Triclinic
$P\bar{1}$
a = 7.956 (2) Å
b = 8.193 (2) Å
c = 9.313 (2) Å
α = 89.89 (1)°
β = 94.79 (1)°
γ = 90.95 (1)°
V = 604.8 (4) Å^3
Z = 2
D_x = 1.23 Mg m^{-3}
D_m not measured

Cell parameters from 25 reflections
θ = 8–14°
μ = 0.070 mm^{-1}
T = 294 K
Square prism
0.40 × 0.25 × 0.25 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2032 measured reflections
1899 independent reflections
924 observed reflections [$I > 3\sigma(I)$]

R_{int} = 0.025
θ_{max} = 23.97°
$h = -9 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = 0 \rightarrow 10$
2 standard reflections
frequency: 60 min
intensity decay: 1.70%

Refinement

Refinement on F
R = 0.047
wR = 0.054
S = 1.613
924 reflections
158 parameters
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0016F_o^4]$

$(\Delta/\sigma)_{max}$ = 0.005
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: none
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)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N1	0.5116 (3)	0.2118 (3)	0.9014 (3)	0.0488 (8)
N2	0.0836 (4)	0.4678 (4)	1.1465 (3)	0.074 (1)
N3	0.2364 (3)	0.2919 (3)	0.8390 (3)	0.0513 (8)
C1	0.3736 (4)	0.2829 (4)	0.9399 (4)	0.044 (1)
C2	0.3625 (4)	0.3470 (4)	1.0784 (3)	0.0409 (9)
C3	0.5009 (4)	0.3433 (4)	1.1786 (4)	0.046 (1)
C4	0.6444 (4)	0.2713 (4)	1.1350 (4)	0.057 (1)
C5	0.6451 (4)	0.2056 (4)	1.0000 (4)	0.052 (1)
C6	0.2084 (4)	0.4155 (4)	1.1158 (4)	0.052 (1)
C7	0.4955 (5)	0.4139 (5)	1.3258 (4)	0.063 (1)
C8	0.7969 (4)	0.1219 (5)	0.9514 (5)	0.074 (1)
C9	0.2153 (4)	0.2301 (4)	0.6968 (3)	0.043 (1)
C10	0.0907 (4)	0.3025 (4)	0.6069 (4)	0.054 (1)
C11	0.0581 (5)	0.2468 (5)	0.4673 (4)	0.063 (1)
C12	0.1469 (5)	0.1197 (5)	0.4163 (4)	0.067 (1)
C13	0.2695 (4)	0.0513 (4)	0.5058 (4)	0.064 (1)
C14	0.3051 (4)	0.1038 (4)	0.6465 (4)	0.058 (1)
H8	0.161 (4)	0.363 (4)	0.859 (4)	0.04 (1)

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

N2—C6	1.146 (5)	N3—C9	1.414 (4)
N3—C1	1.383 (4)	N3—H8	0.87 (3)
C1—N3—C9	129.6 (3)	C9—N3—H8	115 (2)
C1—N3—H8	114 (2)	N2—C6—C2	178.8 (4)

All H atoms were introduced at fixed idealized positions and not refined, except for H8 (attached to N3), which was found by difference Fourier synthesis and refined isotropically.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *BEGIN* in *SDP-Plus* (Frenz, 1985). Program(s) used to solve structure: *MULTAN80* (Main *et al.*, 1980). Program(s) used to refine structure: *LSFM* in *SDP-Plus*. Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *CIF VAX* in *MolEN* (Fair, 1990).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1071). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Allen, F. H., Bellard, S., Brice, M. D., Cartwright, B. A., Doubleday, A., Higgs, H., Hummelink, T., Hummelink-Peters, B. G., Kennard, O., Motherwell, W. D., Rodgers, J. R. & Watson, D. G. (1979). *Acta Cryst.* B**35**, 2331–2339.

Enraf–Nonius (1989). *CAD-4 Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.

Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis*. Enraf–Nonius, Delft, The Netherlands.

Frenz, B. A. (1985). *Enraf–Nonius SDP-Plus Structure Determination Package*. Version 1.1. Enraf–Nonius, Delft, The Netherlands.

Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Universities of York, England, and Louvain, Belgium.

Mefetah, H., Brouant, P., Galy, A. M., Galy, J. P. & Barbe, J. (1995). *Med. Chem. Res.* **5**, 522–533.

Acta Cryst. (1997). C**53**, 102–106

(−)-*cis*-Pinononic Acid: Hydrogen-Bonding Pattern of a δ-Keto Acid

MARIE L. COTÉ, HUGH W. THOMPSON AND ROGER A. LALANCETTE*

Carl A. Olson Memorial Laboratories, Department of Chemistry, Rutgers University, Newark, NJ 07102, USA. E-mail: lalancette@hades.rutgers.edu

(*Received 25 June 1996; accepted 30 September 1996*)

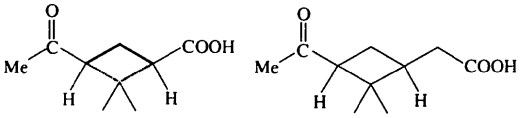
Abstract

In the title compound, (−)-*cis*-3-acetyl-2,2-dimethylcyclobutanecarboxylic acid, $C_9H_{14}O_3$, carboxyl-to-ketone chains (catemers) are formed between screw-related molecules spiraling along the *b* cell axis, with an O—H···O distance of 2.747 (3) Å. The carboxyl C=O

group is not involved in the hydrogen bonding, although its O atom has a close contact of 2.51 (5) Å to a methyl H atom of a neighboring molecule.

Comment

Compared with simple carboxylic acids, keto acids in the solid state offer greater opportunity for variation on the standard pattern of dimeric hydrogen bonding. In most cases, the ketone does not participate in hydrogen bonding and typical mutually hydrogen-bonded dimers result. Less frequently, intermolecular carboxyl-to-ketone hydrogen bonds yield a chain (catemer), typically following a 2_1 screw axis. A survey of X-ray structures of keto acids found that approximately 25% adopt the catemer motif (Thompson, Lalancette & Vanderhoff, 1992; Coté, Thompson & Lalancette, 1996). A third rare arrangement has an internal hydrogen bond (Coté, Lalancette & Thompson, 1996; Thompson, Lalancette & Coté, 1996) and one instance is known of acid-to-ketone dimerization (Abell, Trent & Morris, 1991). We have previously referenced and discussed numerous examples (Thompson, Lalancette & Vanderhoff, 1992; Coté, Thompson & Lalancette, 1996).



(I) (II)

Our discovery that (±)-*cis*-pinonic acid, (II), adopts the less common catemeric motif (Vanderhoff, Thompson & Lalancette, 1986) prompted us to examine the related (−)-*cis*-pinononic acid, (I), containing one less C atom. A view of (I), with its numbering scheme, is presented in Fig. 1. Its conformation has similarities to that adopted by compound (II). The cyclobutane ring in (I) is flexed well out of planarity, with a dihedral angle between the C2—C3—C4 and C2—C1—C4 planes of 154.5 (3)°. In the higher homolog, (II), this dihedral angle was found to be 150.2 (1)° (Vanderhoff, Thompson & Lalancette, 1986); in cyclobutane, this angle is 145° (Meiboom & Snyder, 1967), and in chlorocyclobutane (Kim & Gwinn, 1966), it is 160°. The ketone C=O bond in (I), as in (II), is aimed away from the *gem*-dimethyl group. The acetyl group (C3—C7—O1—C8) forms a dihedral angle of 62.3 (2)° with its half of the cyclobutane ring (C2—C3—C4). The corresponding value in (II) is 57.4 (1)°. The dihedral angle between the C7—O1—C8 and C3—C4—C7 planes is 6.5 (5)° in (I) *versus* 1.9 (4)° in (II).

