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Acetyl-L-carnitine Hydrochloride

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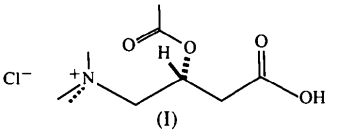
Abstract

The title compound, 2-acetoxy-3-carboxy-*N*,*N*,*N*-trimethyl-1-propanaminium chloride, $C_9H_{18}NO_4^+.Cl^-$, represents a source of activated acetyl groups which are efficiently used for biosynthetic purposes. The crystal structure reported here confirms the extended conformation of the compound predicted from solid-state NMR studies and differs from that previously reported in the literature.

Comment

Acetyl-L-carnitine is involved in the reversible transfer of acetyl groups between carnitine and coenzyme A through the activity of carnitine acetyltransferase (CAT; EC 2.3.1.7). There is considerable interest in the active conformation of acetyl-L-carnitine and it has been suggested that CAT requires the extended conformation of L-carnitine for the forward reaction, and that acetyl-L-carnitine, formed upon acetylation, adopts a folded conformation. These assumptions were supported by X-ray crystallographic data on both compounds (Gandour, Colucci & Fronczek, 1985). However, a recent NMR investigation of carnitine and acetylcarnitine in aqueous solution suggested that the extended conformation predominates for both compounds (Brewster, Hermann & Englard, 1990). A solid-state NMR study (Anderson *et al.*, 1995) of acetyl-L-carnitine, using the REDOR technique (Gullion & Schaefer, 1989*a*,*b*), led to the conclusion that the C(1)···N distance lies between 4.98 and 5.05 Å, clearly indicating an extended conformation of the compound.

Before extending the NMR study to a determination of the CAT-bound conformation of acetyl-L-carnitine, an X-ray analysis of the same crystalline material was performed to check the results of the REDOR-NMR investigation. The present X-ray analysis of acetyl-L-carnitine hydrochloride, (I), found a C(1)···N distance of 5.06 Å, which is in excellent agreement with the NMR results.



(I)

The crystalline molecular conformation of (I) is shown in Fig. 1. The carboxy group is eclipsed with respect to the C(2)—C(3) bond and the ester carbonyl group is in an eclipsed conformation with respect to the C(3)—H bond. All other torsion angles correspond to staggered conformations. There is a hydrogen bond from the carboxy OH group to the Cl^- ion at $(x-\frac{1}{2}, \frac{1}{2}-y, 1-z)$ [H···Cl^- 2.11 (1), O(1*B*)···Cl^- 2.988 (3) Å, O(1*B*)—H···Cl^- 167 (1)°].

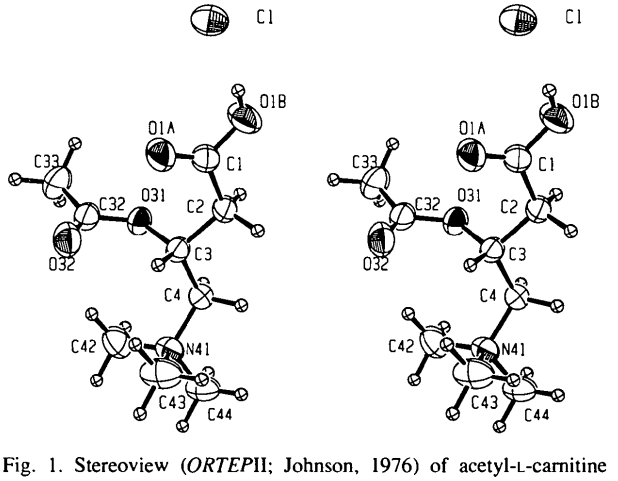


Fig. 1. Stereoview (*ORTEP*II; Johnson, 1976) of acetyl-L-carnitine showing the atomic numbering scheme, the molecular conformation and 50% probability ellipsoids for the non-H atoms. H atoms are shown with constant radii of 0.1 Å.

The Cl^- and ammonium ions form distorted square-centred layers perpendicular to **c** with closest distances of 4.102 (4) ($N^+\cdots Cl^-$), 5.876 (4) ($Cl^-\cdots Cl^-$) and 5.613 (3) Å ($N^+\cdots N^+$). There are no other close intermolecular contacts. A packing diagram is shown in Fig. 2. The absolute configuration of acetyl-L-carnitine was determined by an *R*-factor ratio test (Hamilton, 1964), which indicated the 3*R* configuration at better than the 0.005 level, *i.e.* *R*(3*S*) = 0.0693 and *R*(3*R*) = 0.0543.

