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2-(2-Methyl-5-nitro-1-imidazolyl)ethanol (Metronidazole)

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Abstract. $C_6H_9N_3O_3$, M_r = 171·16, m.p. = 432–435 K, monoclinic, $P2_1/c$, a = 7·034 (2), b = 8·725 (3), c = 12·818 (3) Å, β = 94·51 (2)°, V = 784·2 $Å^3$, D_m = 1·44 (by flotation), D_c = 1·48 Mg m^{-3} for Z = 4, $F(000)$ = 360·0, Mo $K\alpha$ radiation (λ = 0·71069 Å, μ = 0·126 mm^{-1}), crystal size 0·3 × 0·3 × 0·4 mm. The structure was solved by direct methods and refined to an R of 0·035 for 1211 independent reflections with $I > 2\sigma(I)$. The intramolecular bond lengths and bond angles are comparable with the values found in other nitro-substituted compounds. The C(5)—NO_2 group is planar and makes an angle of 4·3° with the imidazole plane. There is one intermolecular hydrogen bond linking the imidazole nitrogen N(3) and the alcoholic oxygen.

Introduction. The structure of metronidazole has been determined as part of an investigation on the structure–activity relationship of 5-nitro-substituted imidazole derivatives. These compounds display a marked activity against both anaerobic protozoa and bacteria.

Metronidazole crystals were supplied by SPECIA (Paris). A set of Weissenberg photographs showed that $h0l$, $l = 2n + 1$ and $0k0$, $k = 2n + 1$ reflections are systematically absent indicating the space group $P2_1/c$. The lattice parameters were calculated by least-squares refinement of the setting angles of 24 reflections using a Syntex $P2_1$ diffractometer and graphite-monochromatized Mo $K\alpha$ radiation. The density was determined by flotation in a mixture of CCl_4 and benzene.

Using the ω-scan technique a total of 2772 reflections in four octants of reciprocal space were measured up to a 2θ value of 50°. After averaging for monoclinic symmetry the set reduced to 1492 reflections, of which 1211 were considered as observed $[I_o > 2\sigma(I_o)]$. The data were corrected for Lorentz and polarization effects but not for absorption.

The scattering factor for H was taken from Stewart, Davidson & Simpson (1965) and those for the other atoms from Cromer & Mann (1968). The structure was solved by direct methods using the programs *SINGEN* and *PHASE* of the XRAY 76 system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Block-diagonal least-squares refinement (including isotropic H atoms) converged at R = 3·5%. A final difference Fourier synthesis indicated no electron density greater than 0·16 e $Å^{-3}$.

The molecular structure is illustrated in Fig. 1 and the atomic coordinates are given in Table 1.†

Discussion. The intramolecular bond lengths shown in Table 2 are calculated from the final atomic coordinates and have not been corrected for thermal motion. The average estimated errors for distances between non-hydrogen atoms are of the order of 0·002 Å; with H atoms included they become ±0·02 Å.

Table 1. *Positional parameters* (×10^4; *for* H ×10^3) *and equivalent isotropic thermal parameters* B_{eq} ($Å^2$) *with e.s.d.'s in parentheses*

	x	y	z	B_{eq} ($Å^2$)
N(1)	2869 (2)	4161 (2)	880 (1)	2·68 (3)
C(2)	2170 (2)	2910 (2)	360 (1)	3·06 (4)
N(3)	1562 (2)	3245 (2)	−625 (1)	3·40 (4)
C(4)	1894 (2)	4765 (2)	−749 (1)	3·16 (4)
C(5)	2692 (2)	5348 (2)	164 (1)	2·69 (4)
N(6)	3227 (2)	6888 (2)	366 (1)	3·56 (4)
O(7)	3066 (2)	7772 (2)	−379 (1)	5·75 (5)
O(8)	3827 (2)	7277 (2)	1247 (1)	5·54 (5)
C(9)	2104 (3)	1358 (2)	820 (2)	4·77 (6)
C(10)	3673 (3)	4190 (2)	1978 (1)	3·44 (5)
C(11)	2254 (3)	4756 (2)	2718 (1)	3·91 (5)
O(12)	631 (2)	3796 (2)	2710 (1)	4·20 (4)
H(4)	156 (2)	532 (2)	−137 (1)	3·8 (4)
H(9*a*)	132 (3)	132 (3)	143 (2)	3·9 (4)
H(9*b*)	336 (3)	98 (3)	98 (2)	4·0 (4)
H(9*c*)	152 (3)	68 (3)	33 (2)	4·4 (4)
H(10*a*)	485 (2)	482 (2)	201 (1)	4·4 (4)
H(10*b*)	406 (2)	312 (2)	213 (1)	8·0 (6)
H(11*a*)	180 (2)	580 (2)	253 (1)	7·9 (6)
H(11*b*)	297 (2)	480 (2)	341 (1)	8·0 (6)
H(12)	76 (3)	315 (2)	320 (2)	6·0 (5)

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† Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34596 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The bond lengths in the heterocyclic five-membered ring are comparable with the values found by neutron diffraction for pure imidazole (Craven, McMullan, Bell & Freeman, 1977). The exocyclic C–C, N–C and C–O distances are reasonable.

