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3,4-Dihydro-2,6,7-trimethyl-4-oxo-3-(2-pyridyl)quinazoline-8-carboxylic Acid

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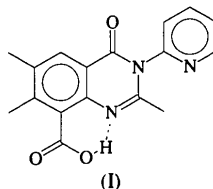
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Abstract

The title compound, C₁₇H₁₅N₃O₃, has a very short intramolecular O—H···N hydrogen bond, which closes a six-membered ring and forces an almost coplanar disposition of the carboxyl group with respect to the quinazoline ring plane. The dihedral angle between the least-squares planes of the quinazoline system and the pyridine ring is 86.8(1)°. The C—H···O hydrogen bonds determine the crystal packing.

Comment

Several 3,4-dihydro-2-methyl-4-oxo-3-arylquinazoline derivatives have been found to be potent anticonvulsants (Vaidaya, Panos, Kite, Ben Iturrian & DeWitt Blanton Jr, 1983). Since biological action seems to be quite sensitive to small structural alterations, X-ray structural analysis may provide insight into activity. Incorporation of a third ring N atom into the molecule, by changing the phenyl ring at the 3-position into α -pyridyl, causes a significant increase in central-nervous-system activity. The title compound, (I), acts as a convulsant, causing deaths at 300 mg kg⁻¹, while its methyl ester is as active an anticonvulsant as methaqualone in the maximal electroshock (MES) test (effective dose ED₅₀ of 52 mg kg⁻¹) and is not neurotoxic.



The strong, intramolecular hydrogen bond O82—H82···N1, which has an O···N distance of 2.494(3) Å, closes a six-membered ring (Fig. 1). By comparison, the value of the O···N distance in 1-phenazinecarboxyl-

ic acid is 2.67 Å (Ji, van der Helm, Hemming & Haymore, 1992). In consequence, the carboxyl group is almost coplanar with the quinazoline ring system: the dihedral angle between the least-squares plane of the quinazoline fragment and the plane defined by the carboxylic acid group is 1.9(5)°. Similar small values of that angle have been observed in related compounds with an intramolecular hydrogen bond; for example, 2.6(1)° in 6-(3-hydroxymethyl-4-oxo-2,5-dioxahex-6-yl)phenazine-1-carboxylic acid (Shoji *et al.*, 1988), 2.3(1)° in bethocyanin (Shin-ya *et al.*, 1991) and 3.5(2)° in 1-phenazinecarboxylic acid (Ji *et al.*, 1992). In contrast, molecules without such an intramolecular interaction have significantly greater dihedral angles; for example, in *p*-cyclopropyl-1-naphthalenecarboxylic acid the value is 12.0(1)° (Drumright, Mas, Merola & Tanko, 1990) and in 1-naphthoic acid 8.4(3)° (Fitzgerald & Gerkin, 1993). The participation of the carboxyl O—H bond in the intramolecular hydrogen bond also causes the antiplanar conformation of the carboxyl group. This conformation is far less stable than the synplanar one and it occurs almost only when it is forced by an intramolecular hydrogen bond (Bernstein, Etter & Leiserowitz, 1994).

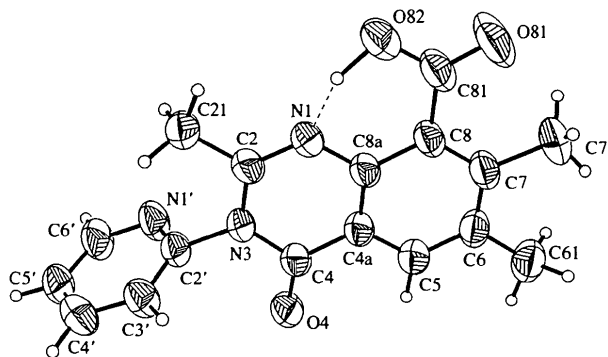


Fig. 1. Displacement ellipsoid representation (Siemens, 1989) (50% probability level) of the title compound, together with the numbering scheme; the H atoms are drawn as spheres with an arbitrary radius. The intramolecular hydrogen bond is depicted as a dashed line.

Both quinazoline and pyridine fragments are nearly planar, with maximum deviations from the least-squares planes of 0.026(3) and 0.010(3) Å, respectively. The large value of the dihedral angle between the least-squares planes of these two fragments, 86.8(1)°, is due to the substituents at positions 2 and 4, which are *ortho* with respect to the C3—C2' bond.

