Chapter 2

Photochemical Studies on Nitroimidazole Drugs (Secnidazole and Dimetridazole) in Photoinduced Electron Transfer (PET) Condition
The nitroimidazoles (1-5) are compounds with a wide range of biological effects, some of which have particular value in human and animal therapeutics. Thus, such 5-nitroimidazoles as metronidazole, tinidazole, dimetridazole, secnidazole and ornidazole have become drugs of choice for human and animal disease, structurally similar drugs are used to treat turkey blackhead and swine dysentery. In addition, the 5-nitroimidazoles are potent antibiotics for anaerobic bacteria. They are bacterial mutagens. Indeed, because they are bacterial mutagens and rodent tumorigens, some concern has been expressed about the safety of these valuable therapeutic agents.¹

The nitroimidazoles have a wide range of biological properties that provide an increasing number of therapeutic applications. Some properties are common to all nitroimidazoles whereas others are characteristic only of certain compounds. Considerable insight may be gained into the mechanism of action of the nitroimidazoles by seeking correlations between their chemical and biological properties. Thus the reduction potential of the nitro group of a nitroimidazole tends to correlate with its relative potency as a mutagen, cytotoxin, or radiation sensitizer. The
apparent obligatory rule of nitro group reduction for biological activity explains why 5-nitroimidazole exhibit selective toxicity for anaerobic micro-organisms.\textsuperscript{2} 5-nitroimidazoles are mainly used against amoebiasis, giardiasis, trichomoniasis, and anaerobic bacterial infections.\textsuperscript{3,4} 4-nitroimidazoles are much less active than the corresponding 5-nitro isomers.\textsuperscript{5} The structure–activity relationships of hundreds of 5-nitroimidazoles have been studied,\textsuperscript{6-11} and comprehensive reviews\textsuperscript{4,12} on their chemistry and pharmacology exist.

The mechanism of biological action of nitroimidazoles, commonly used to treat infection by anaerobic bacteria, depends on the reduction of the nitro group producing intermediate species which interact with DNA, oxidizing it and resulting in strand breaking and double-helix destabilization.\textsuperscript{13,14} Secnidazole [1-(2-hydroxypropyl)-2-methyl-5-nitroimidazole] is an antimicrobial agent. Secnidazole is structurally related to the commonly used 5-nitroimidazoles metronidazole and tinidazole. These drugs share a common spectrum of activity against anaerobic micro-organisms and they appear particularly effective in the treatment of amoebiasis, giardiasis, trichomoniasis and bacterial vaginosis. The most relevant drugs (benznidazole, furazolidone, metronidazole, misonidazole, nifurtimox, nimorazole, nitazoxanide, ornidazole, secnidazole and tinidazole) are characterized with regard to their chemical, chemotherapeutic, toxicological, pharmacokinetic, and pharmacological properties, including the mechanism of action and resistance in certain parasitic protozoa.

Photoinduced electron transfer (PET) reactions are one of the most fundamental processes in chemistry and biology. In chemistry, for example, PET is important
because it has uncovered simple pathways for the synthesis of novel organic molecules. Products formed by PET could be very reactive and can undergo versatile chemical reactions of mechanistic and synthetic significance. Photo-induced electron transfer (PET) is a very important process, with considerable chemical and biological relevance.

With this interest herein we have investigated:


Section [A]

A Biologically Significant Photochemistry of

Secnidazole
[A] A Biologically Significant Photochemistry of Secnidazole

When xenobiotic species such as pharmaceutical products are transported through the blood system into various areas of the body, a range of photophysical and photochemical reactions may possibly occur with the xenobiotic-sunlight interactions, leading to the formation of toxic photoproducts. These xenobiotic-incident sunlight interactions can be very detrimental for living tissues since they can result in photoallergic and phototoxic responses.\(^\text{15}\)

Recently there has been a considerable amount of research toward understanding both the unimolecular deactivation pathway of photoexcited pharmaceutical products and their photosensitizing capability in the presence of biological substrates. Photooxygenation and photoreduction reactions of imidazoles have gained considerable importance in view of the significant biological implications of heterocycles. Their therapeutic action such as antibacterial and antiprotozoal activity is explained one electron reduction of the nitro group to radical anions.

While the photooxygenation product oxadiazole is a cause of cell death in cells treated with nitroimidazole and u.v radiation, since some toxicity of this class of compound has been reported.