The lengths of the $C(5)_{sp^2}$–$N(6)_{sp^2}$ (1·414 Å) bond and the two N–O bonds (1·226 and 1·221 Å) of the nitro group agree very well with those observed in other nitro-substituted compounds such as carnidazole (Blaton, Peeters & De Ranter, 1979) and sulnidazole (Germain, Declercq, Van Meerssche & Koch, 1977). The average estimated error for the bond angles is 0·1°. The average value around C_{sp^3} is 109·4°.

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

1	1·351 (2)	8	1·221 (2)	15	0·95 (2)
2	1·334 (2)	9	1·479 (3)	16	0·93 (2)
3	1·359 (2)	10	1·475 (2)	17	0·99 (2)
4	1·356 (2)	11	1·510 (2)	18	0·99 (2)
5	1·383 (2)	12	1·410 (2)	19	0·99 (2)
6	1·414 (2)	13	0·94 (2)	20	1·00 (2)
7	1·226 (2)	14	0·99 (2)	21	0·84 (2)
1–2	111·5 (1)	5–6	125·5 (1)	11–17	112 (1)
1–5	105·5 (1)	5–10	128·9 (1)	11–18	111 (1)
1–9	124·4 (1)	6–7	116·6 (1)	11–19	111 (1)
1–10	125·5 (1)	6–8	120·0 (1)	11–20	105 (1)
2–3	106·2 (1)	7–8	123·3 (1)	12–19	107 (1)
2–9	124·0 (2)	9–14	112 (1)	12–20	113 (1)
3–4	109·1 (1)	9–15	110 (1)	12–21	110 (1)
3–13	125 (1)	9–16	110 (1)	14–15	113 (2)
4–5	107·6 (1)	10–11	112·4 (1)	14–16	105 (2)
4–6	126·9 (1)	10–17	108 (1)	15–16	106 (2)
4–13	126 (1)	10–18	105 (1)	17–18	107 (1)
		11–12	112·4 (1)	19–20	108 (1)

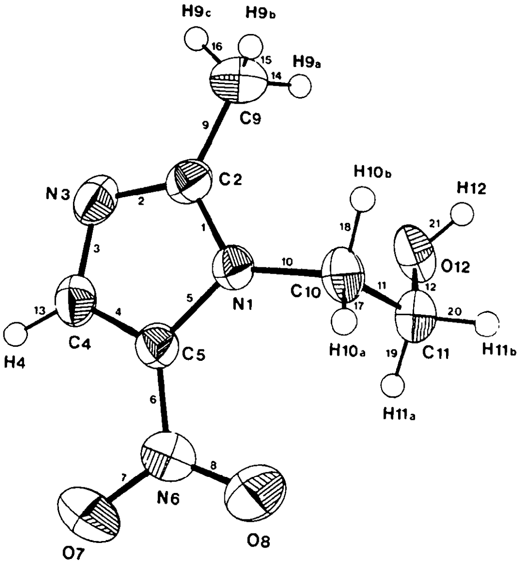

Fig. 1. An *ORTEP* plot (Johnson, 1976) of the title compound. The thermal ellipsoids are plotted at the 50% probability level. Hydrogen atoms are represented by spheres of arbitrary radius.

The coordinates of the plane passing through the imidazole ring and the deviations of the respective atoms from that plane are listed in Table 3. The three atoms in the first neighbourhood of the imidazole ring [C(6), C(9), C(10)] are only slightly displaced from the plane. The C(5)–NO_2 group is planar and makes an angle of 4·3° with the imidazole plane. Torsion angles of the side chain are given in Table 4.

Each molecule forms a hydrogen bond with a symmetrically related neighbour [O(12)–H(12)···N(3)′:O(12)–N(3)′ = 2·816 (2) Å, H(12)···N(3)′ = 1·98 (2) Å, ∠O(12)–H(12)···N(3)′ = 169 (2)°]. The geometry of this hydrogen bond is represented in Fig. 2 which illustrates the crystal packing. (The primed atoms have the symmetry position $x, \frac{1}{2} - y, \frac{1}{2} + z$.)

