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1-Methoxy-3-(2-nitro-1-imidazolyl)-2-propanol (Misonidazole)

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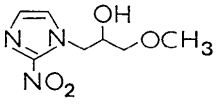
Abstract. $C_7H_{11}N_3O_4$, $M_r = 201$, monoclinic, $P2_1/c$, $a = 6{\cdot}997$ (1), $b = 7{\cdot}862$ (1), $c = 17{\cdot}024$ (3) Å, $\beta = 97{\cdot}06$ (2)°, $U = 929{\cdot}4$ (5) Å^3, $Z = 4$, $D_x = 1{\cdot}44$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0{\cdot}916$ mm^{-1}, $F(000) = 424$, ambient temperature, $R = 0{\cdot}049$ for 1324 unique reflections. All bond lengths and angles have normal values and the planes of the nitro group and imidazole ring form a dihedral angle of 7·9 (1)°.

Introduction. The title compound (misonidazole, NSC-361037, Ro.07-0582) (I) is a radiosensitizer and chemosensitizer of hypoxic tumour cells *in vitro* and *in vivo* (Kennedy, 1987; Stratford, 1982). Despite early disappointing results, recent clinical studies have revealed that misonidazole provides a substantial benefit when used as an adjunct to the radiotherapy of human pharyngeal tumours (Overgaard, Hansen, Jørgensen & Hjelm-Handsen, 1986; Overgaard *et al.*, 1987). In addition, misonidazole is differentially toxic to hypoxic cells *in vitro* (Adams & Stratford, 1986; Kennedy, Teicher, Rockwell & Sartorelli, 1980; Stratford & Adams, 1977) and this property is ascribed to intracellular bioreduction of the nitro group (Whitmore & Varghese, 1986; Silver, McNeil, O'Neill, Jenkins & Ahmed, 1986).



(I)

The work reported herein arose from an investigation into the chemistry of therapeutically useful nitroimidazoles. The structure of a platinum(II) complex of misonidazole has been described (Farrell, Gomes Carneiro, Einstein, Jones & Skov, 1984; Bales *et al.*, 1985) but that of the uncomplexed ligand has until now not been reported.

Experimental. Misonidazole supplied by Dr C. E. Smithen, Roche Products Ltd, Welwyn Garden City, Herts, England. (±)-Racemic material recrystallized from acetone as very pale yellow lath-shaped crystals; melting point 384–384·5 K (lit. 383–384 K: Beaman, Tautz & Duschinsky, 1968).

Crystal of dimensions 0·5 × 0·15 × 0·15 mm selected for data collection. Preliminary unit-cell dimensions and space group from Weissenberg photographs. Accurate cell parameters from least-squares refinement of the θ values of 25 reflections with $13 < \theta < 25°$; Enraf–Nonius CAD-4 diffractometer. Intensity data collected for 1955 reflections in range $-8 \le h \le 8$; $0 \le k \le 9$; $0 \le l \le 20$; nickel-filtered Cu radiation; ω–2θ scan mode; maximum $(\sin\theta)/\lambda$ 0·588 Å^{-1}. Three reference reflections measured after every 60 min X-ray exposure time; variation in intensity sum 5%. No correction made for absorption effects. Final data set consisted of 1580 unique reflections, of which 256 had $F < 6\sigma(F)$ and were thereby designated unobserved.

Structure solved by direct methods (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Full-matrix least-squares refinement on F of overall scale factor and positional and anisotropic thermal parameters for non-hydrogen atoms carried out using *SHELX*76 (Sheldrick, 1976). Weight w assigned to each observed structure factor according to the formula $w = 1/[\sigma^2(F_o) + 0{\cdot}001\,|F_o|^2]$. Analysis of the data in batches corresponding to ranges of F_o and $(\sin\theta)/\lambda$ indicated that this weighting scheme was satisfactory. H atoms located from a difference Fourier synthesis and subsequently fixed in positions calculated assuming idealized geometry and C—H distances 1·0 Å. Hydroxyl H atom (H13) repositioned towards the end of refinement from a difference Fourier synthesis calculated with this atom omitted. All H atoms assigned fixed isotropic thermal parameters $U_{iso} = 0{\cdot}1$ Å^2. Refinement converged to give final residuals $R = 0{\cdot}049$ and $wR = 0{\cdot}058$; maximum ratio of shift to e.s.d. in any parameter in final cycle of refinement was 0·7; final difference Fourier synthesis had maximum and minimum peak heights of 0·26 and −0·39 e Å^{-3} respectively. It was noted that $|F_{obs}|$ was systematically less than $|F_{calc}|$ for strong low-angle reflections; effect attributed to secondary extinction but no extinction coefficient refined due to limitations of correction available in *SHELX*76. Atomic scattering factors taken from *International Tables for X-ray*

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Crystallography (1974). Major computations performed on a VAX 11/750 computer at the Institute of Cancer Research.

