Photolytic Rearrangement of Metronidazole to *N*-(2-Hydroxyethyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide. Crystal Structure of its 4-Nitrobenzoate Derivative

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U.v. irradiation of metronidazole (1-hydroxyethyl-2-methyl-5-nitroimidazole) in oxygen-free aqueous solution leads to rearrangement *via* a labile intermediate to *N*-(2-hydroxyethyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide. The structure has been verified by crystallographic assignment of a 4-nitrobenzoate derivative.

Metronidazole (1-hydroxyethyl-2-methyl-5-nitroimidazole), an antibacterial drug with activity against anaerobic infection,[1] is also effective as a γ-radiation sensitizer of hypoxic cells in cancer radiotherapy.[2] The possibility that toxic intermediates are formed on metabolism or radiolysis has stimulated the effort to define the products of chemical, metabolic, and radiolytic reduction of metronidazole and related compounds.[3–7] The detection, by electron spin resonance spectroscopy, of the nitro radical anion of metronidazole and misonidazole following pulse radiolysis,[8] metabolism with intact *Tritrichomonas foetus* cells,[9] and u.v. photolysis in a reducing environment,[10] suggests that similar products may ensue from each process. The radiolytic reduction of 2-nitroimidazoles was believed to lead to an aminoimidazole, whereas the N^1-alkyl-5-nitroimidazoles gave unstable intermediary products.[4]

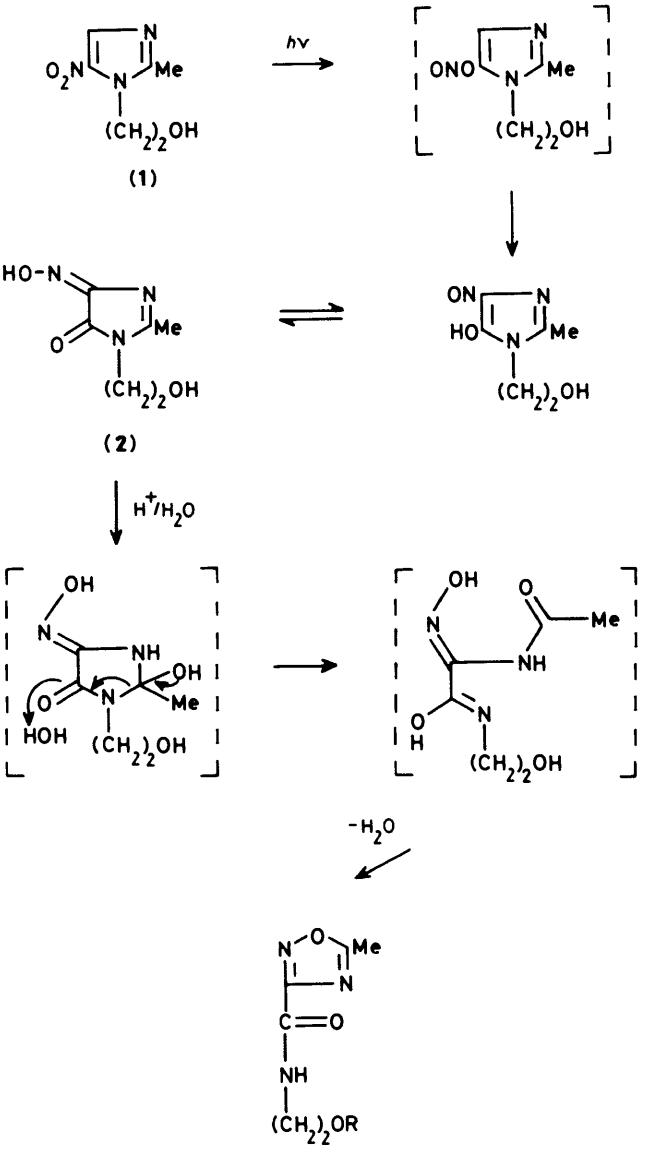
Electrolytic reduction has been used in an attempt to generate the transient products at controlled rates, but a multiplicity of products was obtained.[5] Photolytic reaction has provided a less complex sequence of reactions with a better possibility of obtaining suitable quantities of the major products for identification purposes.

