ORGANIC COMPOUNDS

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Ecstasy: 3,4-Methylenedioxymethamphetamine (MDMA)

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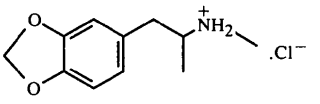
Abstract

The crystal structure of 3,4-methylenedioxymethamphetamine {systematic name: *N*-methyl-1-[3,4-(methylenedioxy)phenyl]-2-aminopropane} hydrochloride, $C_{11}H_{15}NO_2$.HCl, also known as 'ecstasy' or MDMA, has been determined by X-ray diffraction.

Comment

The title compound, MDMA, produces euphoria in humans and although classified by the Federal government as a hallucinogenic phenethylamine, its pharmacological properties and mechanism of action suggests that it should be classified as an entactogen, a new therapeutic class of compounds (Nichols, 1986).



MDMA.HCl

There are several structure–activity relationships which clearly differentiate MDMA from other hallucinogenic amphetamines, such as DOB (2,5-dimethoxy-4-bromoamphetamine) or DOM (2,5-dimethoxy-4-methylamphetamine). *N*-Methylation of hallucinogenic amphetamines attenuates activity three- to tenfold and the *R*(−) configuration is more potent (see Nichols, 1981). For MDMA, *N*-methylation has very little effect on activity and the *S*(+) configuration is more potent. The structure–activity relationship of MDMA is different even when compared with MDA (3,4-methylenedioxyamphetamine), which lacks *N*-methylation. For MDA, the *R*(−) isomer has the greatest potency in an *in vivo* rabbit model for classical hallucinogenic activity (Anderson *et al.*, 1978), whereas the *S*(+) isomer, at the same dose as the *R*(−) isomer, has a greater effect on emotion and empathy (Shulgin, 1973). To begin to understand these differences, we report here the crystal structure of the hydrochloride form of MDMA.

The structure of MDMA is illustrated in Fig. 1. The methylenedioxy ring is essentially coplanar [0.7 (2)°] with the phenyl ring. One interesting structural feature of MDMA is the orientation of the isopropylamine group. In MDMA, the torsion angle which describes the relationship of the α-methyl group (C10) and the phenyl ring is −66.4 (3)°. This is unlike other hallucinogenic amphetamines, such as DOET (2,5-dimethoxy-4-ethylamphetamine), where the α-methyl group is antiplanar with a torsion angle of 178° (Horn *et al.*, 1975), and TMA (2,4,5-trimethoxyamphetamine), where the angle formed by the α-methyl group is 170° (Baker *et al.*, 1973).

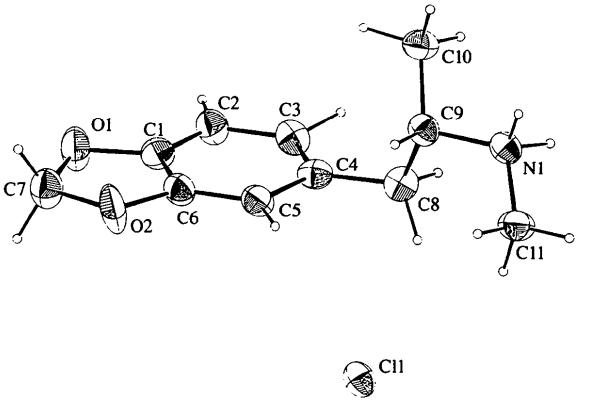


Fig. 1. View of 3,4-methylenedioxymethamphetamine hydrochloride showing 50% probability displacement ellipsoids (Gilmore *et al.*, 1985). H atoms have been drawn as small circles of arbitrary radii.

The relative position of the amino N atom is also different for MDMA when compared with DOET or TMA. The torsion angle formed by the amino N atom in MDMA (C4—C8—C9—N1) is 172.5 (2)°, whereas for DOET it is −62° (Horn *et al.*, 1975) and for TMA, 50° (Baker *et al.*, 1973). For MDMA, *N*-methylation results in a rotation about the C8—C9 bond, giving rise to a torsion angle between the α-methyl (C10) and *N*-methyl (C11) groups of 170.0 (2)°. When comparing the structure of MDMA with DOET or TMA, it appears that the relative position of the α-methyl group (C10) and the amino N atom (N1) are transposed.