Discussion. Atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms are given in Table 1.* The atomic numbering is indicated in Fig. 1, which also shows bond lengths and angles, while Fig. 2 is a stereodrawing of the molecule.

The imidazole ring is planar within experimental error and N21 and C11 lie close to the least-squares plane defined by the ring atoms at distances from it of 0·020 (3) and 0·025 (3) Å respectively. Bond lengths in the nitroimidazole moiety indicate that formula (I) is an appropriate representation of the structure.

Steric hindrance between O22 and H112 [separation 2·386 (2) Å] is reduced by a twist about the C2—N21 bond such that the planes of the imidazole ring and the nitro group at C2 form a dihedral angle of 7·9 (1)°. In addition there is distortion of the exocyclic angles at N1; C2—N1—C11 and C5—N1—C11 are 132·7 (2) and 122·8 (2)° respectively. The situation is thus comparable with that found in the structurally similar 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) (Blaton, Peeters & De Ranter, 1979) in which the planes of the nitro group and imidazole ring are inclined at an angle of 4·3°. The result confirms the conclusion of Bales *et al.* (1985) that steric effects are responsible for the large angle of about 46° between the planes of the nitro group and imidazole rings found in the complex of misonidazole with $PtCl_2$.

Bond lengths and angles in the side chain formed by atoms C11 to C16 have normal values and are consistent with those found by Farrell *et al.* (1984) in the metallo complex; some discrepancies are noted in the values reported by Bales *et al.* (1985).

In the crystal, the molecules are arranged in a head-to-tail fashion with the planes of the imidazole rings parallel. There are no intermolecular distances which are significantly shorter than the sum of the appropriate van der Waals radii.

* Lists of structure factors, anisotropic thermal parameters for non-hydrogen atoms and calculated H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44833 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms of misonidazole*

$U_{eq} = \frac{1}{3}(\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j) \times 10^3$ (Å^2).

	x	y	z	U_{eq}
N1	−0·0838 (2)	0·1972 (2)	0·4028 (1)	36 (1)
C2	−0·1125 (3)	0·0262 (3)	0·4017 (1)	35 (1)
N3	−0·2339 (2)	−0·0252 (2)	0·4492 (1)	39 (1)
C4	−0·2886 (3)	0·1207 (3)	0·4839 (1)	42 (1)
C5	−0·1980 (3)	0·2564 (3)	0·4560 (1)	42 (1)
N21	−0·0177 (3)	−0·0904 (2)	0·3545 (1)	43 (1)
O22	0·1111 (3)	−0·0366 (3)	0·3187 (1)	65 (1)
O23	−0·0700 (3)	−0·2386 (2)	0·3535 (1)	60 (1)
C11	0·0386 (3)	0·3086 (3)	0·3613 (1)	43 (1)
C12	0·2418 (3)	0·3249 (3)	0·4044 (1)	38 (1)
O13	0·2385 (2)	0·3617 (2)	0·4859 (1)	45 (1)
C14	0·3455 (3)	0·4722 (3)	0·3715 (1)	45 (1)
O15	0·3587 (3)	0·4443 (3)	0·2908 (1)	58 (1)
C16	0·4638 (4)	0·5746 (5)	0·2584 (2)	73 (1)

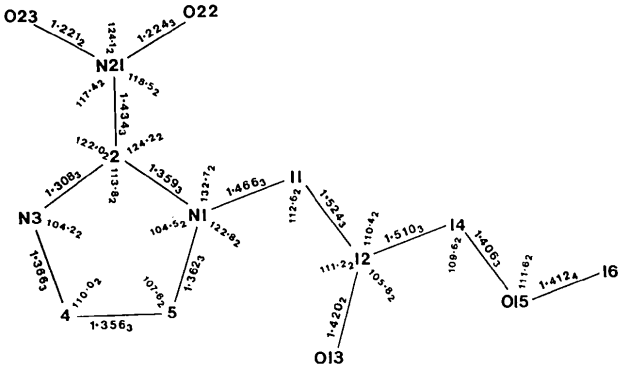

Fig. 1. Schematic diagram of the misonidazole molecule, showing the atomic numbering, bond lengths (Å) and angles (°) with e.s.d.'s given as subscripts.