Results and Discussion

Irradiation with u.v. light of metronidazole (**1**) in oxygen-free neutral aqueous solution results in rearrangement to an intermediate believed to be the 4-hydroxyimino 5-ketone (**2**) detectable by h.p.l.c. analysis, but both thermally and photochemically labile. The formation of the 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,[11] 2-nitrofuran and 2-nitropyrrole,[12] and some α,β unsaturated nitroalkanes.[13]

The final product isolated from the photolysis mixture in high yield (>90% by h.p.l.c. analysis) is a 1,2,4-oxadiazole (**3**) of the same molecular weight as metronidazole. Its formation is envisaged as following hydrolytic cleavage of the imidazole ring and re-cyclization, as shown in the Scheme. A similar reaction has been reported[14] for 4-nitrosoimidazoles, the tautomeric form of the hydroxy imine.

To a very minor extent (<5%), an alternative reaction involving loss of the nitro group was suggested by the detection of small amounts of nitrite ion in the photolysis mixture, also observed by others in radiolytic and photolytic degradation of (**1**).[5,6] H.p.l.c. analysis of the photolysis mixture sampled at various times verified the initial formation of compound (**2**), and its subsequent degradation coincident with the appearance of compound (**3**). The maximum yield of (**2**) was observed when



Scheme.

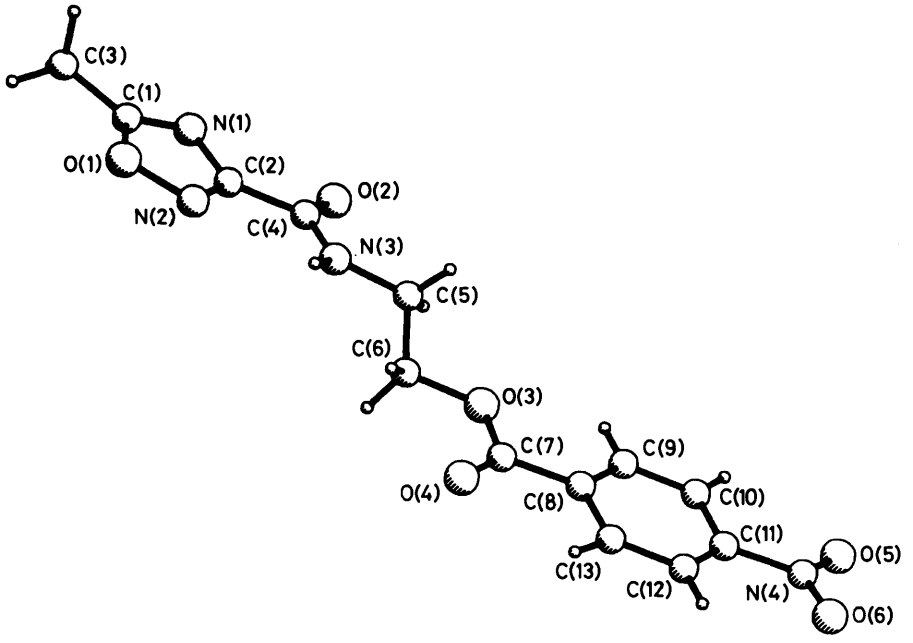


Figure. Perspective diagram of structure of compound (**4**) showing atom numbering

the pH of the irradiation solution was maintained in the range 7—8 by the addition of 1M NaOH. Otherwise, the acidity of the solution increased in the course of the photolysis, thereby accelerating the further reaction of (**2**). Attempts to separate a pure sample of the intermediate for characterization have been unsuccessful owing to its facile breakdown to (**3**).

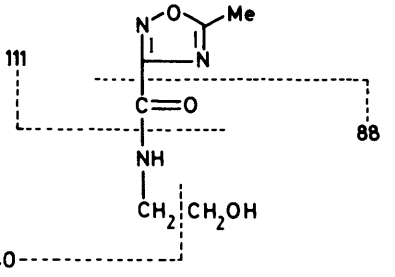
Essentially pure product (**3**) was isolated from the photolysis mixture after almost complete conversion of metronidazole (**1**), and the structure of (**3**) was established by a single crystal *X*-ray diffraction analysis of its 4-nitrobenzoate derivative (**4**), the molecular structure of which is illustrated in the Figure.