In the crystal packing, shown in Fig. 2, the molecules are held together by intermolecular hydrogen bonds between the protonated secondary amine and the chloride ion, with a distance of 3.137 (2) Å from the N1 atom of one MDMA molecule to the chloride ion (Cl1), and a distance of 3.089 (2) Å from the chloride

ion to the N atom of an adjacent MDMA molecule. These distances are similar to those observed for other phenethylamine hydrochloride salts (Bergin, 1971).

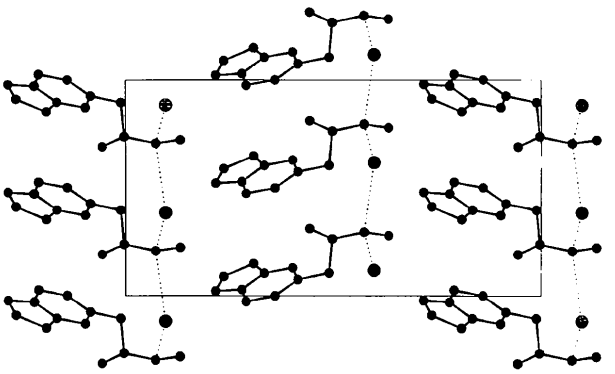


Fig. 2. Packing diagram viewed down the *b* axis with the hydrogen bonding along the a direction shown by dashed lines (Pearce & Watkin, 1994).

Experimental

The title compound was prepared essentially as described previously (Nichols *et al.*, 1986). Recrystallization at room temperature from 2-propanol–diethyl ether gave colorless plate-shaped crystals (m.p. 423–425 K) suitable for X-ray diffraction analysis.

Crystal data

$C_{11}H_{16}NO_2^+.Cl^-$
M_r = 229.71
Orthorhombic
$Pca2_1$
a = 9.3482 (2) Å
b = 7.0493 (3) Å
c = 18.0924 (7) Å
V = 1192.26 (7) Å^3
Z = 4
D_x = 1.280 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 619 reflections
θ = 3.62–28.60°
μ = 0.302 mm^{-1}
T = 161 (2) K
Plate
0.34 × 0.34 × 0.16 mm
Colorless

Data collection

Enraf–Nonius Kappa-CCD diffractometer
φ rotation scans
Absorption correction: none
22647 measured reflections
2415 independent reflections

2259 reflections with $I > 2\sigma(I)$
R_{int} = 0.029
θ_{max} = 28.60°
$h = -10 \rightarrow 10$
$k = -8 \rightarrow 8$
$l = -22 \rightarrow 22$

Refinement

Refinement on F^2
$R(F)$ = 0.036
$wR(F^2)$ = 0.096
S = 1.145
2415 reflections
136 parameters
H atoms riding

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

$w = 1/[\sigma^2(F_o^2) + (0.0329P)^2 + 0.6889P]$ where $P = (F_o^2 + 2F_c^2)/3$

Absolute structure: Flack (1983)
Flack parameter = 0.02 (7)

Table 1. *Selected geometric parameters (Å, °)*

C1—C2	1.363 (4)	C6—O2	1.373 (3)
C1—C6	1.384 (4)	C7—O2	1.429 (3)
C1—O1	1.385 (3)	C7—O1	1.430 (4)
C2—C3	1.408 (4)	C8—C9	1.535 (3)
C3—C4	1.392 (4)	C9—N1	1.497 (3)
C4—C5	1.402 (4)	C9—C10	1.517 (3)
C4—C8	1.507 (3)	C11—N1	1.490 (3)
C5—C6	1.373 (4)		
C2—C1—C6	122.5 (2)	O2—C6—C1	110.2 (2)
C2—C1—O1	128.0 (2)	C5—C6—C1	121.9 (2)
C6—C1—O1	109.5 (2)	O2—C7—O1	108.5 (2)
C1—C2—C3	116.3 (2)	C4—C8—C9	111.1 (2)
C4—C3—C2	121.9 (2)	N1—C9—C10	107.9 (2)
C3—C4—C5	120.3 (2)	N1—C9—C8	110.3 (2)
C3—C4—C8	121.8 (2)	C10—C9—C8	113.3 (2)
C5—C4—C8	117.9 (2)	C1—O1—C7	105.6 (2)
C6—C5—C4	117.2 (2)	C6—O2—C7	105.8 (2)
O2—C6—C5	127.9 (2)	C11—N1—C9	115.3 (2)

A full sphere of data was collected by rotation about the φ axis in 1.0° increments over 180° with 30 s exposures per frame. Dezingering was accomplished by measuring each frame twice. Coverage of all data was 83.1% complete to 28.6° in θ. The θ and κ axes were positioned at 0° and the ω axis was set at 160° during the entire data collection. The crystal-to-detector distance was 27 mm. Crystal decay was monitored by collecting the first frame after data collection and was negligible. All H atoms were located by difference Fourier synthesis and refined with a riding model. U_{iso} values were fixed such that they were $1.1U_{eq}$ of their parent atom and $1.5U_{eq}$ for methyl groups.

