Crystal structure of 1-hydroxymethyl-10 α -methoxy-9,10-dihydrolysergol, C₁₈H₂₄N₂O₃

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Abstract

C₁₈H₂₄N₂O₃, orthorhombic, *P*2₁2₁2₁ (no. 19), *a* = 9.868(1) Å, *b* = 10.877(1) Å, *c* = 15.458(2) Å, *V* = 1659.1 Å³, *Z* = 4, *R*_{gt}(*F*) = 0.065, *wR*_{gt}(*F*) = 0.079, *T* = 293 K.

Source of material

Single crystals of 1-hydroxymethyl-10 α -methoxy-9,10-dihydrolysergol were obtained by partial evaporation of a saturated solution of 1-hydroxymethyl-10 α -methoxy-9,10-dihydrolysergol (IVAX Pharmaceuticals) in methanol (200 mg/10 ml) at ambient temperature (298 K).

Discussion

The semisynthetic ergot derivative nicergoline is an important drug used in dementia and other age associated forms of cognitive impairment [1]. 1-Hydroxymethyl-10 α -methoxy-9,10-dihydro-

lysergol (HMDL), 1-methyl-10 α -methoxy-9,10-dihydrolysergol (MeLuol or MMDL), 10 α -methoxy-9,10-dihydrolysergol (Luol or MDL) and their respective glucuronides are the human nicergoline metabolites [2]. Due to the extensive first-pass metabolism, nicergoline metabolites contribute also to its pharmacological effect [3].

The conformation of 1-hydroxymethyl-10 α -methoxy-9,10-dihydrolysergol (figure, top) is essentially similar to the conformation of 1-methyl-10 α -methoxy-9,10-dihydrolysergol moiety in nicergoline [4,5]. The ergoline A and B rings, forming the indole moiety, are nearly planar (χ^2 test values are 7.81 and 5.99, respectively). The dihedral angle between these two planes is 1.46(6)°. Ring C (C3, C4, C5, C10, C11, C16) possesses distorted *E*₃ conformation (puckering parameters according to Cremer and Pople are *Q* = 0.509(2) Å, φ = −53.1(3)°, θ = 128.1(3)°). Ring D (N6, C5, C10, C9, C8, C7) has ⁴*C*₁ conformation (*Q* = 0.578(2) Å, φ = 81(3)°, θ = 176.4(2)°). The torsion angles about the C/D ring junction C4–C5–C10–C9 and N6–C5–C10–C11 are −176.4(2)° and −176.5(1)°, respectively. Two hydrogen bonds were found O21–H211...N6(*x*+½, −*y*−½, −*z*) and O18–H181...O21(*x*−½, −*y*+½, −*z*) both along *a* axis and cross-linking the parallel chains each other forming infinite sheets in (001) plane (figure, bottom).

Table 1. Data collection and handling.

Crystal:	colorless prism, size 0.14 × 0.28 × 0.50 mm
Wavelength:	Cu <i>K</i> α radiation (1.54180 Å)
μ :	6.97 cm ^{−1}
Diffractionmeter, scan mode:	Enraf-Nonius CAD4, $\omega/2\theta$
$2\theta_{\max}$:	149.73°
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} :	3615, 3293
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2 σ (<i>I</i> _{obs}), 3198
<i>N</i> (<i>param</i>) _{refined} :	209
Programs:	SIR92 [6], CRYSTALS [7], ORTEP-3 [8]

Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(21)	4 <i>a</i>	0.5882	0.2391	0.2774	0.028
H(41)	4 <i>a</i>	0.7119	−0.0017	0.2515	0.020
H(42)	4 <i>a</i>	0.6572	−0.0087	0.1520	0.020
H(51)	4 <i>a</i>	0.9395	0.0121	0.2030	0.015
H(71)	4 <i>a</i>	1.0832	−0.1643	0.1741	0.023
H(72)	4 <i>a</i>	1.0124	−0.2893	0.1370	0.023
H(81)	4 <i>a</i>	0.9726	−0.1877	0.0011	0.023
H(91)	4 <i>a</i>	1.1159	0.0150	0.0763	0.019
H(92)	4 <i>a</i>	1.0590	0.0088	−0.0228	0.019

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Table 2. Continued.

Atom	Site	x	y	z	U _{iso}
H(121)	4a	1.0503	0.2218	-0.0192	0.027
H(131)	4a	1.0170	0.4379	-0.0073	0.032
H(141)	4a	0.8569	0.5249	0.0906	0.027
H(171)	4a	0.7430	0.5353	0.2497	0.033
H(172)	4a	0.6172	0.4671	0.2987	0.033
H(191)	4a	0.8593	-0.2928	0.2490	0.025
H(192)	4a	0.9226	-0.1673	0.2907	0.025
H(193)	4a	0.7607	-0.1758	0.2695	0.025

Table 2. Continued.