The crystal structure consists of independent, rather planar molecules linked by weak Van der Waals forces. The final atomic co-ordinates, selected bond lengths, interbond angles, and dihedral angles, are given in Tables 1—3, and mean planes, thermal parameters, remaining bond lengths and angles are given in Tables 4—6 in the Supplementary material.* The geometry of the 1,2,4-oxadiazole ring is similar to that found by *X*-ray crystallographic analysis of 5-phenyl-1,2,4-oxadiazole-3-carboxamide,[15] 2-amino-3-(5-methyl-1,2,4-oxadiazole-3-yl)-pyridine[16] and *N*,1-bis[5-(3-phenyl)-1,2,4-oxadiazolyl]dimethylamine.[17]

Support for the above structure came from ^1H and ^{13}C n.m.r. spectroscopy. Comparison with the parent metronidazole, showed, in particular, loss of the singlet at δ 7.96, and replacement by a broad, partly resolved triplet centred on δ 7.78, in (**3**) and a weak broad signal at δ 7.32 in (**4**), assigned to the amide proton in the side chain of the oxadiazole. The 2-Me signal at δ 2.52 in (**1**) was shifted to δ 2.68 in both (**3**) and (**4**) 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.[18]

The ^{13}C n.m.r. assignments for C-4 and C-5 of (**1**)[19] 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 structure are 5-Me (12.8), C=O (179.5), and NCH_2 (43.1) corresponding to 2-Me (14.8), C-4 (133.0), and N^1CH_2 (49.8) of (**1**).

High resolution e.i.m.s. of (**3**) showed no molecular ion at *m/z* 171. Major fragments were at *m/z* 140 (base peak), 128 (47% of base peak), 111 (85%), and 88 (30%), suggesting the following fragmentation scheme:



The $M - 46$ (loss of NO_2) peak characteristic of the parent metronidazole was not observed.

The identification of the oxadiazole as the major photoproduct from metronidazole may lead to a better understanding of the mechanism of its metabolism. The reaction mechanism proposed here does not involve the complete reduction of (**1**) to an aminoimidazole as has been suggested as the metabolic pathway.[7] Attempts to identify products from the action of xanthine oxidase or bacterial flora accounted for less than 20% of the original metronidazole. In none of the identified products was the imidazole ring intact, the products being principally aminoethanol, glycine, acetamide, and *N*-(2-hydroxyethyl)-oxamic acid.[7] Similar products and yields were found after electrolytic reduction of (**1**).[5] Such products may arise equally well through an oxadiazole intermediate as *via* an aminoimidazole. In particular, formation of aminoethanol in high yield is possible as a product of enzymatic hydrolysis of the side chain of the oxadiazole than by cleavage of the imidazole ring.

It is possible that the 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.[18] However, the major interest is in the labile intermediate species (**2**) and efforts are now being directed towards its isolation in a stable form for unequivocal identification.

* This is available on request from the Cambridge Crystallographic Data Centre. For details see Instructions for Authors (1987), section 5.6.3, *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

Table 1. Final fractional atomic co-ordinates for compound (**4**)

