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A New Analogue of Nifurtimox

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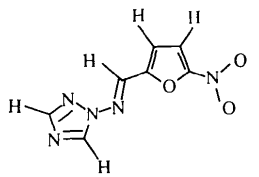
Abstract

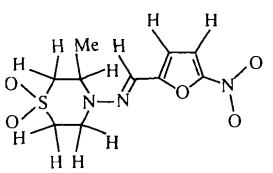
1-{[(5-Nitro-2-furyl)methylene]amino}-1,2,4-triazole, $C_7H_5N_5O_3$, is a new analogue of nifurtimox with activity against *Tripanosoma cruzi*. In the crystal structure, the molecule lies on a mirror plane and has an *E–sZ* conformation along the N=C—C moiety. The molecules are linked through C—H···O and C—H···N interactions.

Comment

Chaga's disease, endemic in Latin America, presents two stages: the acute one, which occurs approximately 10–15 days after infection and may be lethal in some cases, and the chronic phase. Effective drugs for the treatment of the chronic phase are not yet available and those used in the acute phase and in congenital infection, such as nifurtimox, (2), present undesirable side effects associated with their high toxicity (Nagel, 1987; Marr & Docampo, 1986; van Voorhis, 1990). This chemical was also found to be mutagenic in bacteria (Nagel, 1987). These drawbacks led to the synthesis of a new series of nifurtimox analogues with activity against *Trypanosoma cruzi* (Mester *et al.*, 1987), among them compound (1). As the knowledge of the three-dimensional structure of this compound is necessary to try to understand its behaviour at the molecular level, a crystal-structure determination was undertaken.



(1)



(2)

The molecule presents an *E* configuration with respect to the C(5)=N(2) double bond, with a torsion angle N(3)—N(2)—C(5)—C(4) of 180°. The conformation about the C(4)—C(5) bond is *sZ* with a torsion angle O(3)—C(4)—C(5)—N(2) of 0°. The molecule lies on a crystallographic mirror plane. The C(4)—C(5)—H(C5) angle [108.4 (8)°], opposite to the N(2)=C(5) double bond, is smaller than the other angles around C(5), as found in related compounds (Foces-Foces, Cano, Claramunt, Fruchier & Elguero, 1988). The crystal is stabilized by the C—H···O and C—H···N interactions shown in Table 3.

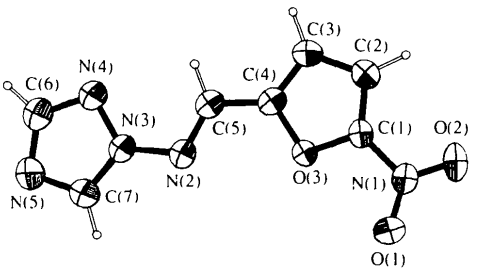


Fig. 1. The molecular structure of $C_7H_5N_5O_3$ showing the atom labelling; 50% displacement ellipsoids are shown for non-H atoms.

Experimental

Crystals were obtained by slow evaporation at 277 K from 1:1 ethanol/methanol solution.

Crystal data

$C_7H_5N_5O_3$
M_r = 207.15
Orthorhombic
Pnma
a = 11.952 (2) Å
b = 6.255 (1) Å
c = 11.708 (2) Å
V = 875.3 (4) Å^3
Z = 4
D_x = 1.572 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 10–22°
μ = 0.119 mm^{-1}
T = 292 K
Irregular
0.50 × 0.25 × 0.17 mm
Deep yellow

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
1340 measured reflections
1027 independent reflections
721 observed reflections [$I > 3\sigma(I)$]

R_{int} = 0.026
θ_{max} = 28°
h = 0 → 15
k = 0 → 8
l = 0 → 15
1 standard reflection
frequency: 30 min
intensity variation: ±0.7%

Refinement

Refinement on F
R = 0.0417
wR = 0.0449
S = 1.68
950 reflections
92 parameters
H atoms: see below

$w = 1/[\sigma^2(|F_o|) + 0.0004|F_o|^2]$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *SHELX*76 (Sheldrick, 1976)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$B_{eq} = (4/3)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
O(1)	0.4421 (2)	1/4	0.1122 (2)	5.63 (9)
O(2)	0.2731 (2)	1/4	0.0469 (2)	6.28 (9)
O(3)	0.3725 (1)	1/4	0.3227 (1)	3.33 (6)
N(1)	0.3408 (2)	1/4	0.1247 (2)	4.21 (9)
N(2)	0.4677 (2)	1/4	0.5401 (2)	3.59 (8)
N(3)	0.5048 (2)	1/4	0.6525 (2)	3.52 (7)
N(4)	0.4365 (2)	1/4	0.7451 (2)	4.72 (9)
N(5)	0.6190 (2)	1/4	0.7968 (2)	4.37 (9)
C(1)	0.2966 (2)	1/4	0.2374 (2)	3.41 (9)
C(2)	0.1908 (2)	1/4	0.2736 (2)	4.4 (1)
C(3)	0.1992 (2)	1/4	0.3934 (2)	4.8 (1)
C(4)	0.3090 (2)	1/4	0.4203 (2)	3.65 (9)
C(5)	0.3618 (2)	1/4	0.5299 (2)	3.80 (9)
C(6)	0.5100 (3)	1/4	0.8280 (2)	4.9 (1)
C(7)	0.6117 (2)	1/4	0.6850 (2)	3.87 (9)

