Crystal structure of 7α-acetyl-6,14-*endo*-ethanotetrahydrothebaine, $C_{23}H_{29}NO_4$

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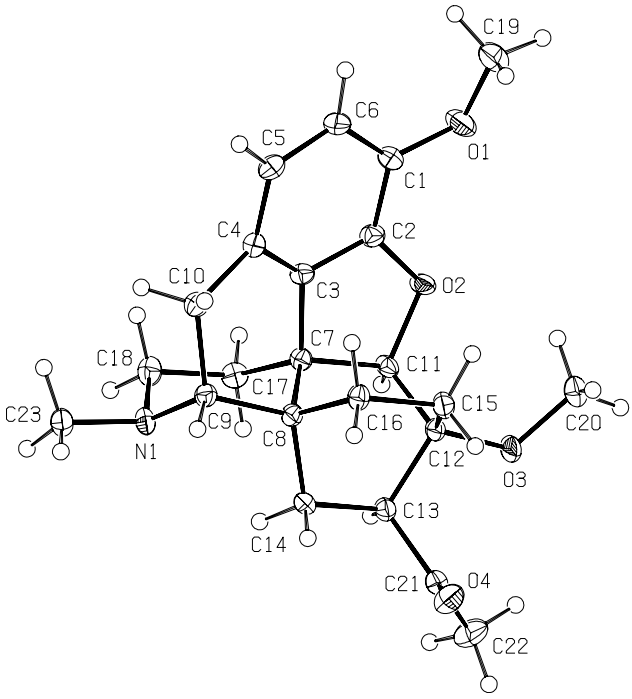

Abstract

$C_{23}H_{29}NO_4$, orthorhombic, $P2_12_12_1$ (no. 19), a = 7.352(2) Å, b = 8.856(2) Å, c = 29.340(6) Å, V = 1910.3 Å^3, Z = 4, $R_{gt}(F)$ = 0.048, $wR_{ref}(F^2)$ = 0.097, T = 193 K.

Source of material

The title compound was synthesized by hydrogenation of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine, preparation was described previously [1]. This hydrogenation can be carried out at 40 °C and 10 atm pressure using a palladium catalyst. Under these conditions the reduction of the keto-group was not observed. A solution of the 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (10 g) in ethanol (300 mL) was hydrogenated in the presence of palladium catalyst (3 g) at 40 °C and 10 atm for 8 hours. Removal of the catalyst by filtration followed by concentration of the solution under reduced pressure afforded the desired compound as a white crystalline solid (10 g). Recrystallization from ethanol gave crystals suitable for X-ray analysis (m.p. 132-134 °C).

Discussion

An increasing demand for medicinal opiates, coupled with a finite supply of natural products such as thebaine has created a special attention to this topic. Opioid analgesics represent one of the most important tools in a sequential approach to pain relief. Buprenorphine is a partial μ-opioid agonist developed as an agent for the treatment of opioid dependence [2] and possesses considerably affinity for both 8- and μ-opioid receptors [3]. These and other unique properties led us to synthesize buprenorphine from thebaine. In a multi-step synthesis of buprenorphine, the hydrogenation of 7α-acetyl-6,14-*endo*-ethenotetra-hydrothebaine is a very important step in which we gained a series of crystals.

The crystal structure determination revealed that the title compound is a polycyclic one with six rings. The molecule consists of a bicyclo[2.2.2]octane ring system with a methoxy group function. The aromatic ring is nearly planar and the piperidine ring adopts a chair conformation with the methyl substitution on the nitrogen at equatorial position. Comparison of the C—O bonds shows that d(O2—C2) = 1.374(4) Å is shorter than d(O2—C11) = 1.473(3) Å and comparable with d(O1—C1) = 1.380(4) Å which is in accord with the conjugation with adjacent aromatic ring.

Table 1. Data collection and handling.

Crystal:	colorless bulk, size 0.2 × 0.3 × 0.4 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.90 cm^{-1}
Diffractometer, scan mode:	Rebuild Syntex P2$_1$/Siemens P3, $\theta/2\theta$
$2\theta_{max}$:	56.1°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	2653, 2653
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 2055
$N(param)_{refined}$:	253
Programs:	SHELXTL [4], SHELXL-97 [5]

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(5A)	4*a*	0.3011	–0.3411	0.1864	0.029
H(6A)	4*a*	0.4179	–0.3952	0.1149	0.029
H(9A)	4*a*	–0.0172	0.0954	0.2348	0.023
H(10A)	4*a*	0.2551	–0.0813	0.2470	0.026
H(10B)	4*a*	0.0752	–0.1372	0.2241	0.026
H(11A)	4*a*	0.3520	0.2980	0.0964	0.023
H(13A)	4*a*	0.1292	0.4551	0.1199	0.024
H(14A)	4*a*	0.0700	0.3866	0.1903	0.025
H(14B)	4*a*	–0.1233	0.3234	0.1774	0.025
H(15A)	4*a*	–0.0127	0.0367	0.0727	0.028
H(15B)	4*a*	–0.1727	0.1489	0.0832	0.028
H(16A)	4*a*	–0.1752	0.0741	0.1550	0.025
H(16B)	4*a*	–0.0174	–0.0401	0.1443	0.025
H(17A)	4*a*	0.5275	0.2382	0.1668	0.027
H(17B)	4*a*	0.3747	0.3579	0.1761	0.027
H(18A)	4*a*	0.4591	0.1083	0.2328	0.031
H(18B)	4*a*	0.4752	0.2790	0.2466	0.031

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Table 2. Continued.

