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Nalidixic Acid

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Abstract. 1-Ethyl-1,4-dihydro-7-methyl-1,8-naphthyridin-4-one-3-carboxylic acid, $C_{12}H_{12}N_2O_3$, monoclinic, $P2_1/c$, $a = 8 \cdot 913$ (3), $b = 13 \cdot 133$ (4), $c = 9 \cdot 371$ (3) Å, $\beta = 99 \cdot 75$ (4)°, $D_m = 1 \cdot 41$, $D_c = 1 \cdot 425$ g cm^{-3} for $Z = 4$. Equi-inclination Weissenberg intensities, scanned with an automatic densitometer. The structure, solved by direct methods, refined to $R = 0 \cdot 0968$.

Introduction. Prismatic crystals, elongated along c, were grown from an ethanol/water solution. Oscillation and Weissenberg photographs indicated that the crystals were monoclinic, with systematic absences $h0l$, $l = 2n + 1$ and $0k0$, $k = 2n + 1$, thus determining the space group to be $P2_1/c$. Cell dimensions were determined from calibrated Weissenberg (Cu $K\alpha$) and precession photographs (Mo $K\alpha$). Intensities were collected by the equi-inclination Weissenberg method with multi-film packs. Layers $hk0$–$hk7$ and $0kl$–$1kl$ were photographed with Ni-filtered Cu $K\alpha$ radiation. The films were scanned by the Science Research Council microdensitometer service, with an Optronics P-1000 Photoscan. 797 unique observed reflexions were obtained after inter-layer scaling and merging of equivalent reflexions. The structure was solved by direct methods with the *PHASE* link of the X-RAY System (Stewart, Kruger, Ammon, Dickinson & Hall, 1972), and all non-hydrogen atoms were located in the first E map. All subsequent calculations were carried out with a set of computer programs written by Dr G. M. Sheldrick. Full-matrix least-squares refinement with individual isotropic thermal parameters, gave an R of $0 \cdot 133$. A difference synthesis failed to reveal all except one hydrogen position, H(12), and so contributions from H atoms initially in calculated positions were in-

cluded. The refinement was terminated after eight cycles of full-matrix least-squares refinement with all non-hydrogen atoms assigned individual anisotropic thermal parameters. The positional parameters of the H atoms were allowed to refine, but with the C–H vectors constrained in magnitude. The parameters were refined in two overlapping blocks. A weighting scheme $w = 1/\{\sigma^2 |F| + 0 \cdot 040198 F^2\}$ was used, and the final R was $0 \cdot 0968$. Tables 1 and 2 list the positional and thermal parameters.*

Discussion. Nalidixic acid (Fig. 1) is a clinically useful antibacterial drug (Gale, Cundliffe, Reynolds, Richmond & Waring, 1972) which acts by inhibiting nucleic acid synthesis in an, as yet, unknown manner. We have determined the structure of this compound as part of a series of studies on such drugs (Neidle & Jones, 1975; Jones & Neidle, 1975).
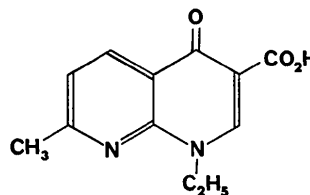

Fig. 1. Nalidixic acid.

Table 1. *Final positional* ($\times 10^4$) *and anisotropic thermal parameters* ($\mathring{A}^2 \times 10^3$) *for the non-hydrogen atoms*

Standard deviations are in parentheses. The thermal parameters are of the form

$$\exp\left[-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+l^2c^{*2}U_{33}+2hka^*b^*U_{12}+2hla^*c^*U_{13}+2klb^*c^*U_{23})\right].$$