The crystal packing is almost exclusively ruled by C—H···O hydrogen bonds, which connect molecules into a three-dimensional structure (Fig. 2). This structure consists of centrosymmetric dimers $R\bar{2}(16)$ (using graph-set notation: Etter, MacDonald & Bernstein, 1990; Bernstein, Davis, Shimoni & Chang, 1995), which,

together with an intramolecular *S*(6) motif, make the second-order centrosymmetric dimeric ring $R_4^4(12)$, and of infinite chains: *C*(5) which connects molecules related by the 2_1 axis along [010], *C*(6) which connects molecules related by unit-cell translation along *y*, and *C*(12), along $[-101]$, built of molecules related by the *n* glide plane. These chains, in turn, close larger second-order rings.

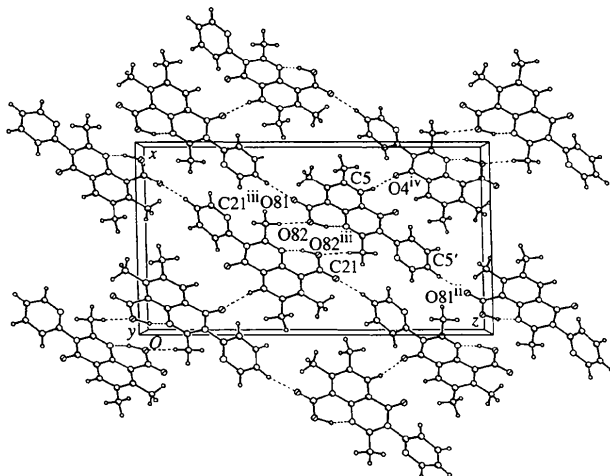


Fig. 2. The packing scheme, as seen along the [010] direction. The dashed lines represent the hydrogen bonds. For clarity, molecules related by the hydrogen bond $C3'-H3' \cdots O4'$, which would make the same structure above and below the drawn one, have not been shown. The symmetry codes are the same as those given in Table 2.

Experimental

The preparation of the title compound has been described elsewhere (Vaidaya *et al.*, 1983). The sample was provided by Dr Blanton Jr and recrystallized from ethanol by slow evaporation.

Crystal data

C₁₇H₁₅N₃O₃
M_r = 309.32
 Monoclinic
*P*2₁/*n*
a = 12.9397 (12) Å
b = 4.9019 (4) Å
c = 23.180 (3) Å
 β = 90.703 (9)°
V = 1470.2 (3) Å³
Z = 4
D_x = 1.397 Mg m⁻³
D_m not measured

Data collection

Enraf-Nonius CAD-4F
 diffractometer
 $\omega/2\theta$ scans
 Absorption correction: none

Cu *K* α radiation
 λ = 1.54178 Å
 Cell parameters from 25
 reflections
 θ = 8–41°
 μ = 0.808 mm⁻¹
T = 293 (2) K
 Plate
 0.3 × 0.3 × 0.1 mm
 Colorless

θ_{\max} = 74.86°
h = 0 → 16
k = 0 → 6
l = -29 → 29

3095 measured reflections
 2978 independent reflections
 2079 reflections with
 $I > 2\sigma(I)$
 $R_{\text{int}} = 0.078$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.053$
 $wR(F^2) = 0.195$
 $S = 1.307$
 2976 reflections
 263 parameters
 All H atoms refined
 $w = 1/[\sigma^2(F_o^2) + (0.0216P)^2 + 1.294P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.001$

3 standard reflections
 frequency: 33 min
 intensity decay: 1.7%

$\Delta\rho_{\max} = 0.213 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.226 \text{ e \AA}^{-3}$
 Extinction correction:
SHELXL93 (Sheldrick,
 1993)
 Extinction coefficient:
 0.0025 (4)
 Scattering factors from
*International Tables for
 Crystallography* (Vol. C)

Table 1. Selected geometric parameters (Å, °)

N1—C2	1.289 (4)	C81—O81	1.203 (4)
N1—C8a	1.391 (4)	C81—O82	1.319 (5)
C8—C81	1.511 (5)		
C2—N1—C8a	120.7 (3)	C2'—N1'—C6'	116.3 (3)
N1—C2—N3	122.3 (3)	C8a—C8—C81	120.3 (3)
N1—C2—C21	119.5 (3)	O81—C81—O82	118.5 (4)
C2—N3—C2'	120.8 (3)	O81—C81—C8	123.2 (4)
C4—N3—C2'	116.8 (2)	O82—C81—C8	118.3 (3)

Table 2. Hydrogen-bonding geometry (Å, °)

