the procedure reported above for 5-bromo-1,2-dimethylimidazole) to give a quantitative yield of the bicyclic compound (**7**). The pure product was distilled using a Kugelrohr apparatus, b.p. 95 °C/2 mmHg (Found: C, 70.9; H, 9.0; N, 20.5. $C_8H_{12}N_2$ requires C, 70.6; H, 8.8; N, 20.6%); ν_{max}(neat) 2 960, 2.924, 2 868, and 1 562 cm^{-1}; δ_H 1.20 (3 H, d, *Me*CH), 2.15 (3 H, s, Me), 2.25–3.55 (3 H, m, CH_2, *CH*Me), 3.75 (2 H, dt, CH_2), and 6.28 (1 H, s, 4-H); *m*/*z* 136 (M^+, 58%), 135 (17), and 121 (M^+ − Me, 100).

(*b*) *Reduction with* $Na/NH_3/Bu^tOH$. 5-Bromo-1-(but-3-en-1-yl)-2-methylimidazole (430 mg, 2 mmol) was treated with Na in NH_3 using the procedure as outlined for 5-bromo-1,2-dimethylimidazole. The blue colour persisted for 10–20 s. Work-up gave a quantitative yield of pure bicyclic compound (**7**). The yield was confirmed using ^1H NMK spectroscopy with an internal standard.

Reduction of 1-*Allyl*-5-*bromo*-2-*methylimidazole*.—A solution of Bu_3SnH (3 mmol), AIBN (0.3 mmol), and 1-allyl-5-bromo-2-methylimidazole was allowed to react in toluene for 48 h using the procedure reported for 5-bromo-1,2-dimethylimidazole to give 1-allyl-2-methylimidazole (91%). The product showed one clean spot on TLC and was not further purified. The TLC behaviour and IR and ^1H NMR spectra were identical with the authentic material. No signs of any other products or unaltered starting imidazole were detected.

1-(*But*-3-*en*-1-*yl*)-2-*methyl*-5-*nitroimidazole*.—2-Methyl-4(5)-nitroimidazole (8.9 g, 70 mmol) and but-3-en-1-yl *p*-toluene sulphonate (17.6 g, 77 mmol) were heated together under a nitrogen atmosphere at 130–140 °C for 18 h. The reaction mixture was cooled then dissolved in $CHCl_3$ and aq. sodium hydroxide (2M). The layers were separated and the aqueous layer extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated to dryness to yield an oil (6.5 g) which was subjected to column chromatography using silica gel as absorbent and $CHHCl_3$/EtOH as eluant. The resulting oil was further purified by formation of the hydrochloride salt. Neutralisation of the salt and recrystallisation from ethanol–hexane gave light yellow crystals of 1-(but-3-en-1-yl)-2-methyl-5-nitroimidazole (1.65 g, 13%), m.p. 52–53 °C; ν_{max} 3 112, 3 076, 1 640, and 1 522 cm^{-1}; δ_H 2.51 (3 H, s, Me), 2.53 (2 H, t, CH_2), 4.41 (2 H, t, NCH_2), 4.80–6.20 (3 H, m, CH–CH_2), and 7.95 (1 H, s, 4-H).

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