At the carboxyl end of the molecule, where the homology resides and more differences are expected, the carboxyl group (O2—C9—O3) forms a dihedral angle of 61.4 (3)° relative to its half of the cyclobutane ring (C1—C2—C4); the corresponding value in

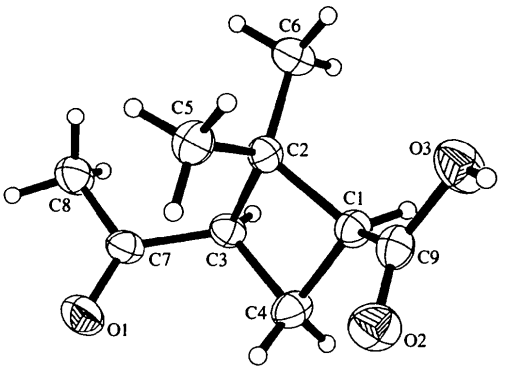


Fig. 1. A view of (I) with its numbering scheme. The *cis*-related H atoms on the cyclobutane ring highlight its bent geometry. Also apparent is the near eclipsed arrangement of the O1 and O2 atoms. The principal methyl group rotamer is shown. Ellipsoids are drawn at the 30% probability level.

(II) is 58.6 (2)° (Vanderhoff, Thompson & Lalancette, 1986). The torsion angles that encompass the carboxyl group [C4—C1—C9—O2 −4.7 (4) and C4—C1—C9—O3 176.5 (3)°] illustrate the alignment of this group with the C1—C4 ring bond. The carboxyl C=O group is turned in the same direction as the ketone C=O group and is almost parallel to it. The torsion angle of these two carbonyl groups is only 2.1 (3)°. Owing to the extra CH_2 group, this *cisoid* arrangement is not present in compound (II), where the corresponding torsion angle is −95.6 (2)°.

The local symmetry of carboxylic acid dimers permits rapid tautomeric H-atom exchange (Meier, Graf & Ernst, 1982; Nagaoka, Terao, Imashiro, Hirota & Hayashi, 1983) and frequently leads to dynamic disordering of the carboxyl group. Denied the symmetric tautomerism of the dimer, catemeric keto acids display highly ordered carboxyl bonds and angles, as is the case with (I). In those carboxyl dimers which are highly ordered, typical C—O bond distances and C—C—O angles are 1.21 and 1.31 Å, and 112 and 123° (Borthwick, 1980). In compound (I), these values are 1.202 (3) and 1.327 (3) Å, and 112.5 (3) and 124.6 (3)°. The corresponding values for compound (II) are 1.201 (2) and 1.329 (2) Å, and 110.7 (1) and 126.1 (1)° (Vanderhoff, Thompson & Lalancette, 1986).

The unit cell and hydrogen-bonding scheme are shown in Fig. 2. Like its homolog (II), compound (I) crystallizes as a catemer whose members are related by a 2_1 screw axis. The single-strand helical chains formed by repetition of the carboxyl-to-ketone hydrogen bond along the *b* axis are very similar to those in compound (II). The *a* and *c* cell dimensions in compound (I), however, are 56 and 81%, respectively, of those found in (II), due in part to halved cell occupancy, but also to an elongation of the helix. In spite of overall shortening of the molecule by 18% (measured from the acid H atom to the ketone O atom), the unit cell in compound (I) is 8%

longer in the direction of the screw axis than it is in (II). This reflects a prolation of the hydrogen-bonding helix, arising from a turning of the hydrogen-bonding axis of the molecule (from the acid H atom to the ketone O atom) toward the **b** direction, analogous to a change in the pitch of a screw. This difference may be quantified as follows: as alluded to above, we define the 'hydrogen-bonding axis' of each molecule as the line connecting its 'donor end', the acid H atom, to its 'receptor end', the ketone O atom. The angle of this axis relative to the screw axis defines the pitch of the helix. In a helix of infinite pitch, the hydrogen-bonding axis would have an angle of 0°, while in one of zero pitch its angle would be 90°. For compound (II), this angle is found to be 51.2°, but for (I), it is 31.5°, showing that the latter molecule, although one CH_2 group shorter, is indeed aligned more nearly parallel to the *b* axis, which lengthens the pitch of the helix, *i.e.* the *b* cell dimension, and results in compression of the other two cell dimensions.