Atom	*x*	*y*	*z*
O(1)	0.837 9(7)	0.340 15(15)	1.027 7(5)
O(2)	0.744 8(8)	0.445 95(15)	0.644 4(5)
O(3)	0.059 2(7)	0.551 76(15)	0.715 6(5)
O(4)	−0.174 0(8)	0.558 50(15)	0.892 5(5)
O(5)	−0.569 7(8)	0.726 25(16)	0.268 9(6)
O(6)	−0.829 4(9)	0.729 22(16)	0.417 3(6)
N(1)	0.963 9(9)	0.366 29(18)	0.823 0(6)
N(2)	0.678 8(9)	0.376 92(18)	0.964 4(6)
N(3)	0.442 1(10)	0.447 45(20)	0.780 1(6)
N(4)	−0.645 2(10)	0.713 19(19)	0.383 4(7)
C(1)	1.001 0(11)	0.336 17(24)	0.935 8(8)
C(2)	0.765 1(11)	0.391 04(21)	0.846 9(7)
C(3)	1.181 0(14)	0.297 74(27)	0.970 0(10)
C(4)	0.646 0(12)	0.430 83(24)	0.745 5(7)
C(5)	0.305 6(15)	0.485 54(29)	0.695 3(9)
C(6)	0.202 7(15)	0.515 08(28)	0.806 9(8)
C(7)	−0.122 5(12)	0.570 21(23)	0.772 4(7)
C(8)	−0.255 6(11)	0.607 43(21)	0.666 5(7)
C(9)	−0.181 1(12)	0.621 89(24)	0.533 7(8)
C(10)	−0.306 6(12)	0.657 01(24)	0.441 5(8)
C(11)	−0.502 3(11)	0.677 27(21)	0.486 6(7)
C(12)	−0.580 1(13)	0.664 06(24)	0.615 9(8)
C(13)	−0.453 4(12)	0.628 78(25)	0.708 1(8)
H(3N)	0.360(10)	0.431 9(20)	0.846(6)
H(3A)	1.217(9)	0.287 8(18)	1.085(7)
H(3B)	1.112(12)	0.268 2(25)	0.911(8)
H(3C)	1.324(11)	0.307 2(20)	0.953(7)
H(5A)	0.168(12)	0.477 7(22)	0.614(7)
H(5B)	0.399(9)	0.506 4(18)	0.653(5)
H(6A)	0.105(9)	0.497 1(19)	0.865(5)
H(6B)	0.335(10)	0.529 6(19)	0.892(6)
H(9)	−0.051(8)	0.609 1(17)	0.502(5)
H(10)	−0.260(9)	0.666 3(17)	0.354(5)
H(12)	−0.718(9)	0.676 9(16)	0.647(5)
H(13)	−0.490(7)	0.616 9(15)	0.804(5)

Table 2. Bond lengths (Å) and angles (°) for compound (**4**)

Atoms	Distance	Atoms	Distance
O(1)–N(2)	1.400(6)	O(1)–C(1)	1.350(6)
O(2)–C(4)	1.223(6)	O(3)–C(6)	1.439(8)
O(3)–C(7)	1.334(7)	O(4)–C(7)	1.199(6)
O(5)–N(4)	1.230(6)	O(6)–N(4)	1.221(6)
N(1)–C(1)	1.288(7)	N(1)–C(2)	1.369(7)
N(2)–C(2)	1.296(7)	N(3)–C(4)	1.329(7)
N(3)–C(5)	1.430(8)	N(4)–C(11)	1.471(8)
C(1)–C(3)	1.468(9)	C(2)–C(4)	1.496(8)
C(5)–C(6)	1.499(9)	C(7)–C(8)	1.488(8)
C(8)–C(9)	1.384(8)	C(8)–C(13)	1.379(8)
C(9)–C(10)	1.371(8)	C(10)–C(11)	1.370(8)
C(11)–C(12)	1.355(8)	C(12)–C(13)	1.377(9)

Atoms	Angle (°)
C(1)–O(1)–N(2)	106.2(4)
C(2)–N(1)–C(1)	102.6(5)
C(5)–N(3)–C(4)	122.1(6)
C(11)–N(4)–O(5)	118.2(6)
N(1)–C(1)–O(1)	112.9(6)
C(3)–C(1)–N(1)	129.3(6)
C(4)–C(2)–N(1)	124.2(5)
N(3)–C(4)–O(2)	126.2(6)
C(2)–C(4)–N(3)	114.8(5)
C(5)–C(6)–O(3)	107.0(5)
C(8)–C(7)–O(3)	111.2(5)
C(9)–C(8)–C(7)	122.1(6)
C(13)–C(8)–C(9)	120.3(6)
C(11)–C(10)–C(9)	118.0(6)
C(12)–C(11)–N(4)	118.3(6)
C(13)–C(12)–C(11)	118.2(6)
C(7)–O(3)–C(6)	116.8(5)
C(2)–N(2)–O(1)	103.2(5)
O(6)–N(4)–O(5)	123.4(6)
C(11)–N(4)–O(6)	118.5(6)
C(3)–C(1)–O(1)	117.6(6)
N(2)–C(2)–N(1)	115.1(5)
C(4)–C(2)–N(2)	120.7(5)
C(2)–C(4)–O(2)	118.9(6)
C(6)–C(5)–N(3)	108.9(6)
O(4)–C(7)–O(3)	124.9(6)
C(8)–C(7)–O(4)	123.9(6)
C(13)–C(8)–C(7)	117.6(6)
C(10)–C(9)–C(8)	120.0(6)
C(10)–C(11)–N(4)	118.0(6)
C(12)–C(11)–C(10)	123.6(6)
C(12)–C(13)–C(8)	120.0(6)