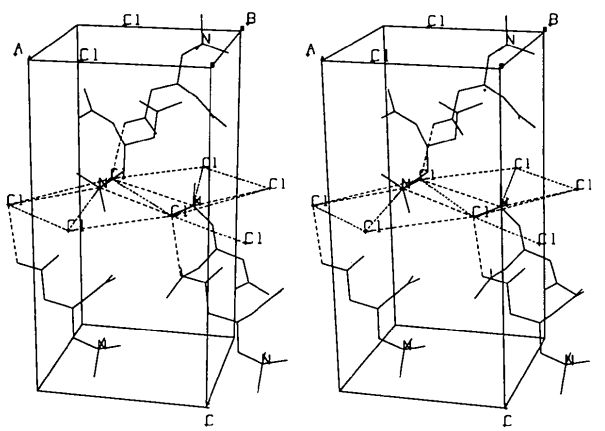


Fig. 2. Stereoview of the crystal packing of acetyl-L-carnitine. O—H···Cl hydrogen bonds are indicated by dashed lines, as is the arrangement of N^+ and Cl^- ions.

Experimental

Crystals of acetyl-L-carnitine hydrochloride (water free) were obtained by vapour diffusion of acetone into a methanol solution saturated with the HCl salt.

Crystal data

$C_9H_{18}NO_4^+.Cl^-$
M_r = 239.70
Orthorhombic
$P2_12_12_1$
a = 8.571 (1) Å
b = 8.842 (1) Å
c = 16.607 (1) Å
V = 1258.5 Å^3
Z = 4
D_x = 1.27 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 25 reflections
θ = 35–45°
μ = 2.81 mm^{-1}
T = 295 K
Prismatic
0.3 × 0.2 × 0.15 mm
Colourless

Data collection

Enraf–Nonius CAD-4F diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scans (Gould & Smith, 1986)
T_{min} = 0.870, T_{max} = 1.000
1515 measured reflections
1496 independent reflections
1480 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.122
θ_{max} = 74.3°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 20$
3 standard reflections
frequency: 60 min
intensity decay: 0.5%

Refinement

Refinement on F
R = 0.0543
wR = 0.0639
S = 3.231
1480 reflections
140 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F) + 0.0007F^2]$
$(\Delta/\sigma)_{max}$ = 0.078
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.42 e Å^{-3}
Atomic scattering factors from *SHELX*76 (Sheldrick, 1976)

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}
C(1)	0.0919 (4)	−0.5582 (4)	−0.29519 (17)	0.0453 (14)
O(1*A*)	0.0033 (3)	−0.4863 (4)	−0.33377 (15)	0.0652 (13)
O(1*B*)	0.2302 (3)	−0.6031 (4)	−0.32137 (17)	0.0741 (16)
C(2)	0.0627 (3)	−0.6108 (4)	−0.20960 (16)	0.0452 (13)
C(3)	−0.1062 (3)	−0.5879 (3)	−0.18404 (16)	0.0401 (12)
C(4)	−0.1232 (3)	−0.6365 (3)	−0.09674 (15)	0.0401 (11)
O(31)	−0.2018 (2)	−0.6856 (2)	−0.23451 (12)	0.0464 (9)
C(32)	−0.3144 (3)	−0.6205 (4)	−0.28029 (17)	0.0515 (15)
O(32)	−0.3496 (3)	−0.4895 (3)	−0.27522 (18)	0.0658 (14)
C(33)	−0.3894 (5)	−0.7342 (6)	−0.3334 (3)	0.0748 (22)
N(41)	−0.2585 (3)	−0.5684 (3)	−0.05053 (15)	0.0458 (11)
C(42)	−0.4126 (4)	−0.6245 (6)	−0.0830 (3)	0.0658 (20)
C(43)	−0.2519 (7)	−0.3977 (4)	−0.0514 (3)	0.0729 (21)
C(44)	−0.2410 (5)	−0.6208 (4)	0.03533 (19)	0.0606 (17)
Cl(1)	−0.19989 (10)	−0.97636 (9)	−0.50770 (5)	0.0574 (5)

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

C(1)—O(1*A*)	1.180 (4)	O(31)—C(32)	1.357 (4)
C(1)—O(1*B*)	1.323 (4)	C(32)—O(32)	1.200 (4)
C(1)—C(2)	1.516 (4)	C(32)—C(33)	1.484 (6)
C(2)—C(3)	1.522 (4)	N(41)—C(42)	1.511 (5)
C(3)—C(4)	1.519 (4)	N(41)—C(43)	1.511 (5)
C(3)—O(31)	1.455 (3)	N(41)—C(44)	1.507 (5)
C(4)—N(41)	1.515 (4)		
O(1*B*)—C(1)—O(1*A*)	124.0 (3)	O(32)—C(32)—O(31)	123.2 (3)
C(2)—C(1)—O(1*A*)	124.6 (3)	C(33)—C(32)—O(31)	110.8 (3)
C(2)—C(1)—O(1*B*)	111.4 (3)	C(33)—C(32)—O(32)	126.0 (3)
C(3)—C(2)—C(1)	112.21 (24)	C(42)—N(41)—C(4)	110.93 (25)
C(4)—C(3)—C(2)	108.67 (23)	C(43)—N(41)—C(4)	111.3 (3)
O(31)—C(3)—C(2)	107.22 (22)	C(43)—N(41)—C(42)	110.9 (3)
O(31)—C(3)—C(4)	109.15 (22)	C(44)—N(41)—C(4)	106.32 (23)
N(41)—C(4)—C(3)	116.38 (23)	C(44)—N(41)—C(42)	108.9 (3)
C(32)—O(31)—C(3)	118.19 (22)	C(44)—N(41)—C(43)	108.2 (3)