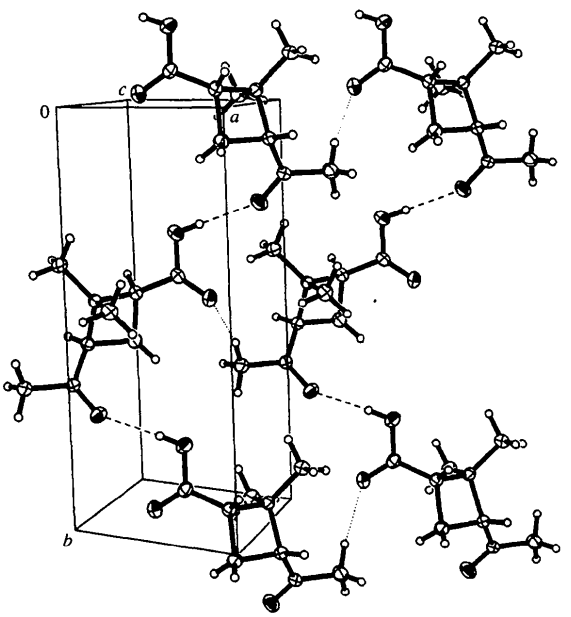


Fig. 2. A packing diagram for (I) showing the single-strand helical catemers connected by dashed lines and following the *b* axis. The close contacts between the uninvolved carboxyl C═O group and a methyl H atom of a neighboring molecule are shown by dotted lines. The principal methyl group rotamer is shown. Ellipsoids are drawn at the 20% probability level.

Apart from the hydrogen-bonding interaction, there is also a close contact of 2.51 (5) Å from the carboxyl O2 atom (which is not involved in the carboxyl-to-ketone catemer) to a methyl H atom on the acetyl group of a neighboring molecule (symmetry code: $1+x$, y, $1+z$). This contact is to the predominant rotamer of the acetyl methyl group, which was found to be rotationally disordered. Such contacts are seen often in dimeric keto acids, with the ketone O atom having a close contact to various types of C-bound H atoms. These C—H···O contacts are thought to represent significant polar attractions (Leiserowitz, 1976; Berkovitch-Yellin & Leiserowitz, 1982) contributing to the overall packing.

The solid-state (KBr) IR spectrum of (I) displays C═O stretching absorption shifts typical for the changes in hydrogen-bonding energy in a catemer *vis-à-vis* a dimer, *i.e.* addition of hydrogen bonding to a ketone and removal of hydrogen bonding from carboxyl C═O. The C═O band for the ketone is at 1689 cm^{-1} and that for the carboxyl is at 1731 cm^{-1}. The corresponding bands for compound (II) are at 1683 and 1733 cm^{-1}, respectively, while typical stretching frequency values for dimeric keto acids are *ca* 1710 cm^{-1} for ketone and 1695 cm^{-1} for carboxyl C═O.

Experimental

Compound (I) has been synthesized by various methods involving oxidation of any of several pinane derivatives (Harispe, Mea & Horeau, 1964; Carlsen & Odden, 1984; Webster, Rivas-Enterrios & Silverstein, 1987). We oxidized (−)-verbenone by epoxidation (Wasson & House, 1963), tosylhydrazone thermolysis (Tanabe, Crowe & Dehn, 1967) and permanganate alkyne cleavage (Krapcho, Larson & Eldridge, 1977) to yield compound (I). Several recrystallizations from absolute ethanol yielded diffraction quality crystals (m.p. 399 K).

Crystal data

$C_9H_{14}O_3$
M_r = 170.20
Monoclinic
$P2_1$
a = 5.8824 (7) Å
b = 12.451 (2) Å
c = 6.7557 (8) Å
β = 110.186 (6)°
V = 464.4 (1) $Å^3$
Z = 2
D_x = 1.217 Mg m^{-3}
D_m = 1.21 (1) Mg m^{-3}
D_m measured by flotation in cyclohexane/CCl_4
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 31 reflections
θ = 10.2–17.3°
μ = 0.090 mm^{-1}
T = 296 (2) K
Plate
0.56 × 0.40 × 0.08 mm
Colorless

Data collection

Siemens $P4$ diffractometer
$2\theta/\theta$ scans
Absorption correction: face-indexed numerical
T_{min} = 0.963, T_{max} = 0.992
1894 measured reflections
1501 independent reflections
859 observed reflections [$F > 4\sigma(F)$]
R_{int} = 0.0524
θ_{max} = 30°
$h = -1 \rightarrow 8$
$k = -1 \rightarrow 17$
$l = -9 \rightarrow 9$
3 standard reflections monitored every 47 reflections
intensity decay: 2.94%