Table 2. *Selected geometric parameters (Å, °)*

O(1)—N(1)	1.220 (3)	O(2)—N(1)	1.218 (3)
O(3)—C(1)	1.349 (3)	O(3)—C(4)	1.372 (3)
N(1)—C(1)	1.421 (3)	N(2)—N(3)	1.389 (3)
N(2)—C(5)	1.271 (3)	N(3)—N(4)	1.357 (3)
N(3)—C(7)	1.333 (3)	N(4)—C(6)	1.309 (4)
N(5)—C(6)	1.353 (4)	N(5)—C(7)	1.312 (3)
C(1)—C(2)	1.334 (4)	C(2)—C(3)	1.406 (4)
C(3)—C(4)	1.350 (4)	C(4)—C(5)	1.430 (3)
C(1)—O(3)—C(4)	104.2 (1)	O(3)—C(1)—C(2)	113.7 (2)
O(1)—N(1)—O(2)	124.7 (2)	N(1)—C(1)—C(2)	130.3 (2)
O(1)—N(1)—C(1)	118.7 (2)	C(1)—C(2)—C(3)	104.4 (2)
O(2)—N(1)—C(1)	116.6 (2)	C(2)—C(3)—C(4)	107.6 (2)
N(3)—N(2)—C(5)	114.0 (2)	O(3)—C(4)—C(3)	110.1 (2)
N(2)—N(3)—N(4)	124.4 (2)	O(3)—C(4)—C(5)	120.2 (2)
N(2)—N(3)—C(7)	125.2 (2)	C(3)—C(4)—C(5)	129.7 (2)
N(4)—N(3)—C(7)	110.4 (2)	N(2)—C(5)—C(4)	121.6 (2)
N(3)—N(4)—C(6)	100.9 (2)	N(4)—C(6)—N(5)	116.5 (2)
C(6)—N(5)—C(7)	101.8 (2)	N(3)—C(7)—N(5)	110.4 (2)
O(3)—C(1)—N(1)	115.9 (2)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
C(6)—H(C6)···O(1^{i})	0.938 (4)	2.492 (3)	3.425 (3)	173.1 (6)
C(7)—H(C7)···O(2^{ii})	0.965 (4)	2.410 (3)	3.331 (3)	159.5 (6)
C(5)—H(C5)···N(5^{iii})	0.965 (4)	2.597 (3)	3.541 (3)	166.9 (6)

Symmetry codes: (i) $x, y, 1+z$; (ii) $\frac{1}{2}+x, y, \frac{1}{2}-z$; (iii) $x-\frac{1}{2}, y, \frac{3}{2}-z$.

Data were corrected for Lp effects. The structure was solved by direct methods. H atoms were included as fixed contributors at positions found in the difference synthesis and refined with an overall isotropic displacement parameter which converged to 0.064 (4) Å². The refinement was by blocked-matrix least-squares methods.

Programs used: *SHELXS86* (Sheldrick, 1985), *SHELX76* (Sheldrick, 1976) and *ORTEP* (Johnson, 1965).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: CR1142). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Chiral α-Hydroxy Acids: Racemic 2-Hydroxy-2,3,3-trimethylbutanoic Acid and 2-Hydroxy-2-trimethylsilylpropanoic Acid

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Abstract

Both $C_7H_{14}O_3$ and $C_6H_{14}O_3Si$ crystallize as racemates from acetone solution, the former incorporating water of crystallization ($C_7H_{14}O_3.0.5H_2O$). The crystal structures display extensive intermolecular hydrogen bonding involving the hydroxy and carboxylic acid groups to give polymeric networks.

Comment

α-Hydroxy acids are well known for their important roles in biochemistry and in synthetic organic chemistry. More recently they have achieved new prominence because of their importance to the cosmetic industry (Marcet, 1993; Hagan, Parrott & Taylor, 1993; Nowak, 1993; Armengol, 1993). We have recently described the reaction of dimethyldioxirane with some alkynes (Murray & Singh, 1993). In some cases these reactions give α-hydroxy acids as products. Thus, the reaction of 4,4-dimethyl-2-pentyne, (1), with dimethyldioxirane, (2), gave a number of products including a small amount (8%) of 2-hydroxy-2,3,3-trimethylbutanoic acid, (3). Similarly, the reaction of 1-(trimethylsilyl)propyne, (4), with (2) gave 2-hydroxy-2-trimethylsilylpropanoic acid, (5), in 93% yield. Acid (3) was recrystallized from