Increased awareness of anaerobic infections and the demonstration of the excellent activity of metronidazole against a wide range of obligatory anaerobic bacteria\(^\text{16-18, 19}\) have raised new medical interest in nitroimidazole drugs. Nitroimidazole drugs have been used for over 20 years, not only as major antimicrobial drugs but also as sensitizers of hypoxic tumors in conjunction with radiotherapy, thus possessing a wider spectrum of useful clinical activity than any
other antibiotic. Nitroimidazole group of drugs displays the range of action both in human and veterinary medicine.

Secnidazole [1-(2-hydroxypropyl)-2-methyl-5-nitroimidazole] (1), a 5-nitroimidazole derivative is used in the treatment of susceptible protozoal infections and in human trichomoniasis. Recent work with several nitroimidazoles suggests that ring opening of partially reduced compound may lead to biologically active agents. For example enzymatic metabolism yields acetamide, a compound known to be carcinogenic. Misonidazole when reduced by enzyme breaks down to glyoxal, whose reactivity with proteins and nucleic acid is well known. The carcinogenicity of nitroimidazoles are reviewed. This prompted us to study the photoreactivity of secnidazole in various conditions.

**Experimental**

**Chemicals**

All chemicals used were of analytical grade. Secnidazole (1), was extracted from commercial medicament Seczol DS (Intas Pharmaceuticals, India). The purity of drug, extracted, was checked by TLC.

**Apparatus**

Photolysis were carried out at room temperature in a photoreactor equipped with medium pressure vapour lamp inserted in a water cooled immersion well with continuous supply of water. IR spectra were recorded as KBr discs on Perkin Elmer model spectrum RXI. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Brucker DRX-300 spectrometer using SiMe$_4$ as internal standard. EIMS mass spectra was recorded on VG-ZAB-HS mass spectrometers at 10 KV accelerating voltage
spectrometer using m-nitrobenzyl alcohol (NBA) matrix. High resolution mass
spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 eV ionization
voltage.

**Irradiation procedure**

A solution of SCZ (150 mg) in doubly distilled water was irradiated for 3 hrs. The pH
of the irradiation solution was maintained in the range 7-8 by addition of 1m NaOH. It
is kept in the dark at 0°C for 15 hrs so that maximum conversion of intermediate
occurred to yield (3). Complete conversion of (1) was monitored by TLC (diethyl
ether: methanol: acetic acid; 90:8:2). Removal of water under reduced pressure and
column chromatography of resulting photoproducts on silica gel yielded compound
(2).

**Characterization of products**

**(E)-4-(hydroxyimino)-1-(2-hydroxypropyl)-2-methyl-1H-imidazol-5(4H)-one** (2):
Yield: 28%; HRMS calcd. for (M⁺) C₇H₁₁N₃O₅ 185.1827, found 185.1815; IR(KBr) :
1608-1423, 1685, 3440-3460 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.9 (s, 3H, H-2), 1.21 (d, 3H,
H-3’), 2.0 (brs, 1H, 2OH), 3.23;2.98 (d, 2H, H-1’), 4.02 (m, 1H, H-2’); ¹³C-NMR
(CDCl₃) δ 22.1 (C-3’), 23.7 (C-CH₃), 47.5 (C-1’), 66.2 (C-2’), 162.9 (C-5), 163 (C-4),
164 (C-2). Anal. Calc. for C₇H₁₁N₃O₅: C 45.40, H 5.99, N 22.69; found: C 45.42, H
5.98, N 22.66. m/z 185 (M⁺).

**N-(2-hydroxypropyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide** (3): Yield: 26%;
HRMS calcd. for (M⁺) C₇H₁₁N₃O₃ 185.1827, found 185.1812; IR(KBr): 1143, 1566,
1670, 3315, 3423 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.21 (d, 3H, H-3’), 2.0 (brs, 1H, OH),
2.35 (s, 3H, H-5), 3.23;2.98 (t, 2H, H-1’), 4.02 (m, 1H, H-2’), 8.0 (t, 1H, NH); ¹³C-
NMR (CDCl₃) δ 13.5 (C-CH₃), 22.1 (C-3′), 50.5 (C-1′), 68.3 (C-2′), 157.9 (C-6), 176.7 (C-5). Anal. Calc. for C₇H₁₁N₃O: C 45.40, H 5.99, N 22.69; found: C 45.43, H 5.97, N 22.67. m/z 185 (M⁺).

