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Structure of the Antimicrobial Agent Cinoxacin

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Abstract. 1-Ethyl-1,4-dihydro-4-oxo[1,3]dioxolo[4,5-*g*]cinnoline-3-carboxylic acid, $C_{12}H_{10}N_2O_5$, $M_r = 262{\cdot}2$, triclinic, $P\bar{1}$, $a = 6{\cdot}946$ (1), $b = 9{\cdot}119$ (2), $c = 9{\cdot}129$ (2) Å, $\alpha = 80{\cdot}42$ (2), $\beta = 83{\cdot}46$ (2), $\gamma = 80{\cdot}66$ (2)°, $V = 560{\cdot}4$ Å^3, $Z = 2$, $D_x = 1{\cdot}552$ g cm^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1{\cdot}5418$ Å, $\mu = 10{\cdot}04$ cm^{-1}, $F(000) = 272$, $T = 293$ K, $R = 0{\cdot}055$ for 1345 independent reflections. A nearly planar three-ring system is observed (maximum angle between the two end rings 1·8°). The ethyl group is approximately perpendicular to the plane [N—N—C—C torsion angle 97·0 (2)°]. A hydrogen bond is formed between the carboxyl and ketone groups (O···H 1·732 Å).

Introduction. Cinoxacin is an antimicrobial agent related to oxolinic acid. It is also active, both *in vitro* (Giamarellon & Jackson, 1975) and *in vivo* (Greenwood & O'Grady, 1978), against a large variety of Gram-negative bacteria, especially against some often found in infections of the urinary tract. (*Escherichia coli, Klebsiella* sp., *Enterobacter* sp., *etc.*). It has been suggested that this is *via* interaction of the compound with the DNA-gyrase, probably a metalloenzyme (Timmers & Sternglanz, 1978).

Experimental. Colorless prismatic crystals grown by slow evaporation of chloroform solution. Crystal 0·10 × 0·26 × 0·14 mm. Unit cell from 15 reflections ($3° < 2\theta < 20°$). Intensity data collected on a Nicolet *R3m* four-circle diffractometer, graphite-monochromated Cu *Kα* radiation. ω-scan, $3 < 2\theta < 115°$ (h: 0 to 7, k: −9 to 9, l: −9 to 9), variable scan rate from 4 to 30° min^{-1}, scan width 1·0°. Two monitor reflections ($1\bar{1}1$ and $01\bar{2}$) with constant intensity (variation <3%). 1345 observed reflections with $I > 2\sigma(I)$ used in structure analysis, 166 unobserved. Lorentz and polarization corrections; no correction for absorption or extinction. $R_{\mathrm{merge}} = 0{\cdot}0142$ from merging equivalent reflections. Structure solved by direct methods and Fourier difference methods using *SHELXTL* (Sheldrick, 1981). Refinement on F by full-matrix least-squares method; anisotropic thermal parameters for all non-hydrogen atoms. H atoms in idealized positions, fixed $U = 0{\cdot}06$ Å^2. Weighting scheme $[\sigma^2(F_o) + G(F_o^{\,2})]^{-1}$, where σ is the estimated standard deviation based on counting statistics and G an adjustable variable; final $G = 0{\cdot}0086$. Max. electron density in final map $< 0{\cdot}5$ e Å^{-3}. $(\Delta/\sigma)_{\max} = 0{\cdot}122$. Scattering factors from *International Tables for X-ray Crystallography* (1974). Calculations performed on a Nova 4S computer. Final $R = 0{\cdot}055$ and $wR = 0{\cdot}073$.

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Table 1. *Atom coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($Å^2 \times 10^3$)

	x	y	z	U_{eq}*
N(1)	3885 (3)	8044 (2)	4364 (2)	32 (1)
N(2)	3709 (3)	7615 (2)	5813 (2)	35 (1)
O(1)	1844 (3)	8904 (2)	9225 (2)	52 (1)
O(2)	3482 (3)	6701 (2)	8821 (2)	56 (1)
O(3)	1335 (3)	11025 (2)	7060 (2)	46 (1)
O(4)	1239 (3)	13677 (2)	1545 (2)	45 (1)
O(5)	2814 (3)	11928 (2)	93 (2)	42 (1)
C(1)	2766 (3)	7965 (3)	8339 (3)	39 (1)
C(2)	2877 (3)	8582 (3)	6704 (3)	34 (1)
C(3)	2106 (3)	10135 (3)	6187 (3)	33 (1)
C(4)	2309 (3)	10563 (2)	4598 (3)	28 (1)
C(5)	1592 (3)	12047 (3)	3936 (3)	34 (1)
C(6)	1823 (3)	12375 (2)	2445 (3)	32 (1)
C(7)	1861 (5)	13444 (3)	52 (3)	53 (1)
C(8)	2743 (3)	11312 (3)	1554 (3)	33 (1)
C(9)	3464 (3)	9862 (2)	2112 (3)	33 (1)
C(10)	3210 (3)	9489 (2)	3685 (2)	30 (1)
C(11)	4771 (4)	6847 (3)	3506 (3)	42 (1)
C(12)	3253 (5)	6144 (3)	2915 (4)	59 (1)