Refinement

Refinement on F^2
$R(F) = 0.0425$
$wR(F^2) = 0.1016$
$S = 0.836$
1501 reflections
119 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0338P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.001$
$\Delta\rho_{max} = 0.124$ e Å^{-3}
$\Delta\rho_{min} = -0.131$ e Å^{-3}
Extinction correction: *SHELXL93* (Sheldrick, 1993)
Extinction coefficient: 0.085 (9)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)
Flack parameter = 0.9 (18)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O1	0.0738 (4)	0.7416 (2)	0.2309 (4)	0.0707 (7)
O2	0.6356 (4)	0.4752 (2)	0.6574 (3)	0.0642 (6)
O3	0.4586 (4)	0.3151 (2)	0.5965 (4)	0.0701 (7)
C1	0.2031 (4)	0.4653 (2)	0.5533 (4)	0.0441 (6)
C2	0.0444 (4)	0.4722 (2)	0.3130 (4)	0.0402 (6)
C3	−0.0451 (5)	0.5847 (2)	0.3677 (4)	0.0425 (6)
C4	0.1731 (5)	0.5867 (2)	0.5740 (4)	0.0516 (7)
C5	0.1965 (5)	0.4836 (2)	0.1716 (4)	0.0529 (7)
C6	−0.1439 (6)	0.3848 (2)	0.2311 (5)	0.0570 (8)
C7	−0.0776 (5)	0.6728 (2)	0.2123 (4)	0.0459 (6)
C8	−0.3044 (5)	0.6718 (2)	0.0229 (5)	0.0644 (9)
C9	0.4551 (5)	0.4213 (2)	0.6094 (4)	0.0480 (7)
H3′	0.612 (7)	0.291 (3)	0.629 (7)	0.10

Table 2. *Geometric parameters (Å, °)*

O1—C7	1.211 (3)	C2—C6	1.514 (4)
O2—C9	1.202 (3)	C2—C5	1.524 (3)
O3—C9	1.327 (3)	C2—C3	1.585 (3)
O3—H3′	0.90 (4)	C3—C7	1.484 (4)
C1—C9	1.501 (4)	C3—C4	1.535 (4)
C1—C4	1.534 (4)	C7—C8	1.496 (4)
C1—C2	1.571 (3)	O2···H8C′	2.51 (5)
C9—O3—H3′	110 (3)	C7—C3—C4	119.6 (2)
C9—C1—C4	118.1 (2)	C7—C3—C2	117.4 (2)
C9—C1—C2	117.6 (2)	C4—C3—C2	89.2 (2)
C4—C1—C2	89.7 (2)	C1—C4—C3	89.3 (2)
C6—C2—C5	110.6 (2)	O1—C7—C3	122.6 (2)
C6—C2—C1	116.0 (2)	O1—C7—C8	120.1 (3)
C5—C2—C1	112.6 (2)	C3—C7—C8	117.3 (2)
C6—C2—C3	117.4 (2)	O2—C9—O3	122.8 (3)
C5—C2—C3	112.2 (2)	O2—C9—C1	124.6 (3)
C1—C2—C3	86.2 (2)	O3—C9—C1	112.5 (3)
C4—C1—C2—C3	−17.6 (2)	C4—C1—C9—O2	−4.7 (4)
C1—C2—C3—C4	17.6 (2)	C2—C1—C9—O2	101.1 (3)
C2—C1—C4—C3	18.2 (2)	C4—C1—C9—O3	176.5 (3)
C2—C3—C4—C1	−18.0 (2)	C2—C1—C9—O3	−77.7 (3)
C2—C3—C7—O1	−98.5 (3)		

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3′···O1^{ii}	0.90	1.87	2.747 (3)	165

