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## Structure of Ronidazole

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**Abstract.** (1-Methyl-5-nitro-2-imidazolyl)methyl carbamate, C<sub>6</sub>H<sub>8</sub>N<sub>4</sub>O<sub>4</sub>, *M<sub>r</sub>* = 200.15, monoclinic, *P*2<sub>1</sub>/*a*, *a* = 10.336 (5), *b* = 7.964 (4), *c* = 10.549 (5) Å, β = 103.90 (2)°, *V* = 842.9 (7) Å<sup>3</sup>, *Z* = 4, *D<sub>m</sub>* = 1.57, *D<sub>x</sub>* = 1.577 Mg m<sup>-3</sup>, λ(Cu Kα) = 1.54178 Å, μ = 1.114 mm<sup>-1</sup>, *F*(000) = 416, *T* = 293 K, final *R* = 0.041 for 1288 unique [*F* ≥ 6σ(*F*)] reflections. The molecules are stacked in planes parallel to the *b* axis. These molecular layers are built up by three hydrogen bonds. A fourth hydrogen bond connects these layers perpendicularly. Substituent effects on the imidazole ring angles are discussed.

**Introduction.** Nitroimidazoles are generally known as antiprotozoic and antibiotic drugs (Edwards, 1981). The investigation of ronidazole is part of an extensive structure–activity study including conformational analysis on room-temperature data as well as charge-density analysis on high-resolution data sets.

**Experimental.** Colourless crystals were obtained from a 1:1 CHCl<sub>3</sub>/1,4-dioxane mixture and were used for density measurements by flotation in *n*-heptane/CCl<sub>4</sub>. A prismatic crystal with approximate dimensions of 0.7 × 0.6 × 0.3 mm was mounted on a Stoe STADI-4 four-circle diffractometer with graphite-monochromated (reflection 200) Cu Kα radiation. The space group, *P*2<sub>1</sub>/*a*, was determined from

observed symmetry and systematic absences. Cell dimensions were obtained by least-squares refinement of accurately determined 2θ values of 24 reflections with 14 ≤ 2θ ≤ 50°. X-ray intensities were collected in the ω/2θ scan mode up to maximum (sinθ)/λ = 0.588 Å<sup>-1</sup> (2θ<sub>max</sub> = 130°) and for 0 ≤ *h* ≤ 12, -9 ≤ *k* ≤ 0, -12 ≤ *l* ≤ 12. Intensities of three standard reflections (202, 211, 112), monitored every hour of radiation, showed no decrease in intensity. A total of 1609 reflections were measured. Symmetry-related reflections were averaged to give 1400 unique reflections of which 1288 with *F* ≥ 6σ(*F*) were used for refinement. *R<sub>int</sub>* on *F* for observed reflections is 0.012. Data reduction with a locally adapted Stoe & Co. (1985) *REDU4* program. Lorentz and polarization corrections were applied. Absorption corrections were performed by the method of North, Phillips & Mathews (1968) based on the observed absorption of seven reflections (200, 310, 411, 511, 611, 711, 812) as a function of φ. The transmission factor varied between 0.81 and 1.00. Structure factors were calculated with scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B) and contracted hydrogen form factors from Stewart, Davidson & Simpson (1965). Anomalous-dispersion corrections were performed for all non-H atoms (Ibers & Hamilton, 1964). The structure was solved by direct methods using *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) which revealed the positions of all non-H atoms. Full-matrix least-squares refinements were performed on *F*, first iso-

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tropically and then anisotropically. All H atoms were located in a difference map. The methyl H atoms were given a temperature factor  $B$  of  $8.0 \text{ \AA}^2$ , other H atoms a  $B$  of  $4.0 \text{ \AA}^2$ . All H-atom positions were refined. An isotropic extinction parameter,  $g = 1.41(4) \times 10^{-5}$ , defined as  $F_{c, \text{corr}} = F_c / (1 + g \text{Lp} F_c^2)$ , was also refined.  $w = 4F^2 / [\sigma^2(F^2) + (0.02F^2)^2]$ . Final  $R = 0.041$ ,  $wR = 0.062$ , with  $S = 4.92$ . Largest parameter shift/e.s.d. =  $0.03$ ,  $-0.22 < \Delta\rho < 0.24 \text{ e \AA}^{-3}$ . The number of reflections per refined parameter was  $1288/152 = 8.5$ . All calculations were performed on Digital PDP-11/73 and MicroVAX 2000 microcomputers using *SDP/VAX* (Frenz, 1985) and *PARST* (Nardelli, 1983).