Data collection: *Kappa-CCD Software* (Enraf–Nonius, 1997). Cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1996). Data reduction: *DENZO* (Otwinowski & Minor, 1996). Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *GX ORTEP* (Gilmore *et al.*, 1985), *MAXUS* (MacKay *et al.*, 1997) and *CAMERON* (Pearce & Watkin, 1994). Software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1318). Services for accessing these data are described at the back of the journal.

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The Effect of 3-Substitution on the Structures of Pyrrole-2-carbaldehydes

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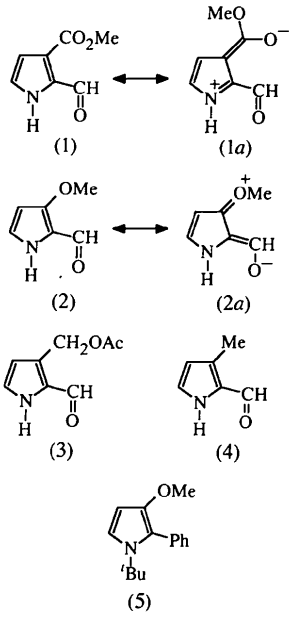
Abstract

In the title compounds, methyl 2-formylpyrrole-3-carboxylate, $C_7H_7NO_3$, and 3-methoxypyrrole-2-carbaldehyde, $C_6H_7NO_2$, the pyrrole rings show little distortion ascribable to the electronic properties of the substituents, whether they are electron donating or electron withdrawing.

Comment

The electronic properties of substituents on unsaturated systems is often found to influence geometry (*e.g.* Blake *et al.*, 1996). We now report the crystal structures of two pyrrole-2-carbaldehydes, one substituted in the 3-position by a strongly electron-withdrawing methoxycarbonyl group, (1), the other similarly substituted with an electron-donating methoxy group, (2), in which the substituents have minimal effect on the structural parameters of the pyrrole ring. Two 3-substituted pyrrole-2-carbaldehydes have been reported previously [(3): Blake *et al.*, 1995; (4): Smith *et al.*, 1985], although (2) is only the third example of a 3-methoxypyrrole to have been structurally characterized (Hunter *et al.*, 1991; Boger & Baldino, 1993).



The aldehyde group is *s*-*Z* with respect to the N atom of the pyrrole in both (1) and (2), at least in part due to the presence of intermolecular hydrogen bonding. The methoxy substituent at C3 and the methyl ester group are both twisted away from the aldehyde function. Both (1) and (2) are planar; maximum deviations are 0.101 Å for O11 in (1) and 0.046 Å for C9 in (2).

The bond lengths in compounds (1)–(3) are compared in Table 1 and surprisingly there is no significant difference between corresponding bonds in the pyrrole rings, with the exception of N1—C2. Here, the distance increases as a function of the substituent in the order CO_2Me [(1), 1.365 (3) Å] < CH_2OAc [(3), 1.377 (4) Å] < OMe [(2), 1.383 (3) Å]. This is consistent with delocalization of the N-atom lone pair into the ester (1*a*). There is a corresponding decrease in the C2—C(aldehyde) bond lengths [1.444 (3), 1.433 (4) and 1.423 (3) Å in (1), (3) and (2), respectively], consistent with delocalization of the methoxy-based lone pair into the aldehyde function (2*a*). In agreement with this, the C3—O8 bond in (2), at 1.348 (3) Å, is significantly shortened in comparison with the model methoxypyrrole (5), where the corresponding bond length is 1.383 (4) Å.

There are no significant differences in the endocyclic bond angles in (1)–(3). The exocyclic bond angles C2—C3—*X* [*X* = CO_2Me in (1), OMe in (2) and CH_2OAc in (3)] increase in the order (2) < (1) < (3) (see Table 1), in accord with the steric bulk of *X*.