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

Although the Flack parameter refines to a value of 0.89, its large error of 184 renders it indeterminate as to the absolute configuration of compound (I). The absolute configuration is known from the synthetic pathway by which it was produced. All non-carboxyl H atoms were found in electron-density difference maps, but were replaced in calculated positions and allowed to refine as riding models on their appropriate C atoms. The carboxyl H3′ atom was found in an electron-density difference map and was allowed to refine isotropically until the latter stages of refinement, where its temperature factor was held at 0.10. Electron-density difference maps in the later stages of refinement revealed the rotationally disordered acetyl methyl group. The H atoms on the acetyl C8 atom were thus removed and replaced with two sets of three H atoms each, such that the H atoms defined a regular hexagon. Each group was allowed to refine, correlated with the other, such that their occupancies summed to unity. The disorder was in a ratio of roughly 6:4. The group U_{iso} values for the H atoms were as follows: 0.056 (6) for the methine (ring) H atoms; 0.064 (6) for the methylene H atoms; 0.063 (4) for the C5 and C6 methyl group H atoms; 0.066 (7) for the acetyl group H atoms. One restraint was used in the refinement, which was the fixing of the y coordinate of the O1 atom due to the space-group constraint.

Data collection: *XSCANS* (Fait, 1991). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL/PC*. Molecular graphics: *SHELXTL/PC*. Software used to prepare material for publication: *SHELXTL/PC*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1213). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Abell, A. D., Trent, J. O. & Morris, K. B. (1991). *J. Chem. Soc. Perkin Trans.* 2, pp. 1077–1083.

Berkovitch-Yellin, Z. & Leiserowitz, L. (1982). *J. Am. Chem. Soc.* **104**, 4052–4064.

Borthwick, P. W. (1980). *Acta Cryst.* B**36**, 628–632.

Carlsen, P. H. J. & Odden, W. (1984). *Acta Chem. Scand. Ser. B*, **38**, 501–504.

Coté, M. L., Lalancette, R. A. & Thompson, H. W. (1996). *Acta Cryst.* C**52**, 1535–1537.

Coté, M. L., Thompson, H. W. & Lalancette, R. A. (1996). *Acta Cryst.* C**52**, 684–687.

Fait, J. (1991). *XSCANS Users Manual.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Harispe, M., Mea, D. & Horeau, A. (1964). *Bull. Soc. Chim. Belg.* **81**, 319–332.

Kim, H. & Gwinn, W. D. (1966). *J. Chem. Phys.* **44**, 865–873.

Krapcho, A. P., Larson, J. R. & Eldridge, J. M. (1977). *J. Org. Chem.* **42**, 3749–3753.

Leiserowitz, L. (1976). *Acta Cryst.* B**32**, 775–802.

Meiboom, S. & Snyder, L. C. (1967). *J. Am. Chem. Soc.* **89**, 1038–1039.

Meier, B. H., Graf, F. & Ernst, R. R. (1982). *J. Chem. Phys.* **76**, 767–779.

Nagaoka, S., Terao, T., Imashiro, F., Hirota, N. & Hayashi, S. (1983). *J. Chem. Phys.* **79**, 4694–4703.

Sheldrick, G. M. (1994). *SHELXTL/PC.* Version 5.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Tanabe, M., Crowe, D. F. & Dehn, R. L. (1967). *Tetrahedron Lett.* pp. 3943–3946.

Thompson, H. W., Lalancette, R. A. & Coté, M. L. (1996). *Acta Cryst.* C**52**, 2372–2376.

Thompson, H. W., Lalancette, R. A. & Vanderhoff, P. A. (1992). *Acta Cryst.* C**48**, 66–70.

Vanderhoff, P. A., Thompson, H. W. & Lalancette, R. A. (1986). *Acta Cryst.* C**42**, 1766–1769.
Wasson, R. L. & House, H. O. (1963). *Org. Synth.* **4**, 552–553.
Webster, F. X., Rivas-Enterrios, J. & Silverstein, R. M. (1987). *J. Org. Chem.* **52**, 689–691.