Experimental

Photolyses were carried out at 25 °C in a Hanovia 1 l photochemical reactor fitted with a 125W medium-pressure mercury arc surrounded by a water-cooled quartz jacket. Oxygen-free nitrogen was bubbled through the solution for 1 h prior to and during the irradiation. Samples were withdrawn at various times and the progress of the reaction monitored by u.v. spectrometry at 320 nm or by h.p.l.c. with a Brownless RP8 reverse phase column and mobile phase of 5mM KH_2PO_4, methanol and tetrahydrofuran (80:19:1). An Altex model 330 isocratic system with fixed wavelength 254 nm detector was used.

U.v. spectra were recorded on a Perkin-Elmer Lambda 5 spectrophotometer, n.m.r. spectra on a JEOL FX90Q spectrometer, and chemical ionization mass spectra on a Finnigan 3200 Quadrupole mass spectrometer.

Photolysis of Metronidazole.—A solution of metronidazole (May and Baker, Melbourne; 100 mg) in doubly distilled water (1 l) was irradiated until h.p.l.c. showed that 85% reaction had occurred (2 h). Before water removal by distillation under reduced pressure, the photolysed solution was stored in the dark at 0 °C for 12 h during which time the intermediate compound decayed to maximise the yield of (**3**). Preparative t.l.c. of the residue on two 20 × 20 cm silica plates with diethyl ether–methanol–acetic acid (89:8:3) afforded clear separation of (**3**) (R_F 0.6) from unchanged (**1**) (R_F 0.8) and more polar material (R_F 0—0.4). The band containing (**3**) was extracted with diethyl ether–methanol (9:1) and after filtration and evaporation, the residue (33 mg) showed one h.p.l.c. peak. Crystallization was possible from tetrahydrofuran at −20 °C, but melting occurred at room temperature. Spectroscopic data was obtained on the non-crystalline product: *N*-(2-hydroxyethyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide $\lambda_{max.}$ 203 nm, ε 3 100 $dm^3\ mol^{-1}\ cm^{-1}$ in MeOH and 3 330 $dm^3\ mol^{-1}\ cm^{-1}$ in 0.1M H_2SO_4; $\nu_{max.}$($CHCl_3$) 1 692, 1 590, and 1 555 cm^{-1}; δ_H (90 MHz; $CDCl_3$; standard Me_4Si) 2.68 (3 H, s, 5-Me), 3.6 (1 H, br, OH), 3.64 (2 H, t, CH_2), 3.78 (2 H, t, CH_2), and 7.78 (1 H, br, NH); δ_C (22.5 MHz; $CDCl_3$; standard CD_3OD 49.5 p.p.m.) 12.8 (5-Me), 158.6 (C-5), 164.7 (C-3), 179.5 (C=O), 43.1 (α-CH_2), and 61.3 (β-CH_2).

4-*Nitrobenzoate-oxadiazole Derivative* (**4**).—The photoproduct (**3**) (46 mg) was dissolved in anhydrous pyridine (1 ml) with 4-nitrobenzoyl chloride (0.2 g), and then warmed to 60 °C for 10 min before the addition of cold water (10 ml). The precipitate was washed with cold 5% aqueous Na_2CO_3 filtered, and recrystallised from ethanol. The best crystals for *X*-ray crystallography were obtained by slow cooling of a hot

Table 3. Selected dihedral angles[a] for compound (**4**)

