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6-Ethyl-9-fluoro-6,7-dihydro-8-(4-hydroxy-piperidino)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic Acid

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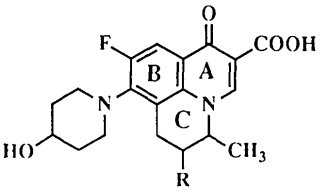
Abstract

The molecular structure of the title compound, $C_{21}H_{25}FN_2O_4$, (1), has been established by X-ray diffraction. The conformation of the methyl and ethyl groups is *gauche*. The methyl group is at a right angle to the 4-quinolone ring, but the ethyl group is equatorial.

Comment

As part of an investigation into structure–activity relationships of quinolone antibacterial drugs, the molecular structure of nadifloxacin, (2), was confirmed by three-dimensional structure analysis (Kido & Hashimoto, 1994). The molecular skeleton of nadifloxacin comprises a system of three six-membered rings, *A*, *B* and *C*. The aromatic rings *A* and *B* of the 4-quinolone moiety are almost coplanar, while the saturated ring *C* is twisted and the methyl group protrudes at a right angle from the 4-quinolone moiety. The same conformation was suggested by molecular-mechanics calculations for an analogous drug, ofloxacin, and this conformation plays an important role in bioactivity (Sato & Matsuhashi, 1991). The determination of the title structure, (1), will contribute to the knowledge of the geometrical effects of various substituents in the position next to the methyl group. An *ORTEP* (Johnson, 1965) drawing of the title compound with the atomic labelling scheme is shown in Fig. 1. Bond distances and angles agree with those of nadifloxacin.



(1) $R = C_2H_5$
(2) $R = H$

The methyl and ethyl groups adopt a *gauche* conformation [C(13)—C(10)—C(11)—C(20) = −66.3 (6)°]. The methyl group protrudes at a right angle from the 4-quinolone moiety but the ethyl group is equatorial. The two C—O bonds of the carboxylic acid group differ in length: C(14)—O(1) and C(14)—O(2) are 1.216 (6) and 1.332 (6) Å, respectively. The intramolecular distance between O(2) and O(3) of 2.543 (6) Å suggests that an intramolecular hydrogen bond exists between the two O atoms.

The piperidine ring adopts a typical chair conformation with N(2) and C(17) deviating −0.687 and 0.660 Å, respectively, from the mean plane through C(15), C(16), C(18) and C(19). Each molecule in the crystal structure is linked to its neighbor by an O(4)—H···O(1) hydrogen bond with a distance of 2.849 (6) Å [O(1) at $\frac{1}{2} - x$, $y - \frac{3}{2}$, $\frac{1}{2} + z$].

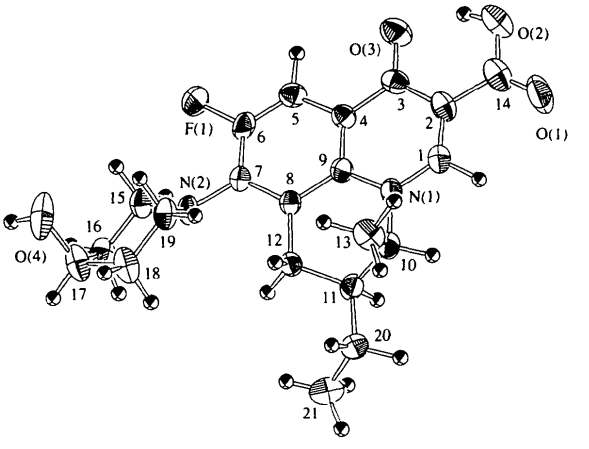


Fig. 1. *ORTEP* (Johnson, 1965) drawing of (1) with the atomic labeling scheme. Ellipsoids are drawn at the 50% probability level and H atoms are represented by spheres of arbitrary size.