2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione(4): Yield: 30%; HRMS calcd. for (M⁺) C₇H₁₁N₃O₅ 217.1815, found 217.1800; IR(KBr): 1370, 1550, 1630, 1685, 1715 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.9 (s, 3H, H-3), 1.21 (d, 3H, H-3′), 2.0 (brs, 1H, OH), 3.23;2.98 (d, 2H, H-1′), 4.02 (m, 1H, H-2′), 9.6 (s, 1H, H-5); ¹³C-NMR (CDCl₃) δ 21.7 (C-3′), 22.2 (C-CH₃), 50.2 (C-1′), 65.7 (C-2′), 163 (C-1), 164 (C-3), 170.8 (C-5). Anal. Calc. for C₇H₁₁N₃O₅: C 38.71, H 5.11, N 19.35; found: C 38.70, H 5.13, N 19.33. m/z 217 (M⁺).

1-(5-amino-2-methyl-1H-imidazol-1-yl)propan-2-ol (6): Yield: 24%; HRMS calcd. for (M⁺) C₇H₁₃N₃O₄ 155.1998, found 155.1985; IR(KBr): 1370, 1400, 1430, 1520, 1615, 3350-3400, 3438-3462 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.18 (d, 3H, H-3′), 2.51 (s, 3H, H-2), 3.4 (m, 1H, H-2′), 3.58 (brs, 1H, OH), 4.00;3.75 (d, 2H, H-1′), 6.98 (s, 1H, H-4), 7.74 (s, 2H, NH₂); ¹³C-NMR (CDCl₃) δ 13.9 (C-CH₃), 28.0 (C-3′), 51.1 (C-1′), 68.3 (C-2′), 120.2 (C-4), 141.9 (C-5), 143.0 (C-2). Anal. Calc. for C₇H₁₃N₃O₄: C 54.17, H 8.44, N 27.08; found: C 54.19, H 8.47, N 27.06. m/z 155 (M⁺).

Result and discussion

Irradiation with u.v light of SCZ (1) in oxygen free neutral aqueous solution results in rearrangement to an intermediate believed to be the 4-hydroxyimino-5-ketone detectable by h.p.l.c analysis. The formation of ketone (2) is suggested to occur via a nitro to nitrite rearrangement by analogy to the postulated mechanism of u.v-induced rearrangement of 9-nitroanthracene, 2-nitofuran and 2-nitopyrrole and some α,β-
unsaturated nitroalkanes. The final product isolated from the photolysis mixture in high yield (93\% by h.p.l.c analysis) is a 1,2,4-oxadiazole (3) of same molecular weight as metronidazole. Its formation includes a hydrolytic cleavage of the imidazole ring and recyclization, as shown in Scheme 2A.1. The structure of photoproducts was assigned on the basis of IR, $^1$H-NMR, $^{13}$C-NMR and elemental analysis studies. Comparison with the parent SCZ, showed, in particular, loss of singlet at $\delta$ 7.96 and replacement by a broad, partly resolved triplet centered on $\delta$ 7.78 in (3). The 2-Me signal at $\delta$ 2.52 in (1) was shifted to $\delta$ 2.68 and is assigned to 5-Me, in agreement with the value of $\delta$ 2.7 for the 5-Me in 5-methyl-1,2,4-oxadiazole.

The $^{13}$C-NMR assignment for C-4 and C-5 of 1 became similar to that of the C-2, confirming the complete rearrangement of the imidazole ring. The other significant assignments for (3) indicative of the change in structures are 5-Me (13.5), C=O (157.9), and NCH$_2$ (50.5) corresponding to 2-Me (10.8), C-4 (133.0), and N’CH$_2$ (41.5) of (1).

High resolution e.i.m.s of (3) showed no molecular ion at m/z 185. Major fragments were at m/z 140 (base peak), 128 (47\% of basepeak), 111 (80\%), and 88 (30\%, none of the peak at m/z 139 (loss of NO$_2$) was observed.
Scheme 2A.1
Scheme 2A.2
The photooxygenation of SCZ give exclusively product (4) 2, 4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione and it is assumed that initially formed endoperoxide in this reaction undergoes transformation to the dioxetane intermediate which subsequently fragments to the final product (Scheme 2A.2).

Product 4 showed a broad singlet at δ 2.0 ppm due to protons of –OH group. A sharp singlet at δ 0.9 ppm, logically upfield to the methyl protons at C-3. This is further supported by the $^{13}$C-NMR value of δ 170.8 ppm for the only unsubstituted carbon.