The intermolecular contact distances almost coincide with the sum of the van der Waals radii of the corresponding atoms. Exceptions occur for the contact

Table 3. *Deviations* (Å) *of atoms from the least-squares plane expressed in the form* $AX + BY + CZ + D = 0$ *where* X, Y, Z *are the coordinates referred to the axes* a, b, *and* c *respectively*

E.s.d.'s for the non-hydrogen atoms are in the range 0·001–0·003 Å.

$$6{\cdot}5801X - 1{\cdot}7938Y - 4{\cdot}6152Z - 0{\cdot}7364 = 0$$

N(1)	−0·002*	N(5)	−0·018
C(2)	0·002*	O(7)	0·062
N(3)	0·002*	O(8)	−0·099
C(4)	0·001*	C(9)	0·026
C(5)	0·000*	C(10)	0·017
		H(4)	−0·04 (2)

* Atoms used to define the least-squares plane.

Table 4. *Torsion angles of the side chain* (°)

O(7)–N(6)–C(5)–N(1)	176·1 (2)
O(8)–N(6)–C(5)–N(1)	−3·4 (3)
C(5)–N(1)–C(10)–C(11)	82·6 (2)
N(1)–C(10)–C(11)–O(12)	61·2 (2)

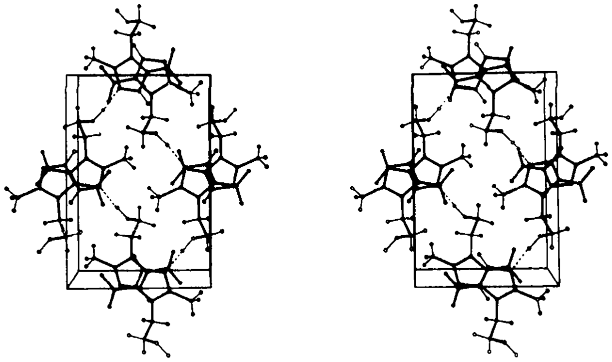

Fig. 2. Stereoscopic packing diagram with hydrogen bonds shown as broken lines.

distances of the O(8) atom of the nitro group with the neighbouring H atoms, *i.e.* O(8)···H(10*a*) = 2·47 (2) Å and O(8)···H(11*a*) = 2·52 (2) Å, which are significantly shorter.

The molecular structure does not show any peculiar feature that might be directly correlated with the pharmacological properties of this product or with the physicochemical determinations (pK_a, log *P*, redox properties) that are under way.

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Structure du (Méthoxycarbonyl)-2 Diméthyl-3,4 Phényl-5 Oxazolidine-1,3 Acétate-2 de Méthyle et Configuration Absolue (2*R*, 4*S*, 5*R*)*

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Abstract. $C_{16}H_{21}NO_5$, $M_r = 307$, orthorhombic, $P2_12_12_1$, $a = 10·222$ (2), $b = 13·921$ (5), $c = 11·321$ (4) Å, $Z = 4$, $V = 1610·98$ Å^3. The structure was solved by direct methods with *MULTAN* 76 ($R = 4·61\%$ for 905 observed reflexions, Cu $K\alpha$ radiation). The crystal structure led to an unequivocal assignment of the absolute configuration of oxazolidine (2*R*, 4*S*, 5*R*) and revealed that the addition of (–)-ephedrine (1*R*, 2*S*) to the dimethyl ester of acetylenedicarboxylic acid, in methanol acidified by acetic acid, gives only one oxazolidine. $\{[\alpha]^{24·91\,°C}_{578\,nm} = -45·1°$ ($c = 1·495$ g/100 ml, methanol), optical purity 100%.$\}$

Introduction. La condensation de l'isomère *erythro* du méthylamino-2 phényl-1 propanol-1 [(–)-éphédrine], de configuration absolue (1*R*, 2*S*), avec l'acétylènedicarboxylate de méthyle en solvant aprotique, conduit à un composé unique de *cis*-addition, présentant la configuration *E*. Cet énaminoester se cyclise selon une réaction de Michael intramoléculaire en une nouvelle oxazolidine (1) (Fig. 1). La réaction s'est révélée stéréospécifique, puisque l'on ne décèle en RMN ^{1}H qu'un seul diastéréoisomère (Bellan, Rossi & Sanchez, 1976).

Une publication précédente (Bellan, Rossi, Chezeau, Roques, Germain & Declercq, 1978) a décrit la structure cristalline et moléculaire ainsi que la configuration absolue (2*S*, 4*R*, 5*R*) de l'oxazolidine (2)

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