Atoms	Angle (°)
C(1)–O(1)–N(2)–C(2)	−1.2
N(2)–O(1)–C(1)–C(3)	−176.0
C(6)–O(3)–C(7)–O(4)	0.0
C(2)–N(1)–C(1)–O(1)	0.5
C(1)–N(1)–C(2)–N(2)	−1.4
O(1)–N(2)–C(2)–N(1)	1.6
C(5)–N(3)–C(4)–O(2)	2.3
C(4)–N(3)–C(5)–C(6)	−144.4
N(1)–C(2)–C(4)–N(3)	174.3
N(2)–C(2)–C(4)–N(3)	−4.1
O(3)–C(7)–C(8)–C(9)	−4.2
O(4)–C(7)–C(8)–C(9)	176.0
N(2)–O(1)–C(1)–N(1)	0.4
C(7)–O(3)–C(6)–C(5)	154.2
C(6)–O(3)–C(7)–C(8)	−179.8
C(1)–N(1)–C(2)–C(4)	−179.8
C(5)–N(3)–C(4)–C(2)	179.8
O(5)–N(4)–C(11)–C(10)	−6.2
O(6)–N(4)–C(11)–C(10)	175.3
N(1)–C(2)–C(4)–O(2)	−8.0
N(3)–C(5)–C(6)–O(3)	−177.8

[a] The angle is positive for A–B–C–D if a clockwise rotation of bond A–B causes it to eclipse C–D, when looking down B–C.

ethanolic solution in a Dewar flask over 2 days. 5-Methyl-*N*-[2-(*p*-nitrobenzoyloxy)ethyl]-1,2,4-oxadiazole-3-carboxamide; m.p. 143—144 °C (Found: C, 48.55; H, 3.85; N, 17.60. $C_{13}H_{12}N_4O_6$ requires C, 48.75; H, 3.78; N, 17.50%); $\lambda_{max.}$ (EtOH) 204 nm, ε 15 300 and 257 nm ε 1 250; δ_H (90 MHz; $CDCl_3$; Me_4Si standard) 2.68 (3 H, s, 5-Me), 3.84 (2 H, t, CH_2), 4.59 (2 H, t, CH_2), 7.32 (1 H, br, NH), and 8.28 (4 H, Ph); δ_C (22.5 MHz; solvent $CDCl_3$–CD_3OD, 1:1; standard CD_3OD 49.5 p.p.m.) 12.8 (5-Me), 157.0 (C-5), 164.3 (C-3), 179.3 (C=O), 39.5 (α-CH_2), 65.1 (β-CH_2), 165.9 (benzoate C=O), 136.2, 131.8, 124.5, and 151.7 (benzene carbons).

Crystal Data for Compound (**4**).—$C_{13}H_{12}N_4O_6$, M = 320.3, Monoclinic, a 5.574(7), b 28.454(29), c 8.753(7) Å, β 103.34(8), V = 1 350.8(23) Å, D_c (Z = 4) 1.33 g cm^{-3}, F(000) 664, space group $P2_1/c$ by systematic absences. Intensity data were measured by ω scan mode within the range $3 < 2\theta < 45°$ on a Nicolet R3m diffractometer using graphite-monochromatized molybdenum radiation (λ = 0.7107 Å) at −120 °C. There was no crystal decomposition. Of the 1 879 unique reflections (including standards) collected (h, k, $\pm l$), 901 were deemed observed [$I \geqslant 3\sigma(I)$].

Solution and Refinement of Structure.—The structure was solved by direct methods[20] and difference Fourier syntheses.[21] All non-hydrogen atoms were refined with anisotropic, and all hydrogen atoms with isotropic thermal parameters. The quantity minimized in full matrix least-squares refinement was $\Sigma w\Delta^2$, where $\Delta = |F_o| - |F_c|$, F_o and F_c are the observed and calculated structure factors respectively and $w = [\sigma(F_o)^2 + 0.0004\ (F_o)^2]^{-1}$. The scattering curves for neutral N, C and O were taken from ref. 22 and those for hydrogen from ref. 23. The final residuals R, R_w were 0.051, 0.054 where $R = \Sigma\Delta/\Sigma|F_o|$, $R_w = (\Sigma w\Delta^2/\Sigma w|F_o|^2)^{\frac{1}{2}}$. Refinement was carried out using program SHELX.[21]

Acknowledgements

Dr. H. T. A. Cheung is thanked for assistance in interpretation of the n.m.r. data.

Note added in proof. The photochemical rearrangement of *N*-substituted 2-methyl-5-nitroimidazoles to 5-methyl-1,2,4-oxadiazole-3-carboxamides has recently been confirmed by *X*-ray analysis of the *N*-methyl derivative (K.-H. Pfoertner and J. J. Daly, *Helv. Chim. Acta*, 1987, **70**, 171.)

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Received 18*th August* 1986; *Paper* 6/1683