Acta Cryst. (1997). C**53**, 106–108

3,5-Dicarboxy-2,6-dimethyl-4-(3-nitrophenyl)pyridinium Nitrate Monohydrate

KRISTIN R. ROWAN AND ELIZABETH M. HOLT

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078, USA. E-mail: chememh@osucc.bitnet

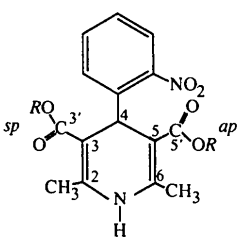
(Received 14 May 1996; accepted 23 September 1996)

Abstract

Energy-minimization studies of the title compound, $C_{15}H_{13}N_2O_6^+.NO_3^-.H_2O$, suggest that the stable conformation of the molecule should be that in which the carboxyl groups are coplanar with the pyridine ring. Isolated in the solid as a pyridinium nitrate monohydrate, the significant rotation of these carboxyl groups from coplanarity with the aromatic ring may be attributed to networks of hydrogen bonding.

Comment

Derivatives of 1,4-dihydropyridine (DHP) are often prescribed as calcium-channel blockers, effective in the treatment of angina and hypertension (Triggle, Langs & Janis, 1989; Hurwitz, Partridge & Leach, 1991). Nifedipine [dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] is the lead compound of this family.



In the majority of the more than 30 reported crystal structures of members of the nifedipine family, the ester carbonyl groups are found to be almost coplanar with the nearest double bond in the DHP ring, with the carbonyl group oriented either *cis* (*sp*, synperiplanar) or *trans* (*ap*, antiperiplanar) with respect to that bond (Triggle, Langs & Janis, 1989).

Decomposition of this family of drugs involves aromatization of the 1,4-dihydropyridine ring to a pyridine moiety (Rowan & Holt, 1995) and is reported to diminish activity significantly in some cases (Loev, Goodman, Snader, Tedeschi & Macko, 1974).

The crystal structures of the decomposition products, *i.e.* dialkyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylates, routinely show the carbonyl groups at C3 and C5 to be rotated significantly from coplanarity with the aromatic ring. This rotation could be construed to inhibit the formation of strong hydrogen bonds on docking of the decomposition product with the purported calcium-channel receptor site (Rowan & Holt, 1996*a*,*b*) and thus to explain their lessened activity.

We have studied a series of derivatives of the nifedipine family, which vary in the identity of the esterification group, in order to understand the role played by the size and bulk of the ester groups in the activity of these compounds. We have also attempted to learn something about the activity of the derivatives by looking at the conformational changes arising upon aromatization of the heterocycle.

To assess whether the crystal structures of these decomposition materials represent stable molecular conformations as would be seen in solution, we have carried out molecular modeling studies on the parent diacid, 4-phenylpyridine-3,5-dicarboxylic acid, as representative of the group of diesterified molecules, and have completed a single-crystal X-ray analysis of this compound.

Molecular-modeling studies (*CS Chem3D Pro*; CambridgeSoft Corporation, 1995) show that there are three minimum-energy conformations of this molecule. All three show carboxyl groups close to coplanarity with the pyridine ring. The two carboxylic acid groups bound to the pyridine ring at C3 and C5 may adopt *sp*,*sp*, *ap*,*ap* or *sp*,*ap* conformations relative to the C2—C3 and C5—C6 bonds of the aromatic ring. The results of the energy-minimization studies show that the order of stability of these three conformations is *sp*,*sp* > *sp*,*ap* > *ap*,*ap*.

Furthermore, the three energy-minimized structures show near but not strict coplanarity of the carbonyl group with the aromatic ring; the C2—C3—C3′—O3′ and C6—C5—C5′—O5′ dihedral angles are 7.54 and 6.29, respectively, for *sp*,*sp*, 1.18 and −176.77 for *sp*,*ap*, and −171.26 and −170.42° for *ap*,*ap*.

The structural literature contains information about two appropriate dicarboxy compounds. Two single-crystal studies of isophthalic acid (1,3-dicarboxybenzene) show the carboxylic acid groups to lie close to the plane of the aromatic ring (Alcala & Martinez-Carrera, 1972; Derissen, 1974), with the deviation of the O atoms from that plane reported to be in the range −0.006 to 0.125 Å and only small rotations from coplanarity being observed for the carboxyl groups (2.8 and 4.7°). Similarly, dinicotinic acid (3,5-dicarboxypyridine) (Takusagawa, Hirotsu & Shimada, 1973) has an approx-