Atom	Site	x	y	z	U _{iso}
H(201)	4a	1.2540	-0.1691	0.0419	0.036
H(202)	4a	1.1802	-0.3024	0.0300	0.036
H(231)	4a	0.7159	-0.0050	-0.1025	0.035
H(232)	4a	0.8809	0.0053	-0.1011	0.035
H(233)	4a	0.7884	0.1229	-0.0724	0.035
H(211)	4a	1.2340	-0.2564	-0.0955	0.050
H(181)	4a	0.6087	0.5916	0.1522	0.050

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O(18)	4a	0.5676(2)	0.5512(2)	0.1929(1)	0.0359(9)	0.0371(9)	0.050(1)	0.0118(7)	0.0065(8)	0.0036(8)
O(21)	4a	1.1907(2)	-0.2026(2)	-0.0774(1)	0.054(1)	0.0298(8)	0.0366(9)	0.0194(8)	0.0192(8)	0.0009(7)
O(22)	4a	0.7969(1)	-0.0105(1)	0.01529(8)	0.0224(7)	0.0283(7)	0.0142(6)	-0.0012(5)	-0.0047(5)	0.0001(5)
N(1)	4a	0.6982(2)	0.3690(2)	0.2018(1)	0.0283(9)	0.0216(9)	0.037(1)	0.0051(7)	0.0075(8)	-0.0027(8)
N(6)	4a	0.8781(2)	-0.1528(2)	0.1627(1)	0.0248(8)	0.0162(7)	0.0131(7)	-0.0002(6)	-0.0032(6)	0.0008(6)
C(2)	4a	0.6568(2)	0.2538(2)	0.2309(1)	0.0246(9)	0.027(1)	0.030(1)	0.0015(8)	0.0086(8)	-0.0032(9)
C(3)	4a	0.7245(2)	0.1635(2)	0.1870(1)	0.0177(8)	0.0238(9)	0.0230(9)	-0.0005(7)	0.0036(7)	-0.0022(8)
C(4)	4a	0.7284(2)	0.0265(2)	0.1908(1)	0.0212(8)	0.0209(9)	0.0181(8)	-0.0012(7)	0.0065(7)	0.0006(7)
C(5)	4a	0.8703(2)	-0.0174(2)	0.1605(1)	0.0167(8)	0.0180(8)	0.0131(8)	-0.0030(6)	-0.0015(6)	-0.0041(7)
C(7)	4a	1.0120(2)	-0.1975(2)	0.1344(1)	0.028(1)	0.0196(9)	0.0231(9)	0.0071(7)	-0.0047(7)	0.0002(7)
C(8)	4a	1.0432(2)	-0.1574(2)	0.0424(1)	0.026(1)	0.0227(9)	0.0214(9)	0.0061(8)	0.0001(7)	-0.0019(8)
C(9)	4a	1.0424(2)	-0.0177(2)	0.0382(1)	0.0173(8)	0.0235(9)	0.0216(9)	0.0036(7)	0.0046(7)	0.0008(7)
C(10)	4a	0.9056(2)	0.0340(2)	0.0686(1)	0.0154(8)	0.0177(8)	0.0162(8)	0.0010(7)	0.0012(7)	0.0008(7)
C(11)	4a	0.9047(2)	0.1741(2)	0.0713(1)	0.0166(8)	0.0217(9)	0.0204(9)	-0.0008(7)	0.0009(7)	0.0011(7)
C(12)	4a	0.9809(2)	0.2546(2)	0.0219(2)	0.026(1)	0.027(1)	0.033(1)	0.0004(8)	0.0121(9)	0.0047(9)
C(13)	4a	0.9616(2)	0.3819(2)	0.0299(2)	0.031(1)	0.026(1)	0.042(1)	-0.0063(9)	0.007(1)	0.0126(9)
C(14)	4a	0.8697(2)	0.4339(2)	0.0866(2)	0.031(1)	0.0164(8)	0.041(1)	-0.0002(8)	-0.0018(9)	0.0055(9)
C(15)	4a	0.7946(2)	0.3528(2)	0.1381(1)	0.0203(9)	0.022(1)	0.032(1)	0.0015(8)	-0.0016(8)	-0.0015(8)
C(16)	4a	0.8119(2)	0.2262(2)	0.1284(1)	0.0160(8)	0.0188(9)	0.0236(9)	0.0009(7)	0.0007(7)	-0.0001(7)
C(17)	4a	0.6597(3)	0.4844(2)	0.2413(2)	0.039(1)	0.026(1)	0.034(1)	0.0069(9)	0.0002(9)	-0.0079(9)
C(19)	4a	0.8532(2)	-0.2010(2)	0.2499(1)	0.042(1)	0.0218(9)	0.0186(9)	-0.0011(8)	-0.0019(8)	0.0029(8)
C(20)	4a	1.1776(3)	-0.2136(2)	0.0132(2)	0.038(1)	0.037(1)	0.033(1)	0.020(1)	0.0056(9)	-0.000(1)
C(23)	4a	0.7954(3)	0.0312(3)	-0.0716(1)	0.035(1)	0.063(2)	0.019(1)	-0.002(1)	-0.0046(9)	0.010(1)

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