The *SHELX*76 (Sheldrick, 1976) program package was used for crystallographic computations.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1131). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Dimeric 3-Vinylindoles as Potential Antitumor Active Compounds: 1,1,3,4-Tetramethyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole and 1,1,3-Trimethyl-4-phenylsulfonyl-3-(1-phenylsulfonyl-1*H*-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole

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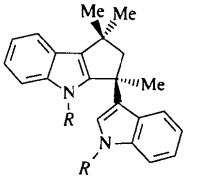
Abstract

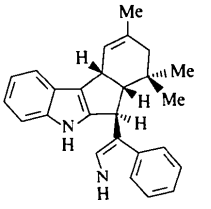
The structures of the title compounds, $C_{24}H_{26}N_2$ and $C_{34}H_{30}N_2O_4S_2$, have been determined from single-crystal X-ray diffraction data. The sterically more demanding phenylsulfonyl group of the second compound gives rise to significant differences, for example, in bond lengths and angles, in comparison with the first compound.

Comment

A variety of [*b*]annellated indoles are of biological interest as antitumor-active substances (Gribble, 1990). We are interested, therefore, in the synthesis and structure of functionalized carbazoles and cyclopentane-annellated indoles (Pindur, 1994; Schollmeyer, Fischer & Pindur, 1993) in order to obtain more information on structure–activity relationships. The compounds reported here, 1,1,3,4-tetramethyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta-[*b*]indole, (1), and 1,1,3-trimethyl-4-phenylsulfonyl-3-(1-phenylsulfonyl-1*H*-indol-3-yl)-2,2,3,4-tetrahydrocyclopenta[*b*]indole, (2), are closely related to the highly antitumor-active tetrahydroindenoindole alkaloid yuehchuken, (3), the indolocyclopenta[*b*]indole unit of which is responsible for its biological activity (Cheng, Chan, Wong & Lai, 1990). Thus, we suggest that compounds (1) and (2) may reveal similar antitumor activity.



(1) R = Me
(2) $R = SO_2Ph$



(3)

For both compounds, the crystal packing shows no significant stacking interactions or hydrogen bonding. The structures of compounds (1) and (2) are shown in Figs. 1 and 2, respectively. The angle between the normals to the least-squares planes of the indole and cyclopenta[*b*]indole partial structures is 79.9° for compound (1) and 86.4° for (2). In both cases, the cyclopentene ring adopts a twist conformation, with atom C11 (IUPAC numbering: C2) lying on the same side of the cyclopenta[*b*]indole plane as the indole substituent and atom C12 (IUPAC numbering: C1) lying on the opposite side of this plane. The sterically more

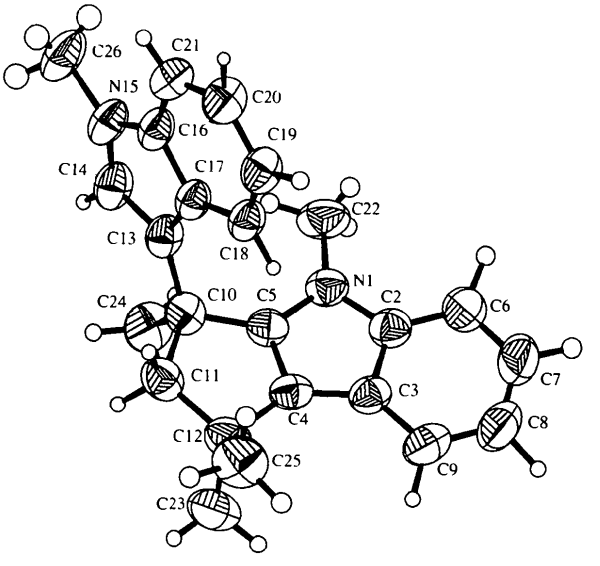


Fig. 1. *ORTEP*II plot (Johnson, 1976) of compound (1) with 50% probability ellipsoids and H atoms as spheres of arbitrary radii.