|	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	1680 (10)	840 (6)	5817 (8)	46 (2)	60 (4)	32 (4)	−5 (3)	11 (4)	−2 (4)
C(2)	1518 (10)	113 (6)	7002 (8)	46 (2)	58 (4)	34 (4)	−10 (3)	15 (4)	4 (4)
N(3)	1322 (7)	633 (4)	8357 (6)	37 (2)	48 (3)	26 (3)	−3 (2)	5 (3)	11 (3)
C(4)	2499 (9)	746 (5)	9401 (8)	41 (2)	39 (3)	44 (4)	4 (3)	21 (4)	8 (3)
C(5)	2462 (7)	1206 (5)	10723 (7)	38 (2)	44 (3)	33 (4)	3 (3)	16 (3)	−2 (3)
C(6)	1026 (8)	1548 (5)	11044 (7)	40 (2)	43 (3)	37 (4)	2 (3)	21 (3)	4 (3)
C(7)	−249 (7)	1441 (5)	9877 (7)	37 (2)	38 (3)	36 (3)	−1 (3)	17 (3)	2 (3)
C(8)	−1728 (9)	1789 (6)	10003 (8)	48 (2)	56 (4)	39 (4)	−4 (3)	12 (4)	0 (3)
C(9)	−2882 (9)	1699 (6)	8856 (8)	51 (2)	41 (4)	60 (5)	−1 (3)	22 (4)	11 (3)
C(10)	−2602 (8)	1228 (5)	7579 (8)	44 (2)	38 (3)	50 (4)	8 (3)	14 (4)	6 (3)
N(11)	−1245 (6)	884 (4)	7411 (6)	39 (2)	46 (3)	33 (3)	1 (2)	11 (3)	2 (3)
C(12)	−94 (8)	996 (5)	8543 (7)	37 (2)	39 (3)	35 (4)	3 (3)	20 (3)	3 (3)
C(13)	−3886 (11)	1088 (7)	6299 (9)	56 (2)	60 (5)	52 (5)	−6 (4)	6 (4)	13 (4)
O(14)	877 (5)	1924 (4)	12249 (5)	51 (2)	63 (3)	38 (3)	−2 (2)	22 (3)	3 (2)
C(15)	3858 (9)	1312 (5)	11782 (8)	46 (2)	51 (4)	42 (4)	4 (3)	21 (4)	−2 (3)
O(16)	3725 (7)	1733 (4)	13037 (6)	60 (2)	81 (4)	38 (3)	−3 (3)	7 (3)	−2 (3)
O(17)	5117 (7)	1024 (4)	11576 (6)	62 (2)	76 (4)	49 (3)	−8 (3)	7 (3)	−3 (3)
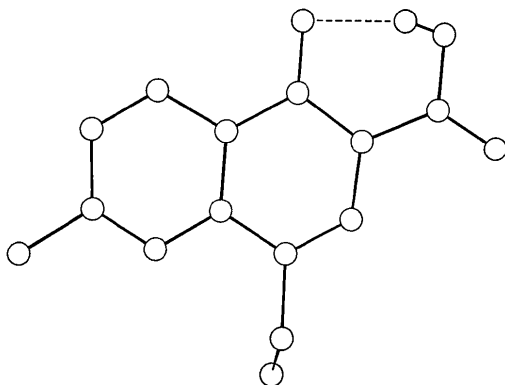
Fig. 2. A projection of the molecule, drawn perpendicular to the aromatic rings.

Table 2. *Fractional coordinates* ($\times 10^3$) *for the hydrogen atoms, with estimated standard deviations in parentheses*

The two digits of the atom numbering denote the atom to which each hydrogen is bonded. An isotropic thermal parameter of 0·05 $\mathring{A}^2$ was assigned to all hydrogen atoms.

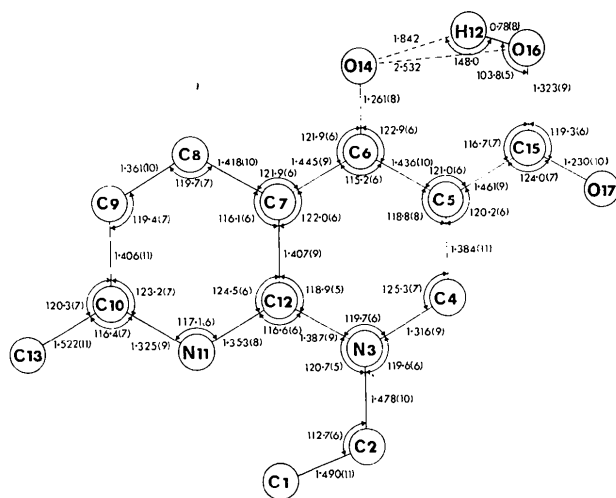|	x	y	z
H(101)	164 (7)	61 (5)	488 (8)
H(201)	273 (9)	134 (5)	602 (7)
H(301)	54 (8)	110 (5)	554 (7)
H(402)	245 (8)	−33 (6)	715 (7)
H(502)	71 (8)	−34 (6)	661 (8)
H(604)	360 (7)	49 (6)	915 (7)
H(708)	−161 (8)	226 (6)	1073 (8)
H(809)	−384 (8)	204 (5)	879 (8)
H(913)	−442 (8)	155 (6)	640 (8)
H(1013)	−414 (7)	31 (6)	604 (7)
H(1113)	−355 (7)	122 (6)	528 (8)
H(1216)	287 (8)	168 (6)	1308 (8)

Fig. 3. Intramolecular bond lengths and angles, with estimated standard deviations in parentheses.