Experimental

Crystal data

$C_{21}H_{25}FN_2O_4$
M_r = 388.44
Orthorhombic
$Pna2_1$
a = 15.387 (2) Å
b = 7.705 (2) Å
c = 16.013 (2) Å
V = 1898 (1) Å^3
Z = 4
D_x = 1.359 Mg m^{-3}
D_m = 1.355 (3) Mg m^{-3}
D_m measured by flotaion in aqueous KI solution

Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 15.2–16.5°
μ = 0.094 mm^{-1}
T = 296 K
Plate-like
0.4 × 0.3 × 0.3 mm
Colorless
Crystal source: from EtOH/H_2O solution

Data collection

Rigaku AFC-5*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
1948 measured reflections
1948 independent reflections
1188 observed reflections [$I > 3\sigma(I)$]

θ_{max} = 25.0°
$h = 0 \rightarrow 18$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 19$
3 standard reflections monitored every 150 reflections
intensity decay: not significant

Refinement

Refinement on F
R = 0.036
wR = 0.040
S = 1.20
1188 reflections
277 parameters
H atoms from difference Fourier maps; only U's refined
$w = 4F_o^2/\sigma^2(F_o^2)$

$(\Delta/\sigma)_{max}$ = 0.33
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: not applied
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
F(1)	0.1474 (2)	−0.0310 (3)	0.9711	4.6 (1)
O(1)	0.1816 (3)	0.7914 (5)	0.6302 (3)	5.8 (2)
O(2)	0.0859 (2)	0.7853 (5)	0.7330 (3)	4.9 (2)
O(3)	0.0715 (2)	0.5136 (4)	0.8220 (3)	4.1 (2)
O(4)	0.3934 (3)	−0.4027 (5)	1.0608 (3)	6.0 (2)
N(1)	0.2847 (2)	0.3171 (4)	0.7022 (3)	2.6 (2)
N(2)	0.3005 (2)	−0.1666 (4)	0.8946 (3)	2.7 (2)
C(1)	0.2497 (3)	0.4703 (6)	0.6799 (3)	3.1 (2)
C(2)	0.1791 (3)	0.5409 (6)	0.7167 (4)	3.3 (2)
C(3)	0.1362 (3)	0.4520 (6)	0.7834 (3)	2.9 (2)
C(4)	0.1732 (3)	0.2864 (5)	0.8067 (3)	2.6 (2)
C(5)	0.1383 (3)	0.1914 (6)	0.8735 (3)	3.0 (2)
C(6)	0.1807 (3)	0.0482 (6)	0.9013 (3)	3.1 (2)
C(7)	0.2560 (3)	−0.0184 (5)	0.8647 (3)	2.5 (2)
C(8)	0.2876 (2)	0.0658 (5)	0.7938 (3)	2.3 (2)
C(9)	0.2485 (3)	0.2222 (6)	0.7675 (3)	2.5 (2)
C(10)	0.3690 (3)	0.2600 (6)	0.6641 (3)	3.0 (2)
C(11)	0.3662 (3)	0.0635 (6)	0.6565 (3)	3.0 (2)
C(12)	0.3601 (3)	−0.0166 (6)	0.7429 (3)	2.7 (2)
C(13)	0.4444 (3)	0.3332 (6)	0.7145 (4)	4.0 (3)
C(14)	0.1495 (3)	0.7132 (6)	0.6884 (4)	4.1 (3)
C(15)	0.2539 (3)	−0.3032 (6)	0.9397 (3)	3.4 (2)
C(16)	0.3068 (4)	−0.4699 (6)	0.9376 (4)	3.8 (2)
C(17)	0.3982 (3)	−0.4447 (6)	0.9741 (4)	4.1 (2)
C(18)	0.4417 (3)	−0.2925 (6)	0.9305 (4)	4.2 (3)
C(19)	0.3854 (3)	−0.1303 (6)	0.9335 (3)	3.1 (2)
C(20)	0.4430 (3)	−0.0041 (6)	0.6058 (4)	3.9 (3)
C(21)	0.4344 (4)	−0.1965 (8)	0.5850 (4)	5.5 (3)