We have investigated the photolysis of secnidazole in the presence of photoelectron donor, N,N-dimethylaniline in dimethylformamide (DMF). Recent reports on metabolic consequences of secnidazole$^{26}$ suggested that the nitro anion radical (5) and amine derivatives thereof are the basic cause of toxicity. This prompted us to study the photoreactivity of secnidazole in a photoelectron transfer (PET) condition (Scheme 2A.3).

Product 6 showed a broad singlet at δ 7.74 ppm due to the –NH$_2$ group protons. A sharp singlet at δ 6.98 was assigned to the only proton present in the imidazole ring. The IR spectra of product 6 show absorption in the region 3350-3400 cm$^{-1}$ which can be attributed to primary NH stretching vibrations.
Scheme 2A.3
The complete reduction of the nitro drug to an amino group requires six electrons per molecule. Theoretically, the reduction can occur in one electron steps. Thus several intermediates are possible, including the nitro anion radical and the nitroso and hydroxylamine derivatives. The nitro anion radical and the hydroxylamine derivative were suggested as the most likely candidates for the toxic intermediates.\textsuperscript{27,28} The probable course of formation of product is shown in Scheme 2A.4. The reduction of nitroimidazole drugs are accompanied by a loss of absorption in the UV region characteristic of the charge transfer band ascribed to the nitro group and an appearance of fluorescence.\textsuperscript{29}
Scheme 2A.4
It was therefore of interest to determine whether other nitroheterocyclic compounds were reduced in mammalian tissues under physiological conditions. Of course all nitroheterocyclic compounds would be expected to be reduced in tissues at rates determined by their one electron reduction potentials, the rates being slower for compounds whose one electron reduction potentials were more negative.\textsuperscript{30} A good deal of indirect evidence points to the importance of nitro group reduction in mediating the biological activity of the nitroimidazoles.

The biological consequences of nitroimidazole anion radical formation is trichomonads are unknown but the known chemistry of the anion free radical\textsuperscript{31} suggests that the reaction of the nitroimidazole radical metabolites may be of toxicological significance. Our results give evidence for the formation of reactive intermediate of nitroimidazole reduction by dimethylaniline.
Section [B]

Bio-Inspired Photochemistry of

Dimetridazole
Dimetridazole (DMZ, 1,2-dimethyl-5-nitroimidazole) is a nitroimidazole drug used in veterinary medicine to control infection of turkey flocks with the protozoal flagellate, which causes histomoniasis (or 'blackhead'), a disease which has been responsible for large losses in the turkey industry. It is also effective against coccidiosis in poultry, and has been used in swine feed for the prevention and treatment of swine dysentery and trichomoniasis. Dimetridazole has been reported to be mutagenic and carcinogenic.\(^{32}\)

Dimetridazole is a 5-nitroimidazole drug, particularly effective in the treatment and prevention of anaerobic microbial human or animal infections. The 5-nitro drugs are prodrugs activated by intracellular reduction of the nitro group, and it is presumed that a short lived reduction product, e.g., the one electron nitro radical anion, is the biologically active species.\(^ {33}\) Although the mechanism of biological activity and cytotoxic action of nitroimidazoles on anaerobic microorganisms is not well understood. It has been correlated to reduction of nitro group. Studies have suggested that the potency of nitro heterocyclic compound depends on the biological system as well as on its properties that determine its one electron reduction potential.\(^ {30}\)

The suggested mechanism for the cytotoxicity of the nitro drugs is that oxygen radicals are responsible for the cytotoxicity in the aerobic cells, and the reduction products of nitro drugs are responsible for the toxicity in the hypoxic cells.\(^{34-36}\)
Experimental

Apparatus

Same as in section [A].

Chemicals

All chemicals used were of analytical grade. Dimetridazole, was obtained from Sigma-Aldrich Chemicals Pvt. Ltd., (New Delhi, India). Melting point, $^1$H-NMR and co-TLC with authentic pure sample determined the purity of dimetridazole.

Irradiation procedure

A solution of DMZ (180 mg) in doubly distilled water was irradiated for 5 hrs. The pH of the irradiation solution was maintained in the range 6-8 by addition of 1M NaOH. It is kept in the dark at $0^\circ$C for 17 hrs so that maximum conversion of intermediate occurred to yield (9). Complete conversion of (7) was monitored by TLC (diethyl ether: methanol: acetic acid; 90:8:2). Removal of water under reduced pressure and column chromatography of resulting photoproducts on silica gel yielded compound (8).