Fig. 2 shows a projection of the molecule, and Fig. 3 details bond lengths and angles for all the non-hydrogen atoms, and for H(12), together with the numbering scheme used. The values found are unexceptional and compare favourably with those reported for the related compounds 1,8-naphthyridine (Clearfield, Sims & Singh, 1972), and 3-ethoxycarbonyl-4-oxo-6-methyl-homopyrimidazole (Sasvári, Horvai & Simon, 1972). Nalidixic acid is slightly though significantly non-planar; Table 3 lists the deviations from various least-squares planes. Each pyridine ring is itself planar within the limits of experimental error, but the ring fusion has induced slight buckling of the ten-membered naph-thyridine ring, presumably because of lone-pair repulsions. Similar buckling effects have been observed in the related compounds mentioned above.

The carboxylic acid H(12) interacts with the carbonyl O(14) to form an intramolecular hydrogen bond; this is the only hydrogen bond in the crystal structure (Fig. 4).

Table 3. *Deviations (in Å) of atoms from the least-squares planes for various parts of the molecule*

Atoms marked with an asterisk have been included in the calculation of the plane.

C(1)	−1·269	−1·269	−1·277
C(2)	0·070	0·059	0·065
N(3)	0·015*	−0·006	0·005
C(4)	0·007*	−0·055	0·032
C(5)	−0·026*	−0·102	−0·002*
C(6)	0·022*	−0·023	0·003*
C(7)	−0·001*	−0·002*	−0·058
C(8)	−0·025	0·010*	−0·125
C(9)	−0·088	−0·011*	−0·223
C(10)	−0·081	0·004*	−0·208
N(11)	−0·048	0·005*	−0·134
C(12)	−0·017*	−0·006*	−0·070
C(13)	−0·106	0·025	−0·271
O(14)	0·069	0·014	0·046
C(15)	−0·070	−0·193	−0·005*
O(16)	−0·060	−0·194	0·000*
O(17)	−0·097	−0·248	0·004*

Nalidixic acid itself is unlikely to function physiologically by interacting directly with a nucleic acid because of strong electrostatic repulsions between the drug and negatively charged nucleic acid phosphate groups. However, an uncharged (putative) metabolite, such as an ethoxycarbonyl derivative, would still have essentially planar geometry, and could well intercalate between base pairs (Shuman & Schwartz, 1975).

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Fig. 4. The *c*-axis projection of the crystal structure.

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(β-Cyanoéthyl)-2 Triméthyl-2,5,5 Cyclohexanedione-1,3

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Abstract. $C_{12}H_{17}NO_2$, orthorhombic, *Pcam*, $a = 14·326$ (3), $b = 9·460$ (2), $c = 9·047$ (2) Å (at 295 K), $Z = 4$, $D_c = 1·122$ g cm^{-3}, $V = 1226·1$ Å^3, $F(000) = 448$, $M = 207·1$, λ(Cu $K\alpha$) = 1·54178, μ(Cu $K\alpha$) = 6·29 cm^{-1}. The structure was solved by a modified symbolic addition procedure. Full-matrix least-squares refinement gave final R_1 and weighted R_2 values of 0·056 and 0·045 for 1128 observed diffractometer reflexions. The molecule is in a special position of symmetry *m*; the cyanoethyl group is equatorial.

Introduction. La (β-cyanoéthyl)-2 triméthyl-2,5,5 cyclohexanedione-1,3 peut exister sous la forme d'un equilibre entre les conformations I et II correspondant aux positions respectivement équatoriale et axiale de la chaîne cyanoéthyle.

Dans une étude précédente (Guy & Winternitz, 1969), des mesures de moment dipolaire ont montré que la (β-cyanoéthyl)-2 méthyl-2 cyclohexanedione-1,3 existe sous la forme I (chaîne cyanoéthyle équatoriale)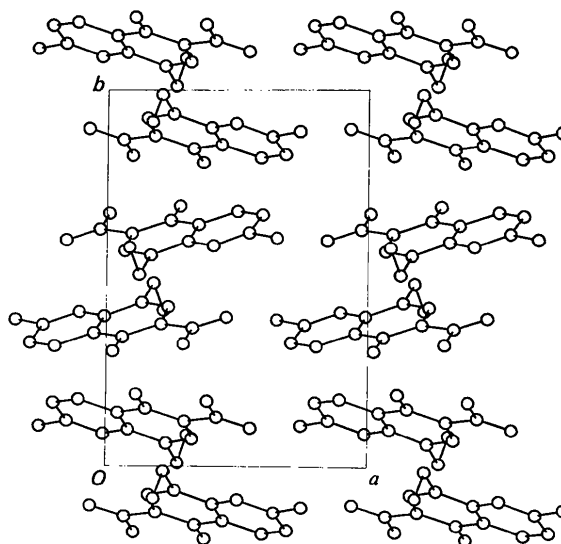, pour laquelle le moment dipolaire dc la molécule est le