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Structure of Oxolinic Acid, a Potent Antibacterial Agent. 1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid, $C_{13}H_{11}NO_5$*

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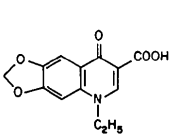
Abstract. $M_r = 261{\cdot}2$, monoclinic, $P2_1/c$, $a = 7{\cdot}182\ (2)$, $b = 10{\cdot}575\ (2)$, $c = 14{\cdot}758\ (2)$ Å, $\beta = 94{\cdot}26\ (1)°$, $V = 1117{\cdot}8$ Å^3, $Z = 4$, $D_x = 1{\cdot}552$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}98$ mm^{-1}, $F(000) = 544$, $T = 294$ K, final $R = 0{\cdot}038$ for 1565 observed reflections. The molecule is planar within $\pm 0{\cdot}12$ Å except for the terminal carbon atom of the *N*-ethyl group, which is displaced 1·36 Å from the mean plane. There is considerable double-bond localization in the benzene-ring moiety, and a significant difference between the two N—C bond lengths in the pyridine ring, the bond adjacent to the benzene ring being longer by 0·058 (2) Å. The crystal structure features a bifurcated hydrogen bond with a strong intramolecular component from the carboxylic acid group to the neighbouring carbonyl oxygen and a weak intermolecular component from the same donor to O(9) in the dioxole ring.

Introduction. Oxolinic acid (1) and the less potent but closely related nalidixic acid (2) belong to a group of highly active antibacterial agents. These compounds cause a preferential and reversible inhibition of DNA synthesis by inhibiting DNA gyrase (Sugino, Peebles, Kreuzer & Cozzarelli, 1977; Gellert, Mizuuchi, O'Dea, Itoh & Tomizawa, 1977). The crystal structure of nalidixic acid was determined by Achari & Neidle (1976) from photographic data and refined subsequently from more precise diffractometric data (Huber, Sake Gowda & Acharya, 1980). The crystal structure of 5-aminooxolinic acid (3), which shows some antibacterial activity as well, has also been investigated (Czugler, Argay, Frank, Mészáros, Kutschabsky & Reck, 1976). It is of some interest to compare the structure of oxolinic acid with these, and with the molecular structures of some other closely related antibacterial agents for which no X-ray data are yet available.



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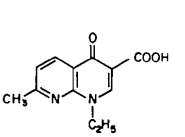

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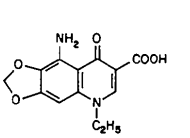

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* Issued as NRCC No. 24238.

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Table 1. *Fractional atomic coordinates* ($\times 10^4$, $\times 10^3$ *for* H *atoms*) *and equivalent isotropic* (*for non-*H *atoms*) *or isotropic* (*for* H *atoms*) *thermal parameters with e.s.d.'s*

$$B_{eq} = \tfrac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a^*_i a^*_j \mathbf{a}_i . \mathbf{a}_j .$$

	x	y	z	B_{eq}/B(Å^2)
N(1)	1673 (2)	3150 (1)	427 (1)	2·8
C(2)	1427 (2)	3507 (2)	1282 (1)	3·0
C(3)	1677 (2)	4719 (2)	1591 (1)	3·0
C(4)	2226 (2)	5692 (2)	995 (1)	2·9
C(41)	2521 (2)	5297 (2)	73 (1)	2·7
C(5)	3083 (2)	6217 (2)	−550 (1)	3·0
C(6)	3345 (2)	5821 (2)	−1405 (1)	3·1
C(7)	3062 (2)	4571 (2)	−1668 (1)	3·1
C(8)	2503 (3)	3654 (2)	−1105 (1)	3·0
C(81)	2236 (2)	4036 (2)	−203 (1)	2·7
O(9)	3907 (2)	6516 (1)	−2119 (1)	4·0
C(10)	3787 (3)	5683 (2)	−2883 (1)	4·1
O(11)	3420 (2)	4435 (1)	−2558 (1)	4·2
C(12)	1354 (3)	1809 (2)	172 (1)	3·6
C(13)	3160 (4)	1091 (2)	130 (1)	4·5
O(14)	806 (2)	4187 (1)	3065 (1)	4·6
C(15)	1294 (3)	4989 (2)	2546 (1)	3·4
O(16)	1506 (2)	6176 (1)	2806 (1)	4·8
O(17)	2431 (2)	6826 (1)	1241 (1)	4·0
H(2)	105 (3)	285 (2)	166 (1)	1·1 (4)
H(5)	324 (3)	704 (2)	−37 (1)	1·4 (4)
H(8)	229 (3)	281 (2)	−130 (1)	1·3 (4)
H(101)	274 (3)	597 (2)	−330 (1)	1·8 (4)
H(102)	499 (4)	565 (3)	−316 (2)	3·2 (5)
H(121)	57 (3)	146 (2)	62 (1)	1·8 (4)
H(122)	60 (3)	179 (2)	−41 (1)	1·4 (4)
H(131)	387 (4)	115 (3)	72 (2)	3·0 (5)
H(132)	391 (4)	145 (3)	−34 (2)	3·3 (5)
H(133)	289 (4)	21 (3)	2 (2)	4·3 (7)
H(16)	196 (5)	665 (3)	231 (2)	5·4 (8)