**Discussion.** An *ORTEP* view (Johnson, 1976) of the title compound with the atomic numbering scheme is shown in Fig. 1. The final atomic coordinates and equivalent isotropic thermal parameters are given in Table 1. Bond lengths and bond angles are given in Table 2.\* The nitro group forms a dihedral angle of  $11.1(1)^\circ$  with the least-squares plane through the imidazole ring atoms. The least-squares plane

\* Lists of H-atom parameters, selected torsion angles, weighted least-squares planes, structure factors and anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54325 (11 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

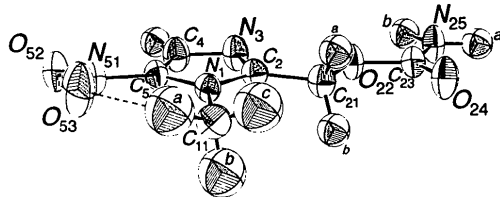


Fig. 1. An *ORTEP* (Johnson, 1976) plot of the title compound with atomic numbering scheme. The ellipsoids enclose 50% probability. The dashed line indicates the intramolecular hydrogen bond.

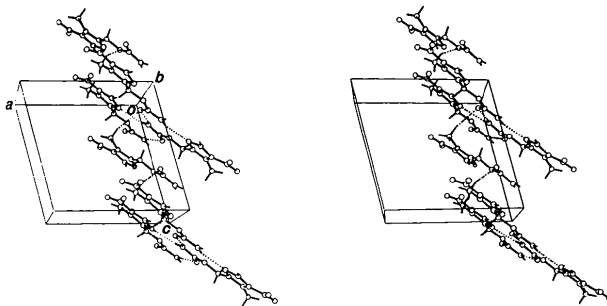


Fig. 2. A *PLUTO* (Motherwell & Clegg, 1978) stereoplot of the crystal showing the packing along  $a$ . Dotted lines indicate intermolecular hydrogen bonds.

Table 1. *Atomic coordinates and equivalent isotropic temperature factors* ( $\text{\AA}^2 \times 10^3$ )

E.s.d.'s on the least significant digit are given in parentheses.  $U_{eq} = (1/3)\sum_i U_{ii} a_i^* a_i$ .

	$x$	$y$	$z$	$U_{eq}$
N1	0.9427 (1)	0.1249 (2)	0.3141 (1)	3.56 (3)
C2	1.0243 (1)	0.0999 (2)	0.2332 (1)	3.62 (4)
N3	1.0680 (1)	0.2412 (2)	0.1933 (1)	4.63 (4)
C4	1.0108 (2)	0.3654 (2)	0.2487 (2)	4.91 (4)
C5	0.9343 (2)	0.2980 (2)	0.3226 (2)	4.09 (4)
C11	0.8671 (2)	-0.0064 (3)	0.3620 (2)	4.94 (4)
C21	1.0583 (2)	-0.0717 (2)	0.1945 (2)	4.18 (4)
O22	1.1440 (1)	-0.0468 (1)	0.1084 (1)	4.39 (3)
C23	1.1932 (2)	-0.1896 (2)	0.0669 (2)	3.89 (4)
O24	1.1645 (1)	-0.3277 (2)	0.0997 (1)	5.49 (4)
N25	1.2731 (1)	-0.1537 (2)	-0.0096 (1)	5.06 (4)
N51	0.8657 (1)	0.3829 (2)	0.4051 (1)	5.40 (4)
O52	0.8575 (2)	0.5367 (2)	0.3938 (1)	7.14 (4)
O53	0.8210 (2)	0.3034 (2)	0.4840 (2)	8.89 (5)

Table 2. *Bond lengths* ( $\text{\AA}$ ) *and bond angles* ( $^\circ$ )

E.s.d.'s on the least significant digit are given in parentheses.

N1—C2	1.350 (2)	C5—N51	1.419 (2)
N1—C5	1.385 (2)	C21—O22	1.428 (2)
N1—C11	1.466 (2)	O22—C23	1.360 (2)
C2—N3	1.319 (2)	C23—O24	1.211 (2)
C2—C21	1.492 (2)	C23—N25	1.317 (2)
N3—C4	1.355 (2)	N51—O52	1.232 (2)
C4—C5	1.347 (3)	N51—O53	1.222 (2)
C2—N1—C5	104.3 (1)	C4—C5—N51	127.9 (2)
C2—N1—C11	125.3 (1)	C21—O22—C23	115.2 (2)
C5—N1—C11	129.8 (1)	O22—C23—O24	122.1 (1)
N1—C2—N3	112.9 (1)	O22—C23—N25	110.7 (2)
N1—C2—C21	122.1 (1)	O24—C23—N25	127.2 (1)
N3—C2—C21	125.0 (2)	C2—C21—O22	105.6 (1)
C2—N3—C4	105.4 (1)	C5—N51—O52	116.6 (1)
N3—C4—C5	109.7 (2)	C5—N51—O53	119.9 (1)
N1—C5—C4	107.7 (2)	O52—N51—O53	123.6 (1)
N1—C5—N51	124.2 (2)		

Table 3. *Geometry of intra- and intermolecular hydrogen bonds* ( $\text{\AA}$ ,  $^\circ$ )

E.s.d.'s on the least significant digit are given in parentheses. H-atom positions are normalized to C—H =  $1.06$  and N—H =  $1.01 \text{ \AA}$  (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987).