* U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

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

N(1)–N(2)	1·313 (3)	N(1)–C(10)	1·391 (3)
N(1)–C(11)	1·463 (3)	N(2)–C(2)	1·318 (3)
O(1)–C(1)	1·316 (3)	O(2)–C(1)	1·211 (3)
O(3)–C(3)	1·248 (3)	O(4)–C(6)	1·358 (2)
O(4)–C(7)	1·422 (3)	O(5)–C(7)	1·429 (3)
O(5)–C(8)	1·357 (3)	C(1)–C(2)	1·503 (3)
C(2)–C(3)	1·451 (3)	C(3)–C(4)	1·434 (3)
C(4)–C(5)	1·422 (3)	C(4)–C(10)	1·414 (3)
C(5)–C(6)	1·341 (3)	C(6)–C(8)	1·397 (3)
C(8)–C(9)	1·371 (3)	C(9)–C(10)	1·417 (3)
C(11)–C(12)	1·510 (5)		
N(2)–N(1)–C(10)	123·4 (2)	N(2)–N(1)–C(11)	114·2 (2)
C(10)–N(1)–C(11)	122·3 (2)	N(1)–N(2)–C(2)	119·9 (2)
C(6)–O(4)–C(7)	107·2 (2)	C(7)–O(5)–C(8)	106·0 (2)
O(1)–C(1)–O(2)	121·8 (2)	O(1)–C(1)–C(2)	115·3 (2)
O(2)–C(1)–C(2)	123·0 (2)	N(2)–C(2)–C(1)	115·1 (2)
N(2)–C(2)–C(3)	124·0 (2)	C(1)–C(2)–C(3)	120·9 (2)
O(3)–C(3)–C(2)	122·4 (2)	O(3)–C(3)–C(4)	122·9 (2)
C(2)–C(3)–C(4)	114·6 (2)	C(3)–C(4)–C(5)	120·6 (2)
C(3)–C(4)–C(10)	119·5 (2)	C(5)–C(4)–C(10)	119·9 (2)
C(4)–C(5)–C(6)	117·7 (2)	O(4)–C(6)–C(5)	129·4 (2)
O(4)–C(6)–C(8)	108·6 (2)	C(5)–C(6)–C(8)	121·9 (2)
O(4)–C(7)–O(5)	107·8 (2)	O(5)–C(8)–C(6)	110·4 (2)
O(5)–C(8)–C(9)	126·0 (2)	C(6)–C(8)–C(9)	123·6 (2)
C(8)–C(9)–C(10)	115·3 (2)	N(1)–C(10)–C(4)	118·6 (2)
N(1)–C(10)–C(9)	119·9 (2)	C(4)–C(10)–C(9)	121·6 (2)
N(1)–C(11)–C(12)	112·2 (2)		

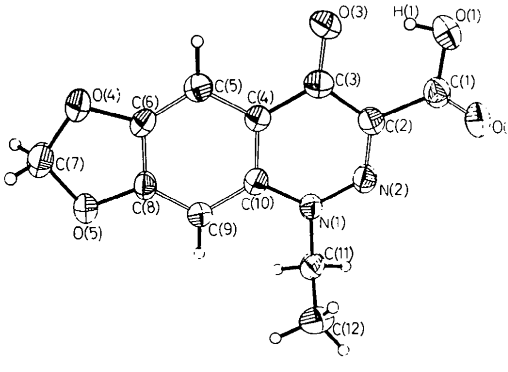

Fig. 1. Molecular diagram of cinoxacin showing the numbering scheme with the ellipsoids at the 50% probability level.

Discussion. Final positional parameters are shown in Table 1.* Bond lengths and bond angles are given in Table 2. A molecular diagram including the numbering scheme is shown in Fig. 1. The values found for bond lengths in the ring containing two O atoms and in the neighboring ring are slightly shorter in cinoxacin than in aminooxolinic acid (Czugler, Argay, Frank, Mészáros, Kutschabsky & Reck, 1976), an effect probably due to the presence of the amino group in the second compound.

The ketone-acid fragment of the molecule also shows shorter bond lengths than those in the corresponding groups in both aminooxolinic acid and nalidixic acid (Huber, Gowda & Acharya, 1980). A hydrogen bond is also observed between the H atom of the carboxyl group and the O atom of the ketone [O(3)···H(1) 1·732 Å] and, as in aminooxolinic acid, this might be the cause of the long C(3)—O(3) bond distance.

The N—N and N—C bond lengths in the N-containing ring also agree with the values reported for other compounds containing similar structural units (van Hummel, van den Ham & Huiszoon, 1979).

The three-ring system is practically planar with a maximum angle of 1·8° between the two end rings. The maximum deviations from planarity in a single ring are found in the O-containing ring.

The N(2)—N(1)—C(11)—C(12) torsion angle is 97·0 (2)° and the ethyl group is approximately perpendicular to the ring system.

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* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, least-squares planes and a full list of bond lengths and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42456 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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