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O82—H82...N1	1.12 (5)	1.44 (5)	2.494 (3)	155 (4)
C3'—H3'...O4'	0.96 (4)	2.31 (4)	3.184 (5)	151 (3)
C5'—H5'...O81 ⁱⁱⁱ	1.00 (4)	2.41 (4)	3.347 (4)	155 (3)
C21—H21C...O82 ⁱⁱⁱ	0.98 (5)	2.41 (5)	3.388 (5)	175 (4)
C5—H5...O4 ^{iv}	1.01 (3)	2.41 (4)	3.387 (4)	164 (3)

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

Data collection: *CAD-4 Software* (Enraf-Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *ENPROC* (Rettig, 1978). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *Stereochemical Workstation* (Siemens, 1989). Software used to prepare material for publication: *SHELXL93*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1307). Services for accessing these data are described at the back of the journal. A difference plot showing clearly the H atom bonded to O82 is also available.

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4,12,16,24-Tetrahydroxycalix[4]arene–Methanol (1/2)

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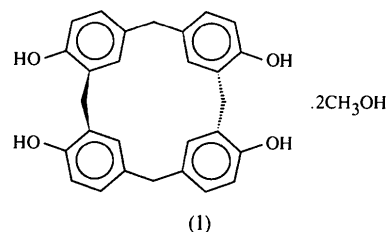
Abstract

The calixarene moiety in the title compound, 4,12,16,24-tetrahydroxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosal(25),3,5,7(26),9,11,13(27),15,17,19(28),21,23-dodecane–methanol (1/2), C₂₈H₂₄O₄·2CH₃O, assumes a 1,2-alternate conformation in the crystalline state which allows two intramolecular O—H···O hydrogen bonds to be formed between pairs of adjacent phenolic OH groups. The molecules are arranged in the crystal to form infinite chains connected *via* intermolecular hydrogen bonds involving the two bridging methanol molecules. 12-Membered cyclic arrays of six hydrogen-bonded OH groups are formed with O···O 2.618(3)–2.742(2) Å.

Comment

Numerous single-crystal structures of calix[4]arenes with the hydroxy groups in *endo*-positions (25,26,27,28-tetrahydroxycalix[4]arenes) are known (see Böhmer, 1995, and references therein). Due to the cyclic array

of intramolecular hydrogen bonds, in all cases these calixarenes assume a more or less distorted cone conformation. We recently described the first X-ray structure of a *tert*-butyl-substituted calix[4]arene with four *exo*-hydroxy groups (Böhmer *et al.*, 1996), which somewhat surprisingly showed a cone conformation nearly identical to its *endo*-isomer. Such calix[4]arenes with four hydroxy groups in *exo*-positions have a still unexplored potential as building blocks, *e.g.* for the preparation of annelated calixarenes. We report here the crystal structure of the unsubstituted parent compound, (1).



Our X-ray analysis establishes that (1) has a 1,2-alternate conformation (Fig. 1) and reveals that two methanol molecules of solvation link the calix[4]arene molecules by O—H···O hydrogen bonds to form infinite rippled chains (Fig. 2) which extend along the *b* direction. In this way, 12-membered (···O—H···)₆ rings with graph-set notation R₆⁶(12) (Bernstein, Davis, Shimoni & Chang, 1995) are formed. The six O atoms of the (···O—H···)₆ rings are in a boat conformation. Hydrogen-bonding details are given in Table 2; the O···O distances are normal and in the range 2.618(2)–2.742(2) Å. There are only van der Waals interactions between the infinite chains.

A common method of describing calix[4]arene conformations is to quote the interplanar angles which the aromatic rings make with the plane of the four methyl-

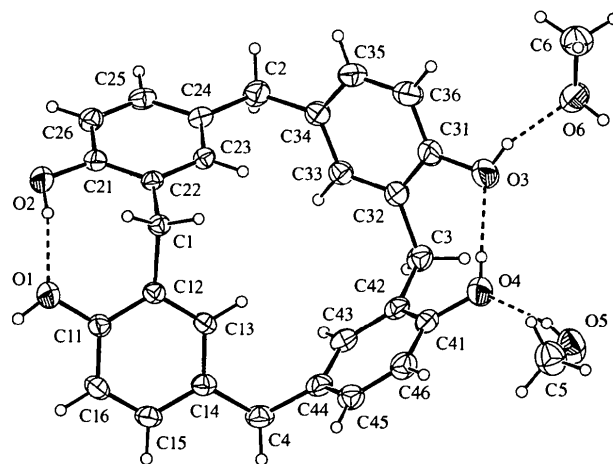


Fig. 1. A view of (1) with the crystallographic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.