Characterization of products

(E)-4-(hydroxyimino)-1, 2-dimethyl-$^1$H-imidazol-5(4H)-one (8): Yield: 32%, HRMS calcd. for (M$^+$) C$_5$H$_7$N$_3$O$_2$ 141.1296, found 141.1275; IR(KBr): 1605-1425, 1687, 3435-3462 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 0.9 (s, 3H, H-2), 2.0 (br, 1H, OH), 2.74 (s, 3H, H-1); $^{13}$C-NMR (CDCl$_3$) $\delta$ 23.4 (C-CH$_3$), 27.0 (C-1), 163.0 (C-4), 163.2 (C-5), 164 (C-2). Anal. Calc. for C$_5$H$_7$N$_3$O$_2$: C 42.55, H 5.00, N 29.77; found: C 42.53, H 5.02, N 29.76. m/z 141 (M$^+$).
**N, 5-dimethyl-1,2,4-oxadiazole-3-carboxamide (9):** Yield: 30%, HRMS calcd. for (M⁺) C₅H₇N₃O₂ 141.1296, found 141.1274; IR(KBr): 1556, 1587, 1682, 3340 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.35 (s, 3H, H-5), 2.74 (d, 3H, H-8), 8.0 (m, 1H, NH); ¹³C-NMR (CDCl₃) δ 13.5 (C-CH₃), 26.0 (C-8), 158.2 (C-6), 176.7 (C-5). Anal. Calc. for C₅H₇N₃O₂: C 42.55, H 5.00, N 29.77; found: C 42.56, H 5.03, N 29.74. m/z 141 (M⁺).

**(1-methyl-5-nitro-1H-imidazol-2-yl) methanol (10):** Yield: 34%, HRMS calcd. for (M⁺) C₅H₇N₃O₃ 157.129, found 157.112; IR(KBr): 1350, 1427, 1460, 1520, 1617 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.0 (br, s, 1H, OH), 3.63 (s, 3H, H-1), 4.79 (s, 2H, H-2); ¹³C-NMR (CDCl₃) δ 21.3 (C-1), 51.4 (C-CH₂), 128.4 (C-4), 141.1 (C-5), 158.1 (C-2). Anal. Calc. for C₅H₇N₃O₃: C 38.22, H 4.49, N 26.74; found: C 38.20, H 4.46, N 26.73. m/z 157.

**2, 4-(N-methyl) diaza-3-methyl-1-nitro-1, 5-dione (11):** Yield: 36%, HRMS calcd. for (M⁺) C₅H₇N₃O₄ 173.1284, found 173.1270; IR(KBr): 1372, 1552, 1633, 1686, 1718 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.9 (s, 3H, H-3), 2.74 (s, 3H, H-2), 9.6 (s, 1H, H-5); ¹³C-NMR (CDCl₃) δ 21.9 (C-CH₃), 29.7 (N-CH₃), 164 (C-1), 164 (C-3), 170.8 (C-5). Anal. Calc. for C₅H₇N₃O₄: C 34.69, H 4.08, N 24.27; found: C 34.67, H 4.07, N 24.29. m/z 173 (M⁺).

**1, 2-dimethyl-1H-imidazol-5-amine (12):** Yield: 28%, HRMS calcd. for (M⁺) C₅H₉N₃ 111.1466, found 111.1446; IR(KBr): 1237, 1300, 1372, 1393, 1452, 1532, 1592,1653, 3100 and 3382 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.42 (s, 3H, H-2), 3.63 (s, 3H, H-1), 4.0 (s, 2H, NH₂), 6.8 (s, 1H, H-4); ¹³C-NMR (CDCl₃) δ 11.5 (C-CH₃), 20.5 (C-1), 123 (C-4),
126 (C-5), 141.8 (C-2). Anal. Calc. for C₅H₉N₃: C 54.03, H 8.16, N 37.81; found: C 54.05, H 8.14, N 37.82. m/z 111 (M⁺).