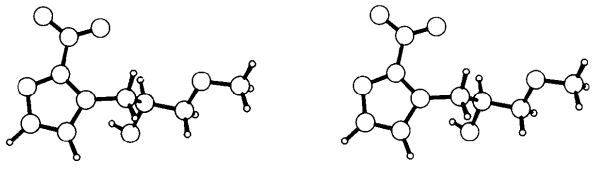

Fig. 2. Stereodrawing of the misonidazole molecule.

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Structure of the *cis–cisoid–cis* Isomer of 2,3,11,12-Tetra-anisyl-18-crown-6: *rel*-(2*R*,3*S*,11*R*,12*S*)-2,3,11,12-Tetrakis(4-methoxyphenyl)-1,4,7,10,13,16-hexaoxacyclooctadecane

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Abstract. $C_{40}H_{48}O_{10}$, $M_r = 689$, triclinic, $P\bar{1}$, $a = 10{\cdot}960\,(2)$, $b = 13{\cdot}194\,(2)$, $c = 13{\cdot}785\,(4)$ Å, $\alpha = 85{\cdot}76\,(2)$, $\beta = 81{\cdot}87\,(2)$, $\gamma = 73{\cdot}14\,(1)°$, $V = 1889$ Å^3, $Z = 2$, $D_x = 1{\cdot}21$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}67$ mm^{-1}, $F(000) = 736$, room temperature, $R = 0{\cdot}073$ for 3294 observed reflections with $|F_o| > 3\sigma(|F_o|)$. There are two *anti* and four *gauche* OCH_2-CH_2O units present in the conformation adopted by the 18-membered ring of the title compound (1): two of the anisyl groups are axial and two are equatorial: the vicinal groups have a *gauche* relationship to each other.

Introduction. There has been considerable interest of late in the solid-state structures of 2,3,11,12-tetra-aryl-18-crown-6 derivatives, such as (1)–(5) (Fig. 1), where the four anisyl substituents have the *cis–cisoid–cis, cis–transoid–cis, trans–cisoid–trans, trans–transoid–trans* and *cis–trans* configurations respectively. They provide (Weber, Sheldrick, Burgemeister, Dietl, Mannschreck & Merz, 1984) an ideal set of configurational diastereoisomers on which to investigate (Merz, Eichner & Tomahogh, 1981) the dependence of metal (*e.g.* Na^+ and K^+) and inorganic (*e.g.* H_3O^+ and NH_4^+) ion complexation strengths upon relative configurations. Unlike the analogous series of dicyclohexano-18-crown-6 derivatives (Burden, Coxon, Stoddart & Wheatley, 1977), where the fused six-membered rings introduce (Coxon, Laidler, Pettman & Stoddart, 1978) additional rigid configurational constraints into the macrocyclic polyether ring, the 2,3,11,12-tetraphenyl-18-crown-6 derivatives (6)–(10) shown in Fig. 1 are only subject to configurational influences and associated nonbonded interactions between the four substituents. Furthermore, since the *trans–transoid–trans* (4) and *cis–trans* (5) isomers are chiral, the potential exists (Stoddart, 1987*a*,*b*) to employ them either as chiral reagents (Allwood, Shahriari-Zavareh, Stoddart & Williams, 1984) or as chiral catalysts (Colquhoun, Stoddart & Williams, 1986). In exhibiting their molecular recognition properties, chiral crown ethers can also discriminate between enantiomeric substrates. Indeed, the (*RRRR*)-enantiomer of the *trans–transoid–trans* isomer (4) has been shown (Dietl, Merz & Tomahogh, 1982) to extract (*R*)-phenylglycine methyl ester hydroperchlorate preferentially into deuteriochloroform from an aqueous solution of its

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