	D—H	D...A	H...A	D—H...A
C11—H11A...O53 <sup>i</sup>	1.06	2.875 (3)	2.160 (2)	122.7 (2)
C11—H11B...O24 <sup>ii</sup>	1.06	3.317 (3)	2.314 (1)	157.2 (2)
N25—H25A...N3 <sup>iii</sup>	1.01	2.947 (2)	2.130 (1)	136.6 (1)
N25—H25B...O24 <sup>iv</sup>	1.01	2.890 (2)	1.900 (2)	165.9 (1)

Symmetry code: (i)  $x, y, z$ ; (ii)  $x - \frac{1}{2}, -y - \frac{1}{2}, z$ ; (iii)  $-x + \frac{1}{2} + 2, y - \frac{1}{2}, -z$ ; (iv)  $-x + \frac{1}{2} + 2, y + \frac{1}{2}, -z$ .

through all the atoms of the carbamoyloxymethyl substituent, except H21A and H21B, is  $2.07(6)^\circ$  out of the imidazole plane. Fig. 2 shows the planes parallel to the  $b$  axis in which the molecules are stacked. Inspection of non-bonding distances shorter than the sum of the van der Waals radii reveals the hydrogen bonds summarized in Table 3. The orientations of the H atoms of the methyl group are determined by both an intramolecular hydrogen

bond (H11A...O53) and an intermolecular hydrogen bond (H11B...O24). This intermolecular hydrogen bond forms the connection between the molecular layers in the crystal. The hydrogen bonds between the carbamoyl H atoms (H25A, H25B) and the adjacent O24 and N3 atoms lie in these layers perpendicular to the *ac* plane.

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## Structure of the Methyl Esters of Barbatic and Evernic Acids: Natural *para*-Depside

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**Abstract.** Methyl 2-hydroxy-4-(2-hydroxy-4-methoxy-3,6-dimethylbenzoyloxy)-3,6-dimethylbenzoate (barbaticin),  $C_{20}H_{22}O_7$ ,  $M_r = 374.4$ , triclinic,  $P\bar{1}$ ,  $a = 4.750$  (1),  $b = 7.178$  (1),  $c = 27.621$  (2) Å,  $\alpha = 82.37$  (1),  $\beta = 88.42$  (1),  $\gamma = 80.87$  (1)°,  $V = 921.6$  Å<sup>3</sup>,  $Z = 2$ ,  $D_m$  (floatation in KI/H<sub>2</sub>O) = 1.37,  $D_x = 1.349$  g cm<sup>-3</sup>,  $\lambda(\text{Mo } K\alpha) = 0.71073$  Å,  $\mu = 0.63$  cm<sup>-1</sup>,  $F(000) = 396$ , room temperature,  $R = 0.049$  for 2119 reflections. Methyl 2-hydroxy-4-(2-hydroxy-4-methoxy-6-methylbenzoyloxy)-3,6-dimethylbenzoate (evernin),  $C_{19}H_{20}O_7$ ,  $M_r = 360.4$ , monoclinic,  $P2_1/c$ ,  $a = 5.100$  (1),  $b = 27.323$  (2),  $c = 12.816$  (1) Å,  $\beta = 98.84$  (1)°,  $V = 1764.7$  Å<sup>3</sup>,  $Z = 4$ ,  $D_m$  (floatation in KI/H<sub>2</sub>O) = 1.37,  $D_x = 1.356$  g cm<sup>-3</sup>,  $\lambda(\text{Mo } K\alpha) = 0.71073$  Å,  $\mu = 1.0$  cm<sup>-1</sup>,  $F(000) = 760$ , room temperature,  $R = 0.044$  for 2086 reflections. In both compounds two highly substituted phenyl rings are bridged by an ester group, and are inclined to one another [by 106.1 (1)° in barbaticin and 88.6 (1)° in evernin]. There are two strong intramolecular hydrogen bonds, involving the hydroxyl substituents

and the adjacent ester carbonyl groups, in both compounds.

**Introduction.** Depsides form a large group of secondary metabolites of lichens. Their biosynthesis follows the acetate–polymalonate pathway with the basic structural unit being phenyl benzoate. Their synthesis is difficult owing to the large number and nature of the substituents, often hydroxyl groups, on the two aromatic rings, see Table 1. The majority of known depsides can be divided into two groups; the first are derived from orcinol-type units, the second from  $\beta$ -orcinol-type units. The intermolecular esterification of two or three identical units or analogues, leads to two major classes of depsides; the *para*-depsides and the tridepsides (Culberson, 1969). Barbatic acid is found in the majority of lichens of genera *Usnea* and was first isolated in the last century (Stenhouse & Groves, 1880). Later coccellic acid, from *Cladonia coccifera*, was shown to be identical to barbatic acid (Asahina & Fuzikawa, 1934), which was isolated by the same authors from *Cladonia amourocrea*. A little earlier it had been

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