Experimental. Colourless prismatic crystals grown from dimethyl sulfoxide solution. Specimen 0·15 × 0·10 × 0·30 mm, CAD-4 diffractometer, Ni-filtered Cu $K\alpha$ radiation, cell parameters calculated by least-squares refinement on setting angles of 25 reflections with $25 < \theta < 50°$; integrated intensities measured by $\omega/2\theta$ scans, scan width $\Delta\omega(°) = 1{\cdot}5(0{\cdot}7 + 0{\cdot}2 \tan\theta)$, scan speed 0·45–5·0° min^{-1}; two standards, monitored every 3000 s, showed intensity fluctuations of ±2·5% from mean; 2350 independent (*hkl* and *hk*$\bar{l}$) reflections ($\theta \leq 77{\cdot}5°$), 1565 [with $I > 2\sigma(I)$] considered observed; net intensities, after scaling, corrected for Lorentz and polarization, not for absorption. Structure solved by symbolic addition procedure and refined by block-diagonal least-squares calculations, minimizing $\sum w(\Delta F)^2$; all H atoms located on difference map and refined isotropically, non-hydrogen atoms anisotropically. $w = w_1 w_2$ ($w_1^{1/2} = 25{\cdot}0/|F_o|$ if $|F_o| > 25{\cdot}0$, $w_1 = 1{\cdot}0$ otherwise, $w_2 = \sin^2\theta/0{\cdot}4$ if $\sin^2\theta < 0{\cdot}4$, $w_2 = 1{\cdot}0$ otherwise). Scheme made $\langle w\Delta F^2 \rangle$ essentially independent of $|F_o|$ and $\sin^2\theta$. Three strong reflections, apparently affected by extinction, and 'unobserved' reflections assigned zero weights in refinement. Final $R = 0{\cdot}038$, $wR = 0{\cdot}040$ for all observed reflections; scattering factor values taken from *International Tables for X-ray Crystallography* (1974); calculations done with the NRC set of crystallographic programs (Ahmed, Hall, Pippy & Huber, 1973) unless otherwise noted; $(\Delta/\sigma)_{max} = 0{\cdot}34$ and $(\Delta/\sigma)_{av} = 0{\cdot}10$, $\Delta\rho = 0{\cdot}18$ to $-0{\cdot}28$ e Å^{-3}. Final atomic coordinates are listed in Table 1.* An *ORTEP* drawing (Johnson, 1971) of the molecule showing the numbering scheme is presented in Fig. 1, and bond lengths and valence angles are shown in Fig. 2. The C—H and O—H distances vary from 0·92 to 0·99 Å with e.s.d.'s of 0·02–0·03 Å, and the angles involving H atoms are in the normal range.

Discussion. The non-hydrogen atoms, except for C(10) and C(13), are nearly coplanar, showing maximum deviations of ±0·025 (2) Å from a mean plane calculated through them. Excluding the carboxyl group and O(17) from the mean-plane calculation reduces the deviations of the remaining 13 atoms to 0·012 (2) Å.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39988 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

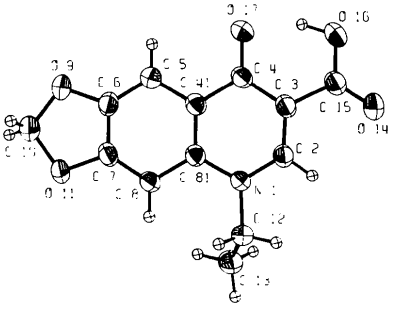


Fig. 1. A view of the oxolinic acid molecule, showing the atom numbering scheme. The ellipsoids enclose 50% probability and the hydrogen atoms are shown as spheres of 0·1 Å radius.