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

F(1)—C(6)	1.372 (5)	C(4)—C(9)	1.408 (5)
O(1)—C(14)	1.216 (6)	C(5)—C(6)	1.358 (6)
O(2)—C(14)	1.332 (6)	C(6)—C(7)	1.396 (6)
O(3)—C(3)	1.264 (5)	C(7)—C(8)	1.395 (6)
O(4)—C(17)	1.429 (7)	C(8)—C(9)	1.411 (6)
N(1)—C(1)	1.346 (5)	C(8)—C(12)	1.521 (6)
N(1)—C(9)	1.392 (5)	C(10)—C(11)	1.519 (6)
N(1)—C(10)	1.500 (5)	C(10)—C(13)	1.522 (6)
N(2)—C(7)	1.415 (5)	C(11)—C(12)	1.518 (6)
N(2)—C(15)	1.464 (5)	C(11)—C(20)	1.525 (6)
N(2)—C(19)	1.475 (5)	C(15)—C(16)	1.521 (6)
C(1)—C(2)	1.351 (6)	C(16)—C(17)	1.537 (7)
C(2)—C(3)	1.431 (7)	C(17)—C(18)	1.520 (7)
C(2)—C(14)	1.475 (7)	C(18)—C(19)	1.521 (7)
C(3)—C(4)	1.446 (6)	C(20)—C(21)	1.525 (7)
C(4)—C(5)	1.403 (6)		
C(1)—N(1)—C(9)	120.1 (4)	C(7)—C(8)—C(12)	119.9 (4)
C(1)—N(1)—C(10)	119.7 (3)	C(9)—C(8)—C(12)	120.6 (4)
C(9)—N(1)—C(10)	119.8 (3)	N(1)—C(9)—C(4)	118.6 (4)
C(7)—N(2)—C(15)	120.7 (3)	N(1)—C(9)—C(8)	120.2 (4)
C(7)—N(2)—C(19)	114.8 (3)	C(4)—C(9)—C(8)	121.2 (4)
C(15)—N(2)—C(19)	111.2 (3)	N(1)—C(10)—C(11)	107.5 (4)
N(1)—C(1)—C(2)	124.0 (4)	N(1)—C(10)—C(13)	109.6 (4)
C(1)—C(2)—C(3)	120.3 (4)	C(11)—C(10)—C(13)	115.7 (4)
C(1)—C(2)—C(14)	118.5 (5)	C(10)—C(11)—C(12)	109.5 (4)
C(3)—C(2)—C(14)	121.2 (5)	C(10)—C(11)—C(20)	111.2 (4)
O(3)—C(3)—C(2)	123.3 (4)	C(12)—C(11)—C(20)	113.2 (4)
O(3)—C(3)—C(4)	121.0 (4)	C(8)—C(12)—C(11)	111.3 (4)
C(2)—C(3)—C(4)	115.7 (4)	O(1)—C(14)—O(2)	120.2 (5)
C(3)—C(4)—C(5)	120.4 (4)	O(1)—C(14)—C(2)	123.8 (5)
C(3)—C(4)—C(9)	121.3 (4)	O(2)—C(14)—C(2)	116.0 (5)
C(5)—C(4)—C(9)	118.2 (4)	N(2)—C(15)—C(16)	109.5 (4)
C(4)—C(5)—C(6)	119.4 (4)	C(15)—C(16)—C(17)	112.0 (4)
F(1)—C(6)—C(5)	116.7 (4)	O(4)—C(17)—C(16)	110.5 (5)
F(1)—C(6)—C(7)	119.3 (4)	O(4)—C(17)—C(18)	107.2 (4)
C(5)—C(6)—C(7)	124.0 (4)	C(16)—C(17)—C(18)	109.0 (4)
N(2)—C(7)—C(6)	123.7 (4)	C(17)—C(18)—C(19)	111.6 (4)
N(2)—C(7)—C(8)	118.8 (4)	N(2)—C(19)—C(18)	109.6 (4)
C(6)—C(7)—C(8)	117.4 (4)	C(11)—C(20)—C(21)	112.4 (4)
C(7)—C(8)—C(9)	119.4 (4)		

Data collection: *AFC/MSC* (Rigaku Corporation, 1988). Cell refinement: *AFC/MSC*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *MITHRIL* (Gilmore, 1984). Program(s) used to refine structure: *TEXSAN LS*. Software used to prepare material for publication: *TEXSAN FINISH*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AS1135). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Organophosphorus Insecticides. 16. Azinphos Ethyl: *O,O*-Diethyl *S*-{[4-Oxo-1,2,3-benzotriazin-3(4*H*)-yl]methyl} Phosphorodithioate, $C_{12}H_{16}N_3O_3PS_2$

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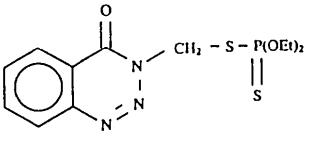
Abstract

In the title compound, a P···δ(+)-C-atom distance is observed in the solid state which falls within the range of literature values for the span of $\delta(-)\cdots\delta(-)$ charges in the active site of insect acetylcholinesterase (AChE), but is outside the range for mammalian AChE. The structure of azinphos ethyl is comparable to that of the methyl analog.