**Result and discussion**

Irradiation with u.v light of DMZ (7) in oxygen free neutral aqueous solution results in rearrangement to an intermediate believed to be the 4-hydroxyimino-5-ketone detectable by h.p.l.c analysis. The formation of ketone (8) is suggested to occur via a nitro to nitrite rearrangement by analogy to the postulated mechanism of u.v-induced rearrangement of 9-nitroanthracene, 2-nitrofuran and 2-nitropyrrrole and some α,β-unsaturated nitroalkanes. The final product isolated from the photolysis mixture in high yield (92% by h.p.l.c analysis) 1, 2, 4-oxadiazole (9) of same molecular weight as dimetridazole. Its formation includes a hydrolytic cleavage of the imidazole ring and recyclization, as shown in scheme 2B.5. The structure of photoproduts was assigned on the basis of IR, ¹H-NMR, ¹³C-NMR and elemental analysis studies. Comparison with the parent DMZ, showed, in particular, loss of singlet at δ 7.94 and replacement by δ 7.76 in (9). The 2-Me signal at δ 2.42 in (7) was shifted to δ 2.35 and is assigned to 5-Me, in agreement with the value of δ 2.7 for the 5-Me in 5-methyl-1, 2, 4-oxadiazole.

The ¹³C-NMR assignments for C-4 and C-5 of 7 became similar to that of the C-2, confirming the complete rearrangement of the imidazole ring. The other significant assignments for (9) indicative of the change in structure are 5-Me (13.5), C=O (158.2), and N-CH₃ (26.0) corresponding to 2-Me (10.5), C-4 (128.6), and NCH₃ (21.0) of (7).
Scheme 2B.5
The photooxegenation of DMZ give exclusively product 2, 4-(N-methyl) diaza-3-methyl-1-nitro-1, 5-dione (11) and (1-methyl-5-nitro-1H-imidazol-2-yl) methanol (10) and it is assumed that initially formed endoperoxide in this reaction undergoes transformation to the dioxetane intermediate which subsequently fragments to the final product. The product (1-methyl-5-nitro-1H-imidazol-2-yl) methanol (10) is also formed on the oxidation of dimetridazole. Thus, the main metabolite of DMZ results from oxidation of the side chain in the C-2 position of the imidazole ring. The mass spectra of product (10) and dimetridazole show similar fragmentation patterns. Both show losses of NO\textsubscript{2} from their protonated molecular ion and ring cleavage to yield an ion consistent with the formula C\textsubscript{3}H\textsubscript{5}N. The DMZ-OH spectrum demonstrates additional losses of H\textsubscript{2}O and hydrogen. The protonated molecular ion is present at m/z 158. The base peak is the ion at m/z 140 and is postulated to result from the loss of H\textsubscript{2}O from the alcohol functionality. The loss of NO\textsubscript{2} (m/z, 46) from the protonated molecular ion forms the ion at m/z 112. The loss of two hydrogen atoms from the ion at m/z 112 accounts for the ion at m/z 110. The ion at m/z 55 emanates from a ring cleavage of the nitroimidazole to yield a fragment ion C\textsubscript{3}H\textsubscript{5}N. The protonated molecular ion and base peak at m/z 142 loss NO\textsubscript{2} to form the ion at m/z 96. As postulated for the metabolite spectra the ion observed at 55 (C\textsubscript{3}H\textsubscript{5}N) formed from the imidazole ring cleavage (Scheme 2B.6).
Scheme 2B.6
We have investigated the photolysis of dimetridazole in the presence of photoelectron donor, N,N-dimethylaniline in dimethylformamide (DMF). Recent reports on metabolic consequences of dimetridazole suggested that the nitro anion radical (13) and amine derivatives thereof are the basic cause of toxicity. We have recently demonstrated the biologically significant photochemistry of secnidazole in relation to its cytotoxic activity. In continuation of our interest in bio-inspired photochemistry we now report photoreactivity of dimetridazole in a photoelectron transfer (PET) condition (Scheme 2B.7).
Scheme 2B.7
The complete reduction of the nitro drug to an amino group requires six electrons per molecule. Theoretically, the reduction can occur in one electron steps. Thus several intermediates are possible, including the nitro anion radical and the nitroso and hydroxylamine derivatives. The nitro anion radical and the hydroxylamine derivative were suggested as the most likely candidates for the toxic intermediates.\textsuperscript{27,28} The probable course of formation of product is shown in Scheme 2B.8. Our results give evidence for the formation of reactive intermediates of nitroimidazole reduction by dimethylaniline.
Scheme 2B.8
References


21. Silvia N. J. Moreno and Roberto Docampo. Environmental Health Perspectives, 1985, 64, 199.