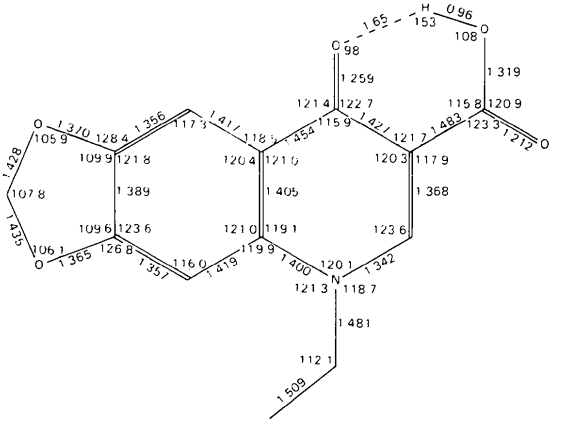


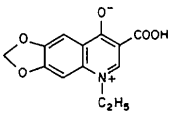
Fig. 2. Bond lengths (Å) and angles (°). E.s.d.'s for the bond lengths not involving H atoms are 0·002–0·003 Å and for the bond angles 0·14–0·18°.

The two out-of-plane atoms, C(10) and C(13), deviate by 0·116 (2) and −1·359 (2) Å respectively. In aminooxolinic acid the overall planarity and deviations are very similar to the present results, while in nalidixic acid both rings show significantly larger deviations from planarity.

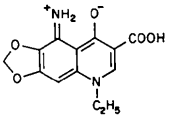
The *N*-ethyl substituent in oxolinic, aminooxolinic and nalidixic acids is not exactly perpendicular to the ring plane, but is slightly rotated about the C—N bond away from the carboxyl group. The C(2)—N(1)—C(12)—C(13) torsional angle in these compounds is −102·3 (2), −97·5 and −99·0° respectively. The conformation may be governed, at least partially, by non-bonded contacts; the H(121)···H(2), H(122)···H(8), and C(13)···H(8) distances here are 2·14, 2·14 and 2·82 Å respectively.

The two pyridine C—N bonds differ by 0·058 Å. Similar differences occur in nalidixic acid (0·059 Å) and aminooxolinic acid (0·049 Å), and a slightly smaller one (0·022 Å) in melochinone, a molecule having a 4-quinolinone skeleton (Kapadia, Paul, Silverton, Fales & Sokoloski, 1975). A qualitatively similar (but larger) effect observed in 1-methyl-2-quinolinone hydrogen hexafluoroarsenate (Calleri & Speakman, 1969) was ascribed to a considerable contribution of an ionic resonance structure (N^+, O^-) and an analogous structure (4) can be envisaged for the *para* carbonyl.

The C(4)=O(17) bond of 1·259 (2) Å is similar to that found in nalidixic acid [1·254 (3) Å] and melochinone [1·256 (3) Å], but appreciably less than the C(4)=O(17) bond in aminooxolinic acid [1·276 (5) Å], the latter value being somewhat affected by an extra intramolecular hydrogen bond from the amino group to O(17). A pattern of differences in bond lengths between oxolinic acid and aminooxolinic acid [lengthening of C(4)—O(17), C(5)—C(6), C(7)—C(8) and C(41)—C(81) and shortening of C(6)—C(7), C(8)—C(81) and C(4)—C(41) in the amino derivative] is probably due to a substantial contribution of another resonance structure, (5), for that compound. The influence of the amino substituent on the endocyclic angles in ring *B* of aminooxolinic acid (compared with oxolinic acid) agrees qualitatively with the effect of an amino group in mono- and disubstituted benzene derivatives (Domenicano & Murray-Rust, 1979). The changes in α, β, γ and δ angles (β and γ are averaged) are −1·8, 0·6, 0·8 and −0·9° respectively and those reported by Domenicano & Murray-Rust are −1·2, 0·2, 1·0 and −1·3°. Differences in endocyclic angles are also observed at the oxygen atoms in the five-membered ring; in oxolinic acid these average 106·0 (1)° and in the amino derivative the average is 104·3 (3)°. That ring is more puckered [C(10) is 0·14 Å out of plane as compared to 0·072 (2) Å in the present structure]. Apart from the differences noted, agreement of bond distances and angles is very good for the two molecules. It may be of interest that both structures, although not isomorphous, have quite similar cell constants, and remarkably similar values of atomic coordinates, after shifting the origin and reversing signs.



(4)



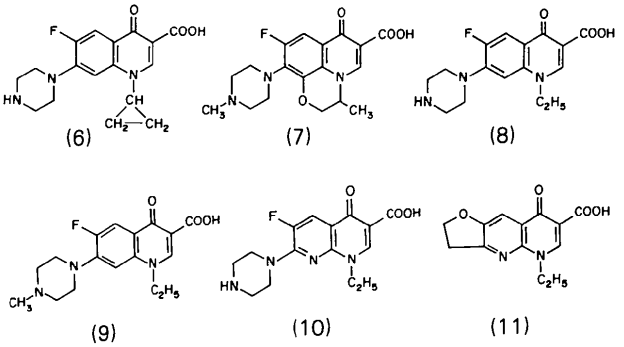
(5)