Comment

The crystal and molecular structure of azinphos ethyl (ethyl guthion, *O,O*-diethyl *S*-{[4-oxo-1,2,3-benzotriazin-3(4*H*)-yl]methyl} phosphorodithioate) was undertaken as part of an ongoing study of the structures of organophosphorus (OP) insecticides (Baughman & Yu, 1982, and references therein). The determination of accurate three-dimensional structures of a series of OP's should give better insight into any structure–activity related interactions between P···δ(+) centers in the insecticide and $\delta(-)\cdots\delta(-)$ centers in acetylcholinesterase (AChE).



Azinphos ethyl

As in azinphos methyl (Rohrbaugh, Meyers & Jacobson, 1976), the ring system of azinphos ethyl is essentially planar (see Fig. 1 and Table 1). Both the methylene groups in azinphos ethyl and the methyl groups in azinphos methyl generally point towards the S2 atom which is common to both molecules. The S2—P—O—C torsion angles are between ±65° [−50.4 (3) and 44.6 (5)° in azinphos ethyl; −62 and −36° in azinphos methyl]. In both molecules, S1 is just on the O1 side of the molecule [N2—N3—C8—S1 = −94.3 (3)° for azinphos ethyl and −119° for azinphos methyl]. However, the thiophosphate groups are twisted away from the O1 side of each molecule [P—S1—C8—N3 = 127.5 (3) for azinphos ethyl, 110° for azinphos methyl]. Both azinphos molecules have a nearly planar zigzag S2—P—S1—C8 group [torsion angles −179.0 (3) (azinphos ethyl) and −178° (azinphos methyl)]. In azinphos ethyl, the P—O3—C9—C10 group is essentially in a zigzag configuration, but P—O2—C11—C12 is not [torsion angles 167.9 (4) and 105.9 (4)°, respectively].

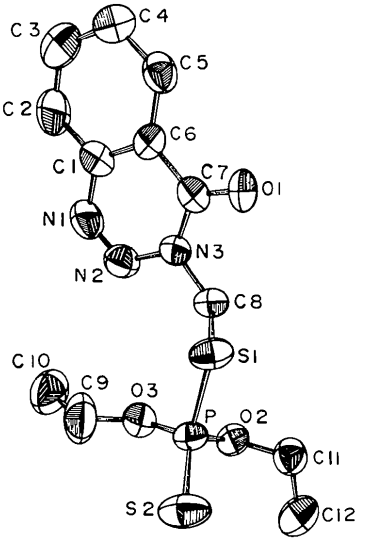


Fig. 1. The azinphos ethyl molecule showing 50% probability ellipsoids for the non-H atoms.

As noted previously (Baughman & Jacobson, 1978), certain P···δ(+)-center distances may give some insight into the toxicity and activity of OP's. For insect AChE, the range of $\delta(-)$ site separations (*i.e.* active-site distances) in AChE is 5.0–5.5 Å (Hollingworth, Fukuto & Metcalf, 1967) or 4.5–5.9 Å (O'Brien, 1963). P and C7 appear to be the most likely atoms in azinphos ethyl to be both electron deficient and at a distance within these ranges. The P···C7 separation in the solid state of azinphos ethyl is 5.21 Å, while the corresponding distance for the methyl analog is 4.83 Å. The fact that the azinphos ethyl molecule has at least one P···δ(+) distance in the 'tighter' of the two cited ranges may have an influence on the insect toxicity of the title compound.

Since azinphos ethyl has a low mammalian LD50 value of 9 mg kg^{-1} (Thompson, 1984), a comparison with the $\delta(-)$ site-separation distance in mammalian