As in nalidixic and aminooxolinic acids, the present structure features a strong intramolecular hydrogen bond between O(16) of the carboxyl group and O(17), the adjacent carbonyl oxygen. A quasi six-membered ring is formed (see Fig. 2) in which the non-hydrogen atoms deviate only ±0·005 (2) Å from coplanarity. This ring makes a dihedral angle of 1·6 (1)° with the quinoline ring system. The hydrogen-bond system may be bifurcated, as there seems to be a weak intermolecular hydrogen bond from the same donor [O(16)] to O(9) of an adjacent molecule (related by the glide plane). H(16) is displaced by 0·06 (4) Å from the plane through O(16), C(15), C(3), C(4), O(17) toward O(9′), and is only 0·07 (4) Å from the plane through O(9′), O(16), O(17). The O(9′)···H(16) and O(9′)···O(16) distances are 2·50 (4) and 2·986 (2) Å respectively, and the O(16)—H(16)···O(9′) angle is 111 (2)°. The H(16′)···O(9) direction makes angles of 102·3 (8) and 119·1 (8)° with O(9)—C(10) and O(9)—C(6) respectively, reasonably close to tetrahedral values. Thus all geometrical factors are consistent with the hypothesis of a bifurcated hydrogen bond with weak intermolecular component. All other intermolecular contacts are normal. The molecules form zigzag chains along the *z* axis.

Timmers & Sternglanz (1978) have suggested that oxolinic and nalidixic acids may exert their antibacterial activity by forming a complex *in situ* involving the 4-keto oxygen atom and the ionized 3-carboxylic acid with a divalent cation in a metalloprotein involved in DNA replication. Many related compounds have been synthesized recently, of which the following are highly active antibiotics (Goodman, Fliegelman, Trenholme & Kaplan, 1984; Van Caekenberghe & Pattyn, 1984): Bay o 9867 ≡ ciprofloxacin (6) (Wise, Andrews & Edwards, 1983); DL-8280 ≡ ofloxacin (7) (Sato, Matsuura, Inoue, Une, Osada, Ogawa & Mitsuhashi, 1982); AM-715 ≡ norfloxacin (8) (Ito, Hirai, Inoue, Koga, Suzue, Irikura & Mitsuhashi, 1980); 1589 RB ≡ pefloxacin (9) (Goueffon, Montay, Roquet & Pesson, 1981); AT-2266 ≡ enoxacin (10) (Shimizu, Takase, Nakamura, Katae, Inoue, Minami, Nakata & Sakaguchi, 1980); DJ-6783 (11) (Osada, Une, Ogawa & Satoh, 1980). All members of this family have in common the 4-oxo-pyridine-3-carboxylic acid moiety, consistent with Timmers & Sternglanz's

hypothesis. However, the more active compounds (and oxolinic acid, whose activity is approximately next in the series) have, in addition, a very electronegative substituent (F or O) at C(6), which might be a hydrogen-bond acceptor. Furthermore, the N(1) substituent may be important. Albrecht (1977) has noted that ethyl or propyl groups show maximum antibacterial activity in a series of related compounds with ten different substituents in the 1-position; a hydrophobic interaction with the gyrase protein seems possible. In the three compounds with *N*-ethyl groups studied by X-ray diffraction, the *N*-ethyl conformations are remarkably similar (see above), and the N(1) substituents in (6) and (7) can be thought of as spatially analogous. In all these cases there is some conformational similarity to the natural nucleosides, suggesting a possible template-blocking role for these drugs.

We wish to thank Dr R. D. Westland, Warner-Lambert Co., Pharmaceutical Research Division, for the gift of the material.



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2,5-Dichloro-2,5-dimethyl-2,5-disilahexane, $C_6H_{16}Cl_2Si_2$

BY YU. E. OVCHINNIKOV, V. E. SHKLOVER, YU. T. STRUCHKOV, YU. P. POLYAKOV AND L. E. GUSELNIKOV

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Abstract. $M_r = 215{\cdot}3$, triclinic, $P\bar{1}$, $a = 6{\cdot}143$ (2), $b = 6{\cdot}179$ (3), $c = 9{\cdot}074$ (3) Å, $\alpha = 104{\cdot}52$ (3), $\beta = 93{\cdot}07$ (3), $\gamma = 117{\cdot}13$ (3)°, $V = 291{\cdot}0$ (2) Å^3, $Z = 1$, $D_x = 1{\cdot}228$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}697$ mm^{-1}, $F(000) = 114$, $T = 150$ K, $R = 0{\cdot}020$ for 769 observed reflections. The molecule is centrosymmetric; the CSiCCSiC moiety is nearly planar. The Si–Cl bond is rather long [2·091 (1) Å]; other bond

0108-2701/85/071055-03$01.50