Atom	Site	*x*	*y*	*z*	U_{iso}
H(19A)	4*a*	0.4610	–0.3623	–0.0049	0.067
H(19B)	4*a*	0.3016	–0.3900	0.0296	0.067
H(19C)	4*a*	0.5023	–0.4271	0.0437	0.067
H(20A)	4*a*	0.0917	0.2845	–0.0238	0.049
H(20B)	4*a*	–0.0223	0.1618	0.0020	0.049
H(20C)	4*a*	0.1904	0.1625	0.0060	0.049

Table 2. Continued.

Atom	Site	*x*	*y*	*z*	U_{iso}
H(22A)	4*a*	–0.2213	0.6696	0.0772	0.054
H(22B)	4*a*	–0.0616	0.5984	0.0491	0.054
H(22C)	4*a*	–0.0225	0.6736	0.0964	0.054
H(23A)	4*a*	0.2756	0.2548	0.3117	0.040
H(23B)	4*a*	0.2835	0.0810	0.3017	0.040
H(23C)	4*a*	0.0950	0.1623	0.3063	0.040

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	4*a*	0.2182(4)	0.2038(3)	0.24663(8)	0.027(1)	0.023(1)	0.014(1)	–0.003(1)	–0.002(1)	–0.001(1)
O(1)	4*a*	0.4475(4)	–0.2088(3)	0.04378(8)	0.062(2)	0.024(1)	0.024(1)	0.008(1)	0.011(1)	–0.003(1)
O(2)	4*a*	0.3488(3)	0.0833(2)	0.07308(7)	0.035(1)	0.020(1)	0.018(1)	0.009(1)	0.009(1)	0.0022(9)
O(3)	4*a*	0.0718(3)	0.3224(2)	0.04233(7)	0.043(1)	0.023(1)	0.013(1)	0.004(1)	0.000(1)	0.0024(9)
O(4)	4*a*	–0.2904(3)	0.4149(3)	0.10700(8)	0.026(1)	0.036(1)	0.032(1)	0.005(1)	0.001(1)	0.009(1)
C(1)	4*a*	0.4015(5)	–0.1853(4)	0.0888(1)	0.027(2)	0.028(2)	0.021(2)	0.007(2)	0.004(1)	–0.003(1)
C(2)	4*a*	0.3650(4)	–0.0382(4)	0.1019(1)	0.023(2)	0.019(2)	0.022(2)	0.002(1)	0.002(1)	0.002(1)
C(3)	4*a*	0.3224(4)	–0.0050(3)	0.1466(1)	0.017(2)	0.019(2)	0.021(2)	0.002(1)	0.002(1)	0.000(1)
C(4)	4*a*	0.2840(5)	–0.1148(4)	0.1783(1)	0.020(2)	0.022(2)	0.019(2)	–0.000(1)	–0.001(1)	0.001(1)
C(5)	4*a*	0.3202(5)	–0.2634(4)	0.1657(1)	0.027(2)	0.020(2)	0.026(2)	0.001(2)	–0.001(2)	0.005(1)
C(6)	4*a*	0.3851(5)	–0.2965(4)	0.1219(1)	0.029(2)	0.018(2)	0.027(2)	0.003(2)	–0.001(2)	–0.002(1)
C(7)	4*a*	0.2718(4)	0.1581(3)	0.1507(1)	0.019(2)	0.017(2)	0.017(1)	–0.001(1)	0.002(1)	0.001(1)
C(8)	4*a*	0.0785(4)	0.1612(3)	0.1713(1)	0.021(2)	0.017(1)	0.016(1)	–0.000(1)	0.000(1)	0.002(1)
C(9)	4*a*	0.1030(4)	0.0969(3)	0.2204(1)	0.021(2)	0.021(2)	0.017(1)	0.002(1)	0.001(1)	0.002(1)
C(10)	4*a*	0.1772(5)	–0.0687(3)	0.2206(1)	0.026(2)	0.019(2)	0.020(2)	–0.000(1)	0.002(1)	0.004(1)
C(11)	4*a*	0.2729(5)	0.2097(3)	0.09966(9)	0.028(2)	0.015(1)	0.015(1)	0.000(1)	0.006(1)	0.000(1)
C(12)	4*a*	0.0790(5)	0.2528(3)	0.08644(9)	0.029(2)	0.018(1)	0.012(1)	0.004(2)	0.002(1)	0.002(1)
C(13)	4*a*	0.0279(4)	0.3832(4)	0.1196(1)	0.026(2)	0.018(2)	0.016(1)	0.000(1)	–0.000(1)	0.000(1)
C(14)	4*a*	0.0044(5)	0.3226(3)	0.1691(1)	0.026(2)	0.019(2)	0.016(1)	0.003(2)	0.001(1)	–0.003(1)
C(15)	4*a*	–0.0510(5)	0.1191(4)	0.0923(1)	0.032(2)	0.022(2)	0.017(2)	–0.001(2)	–0.003(1)	–0.001(1)
C(16)	4*a*	–0.0531(4)	0.0652(4)	0.1427(1)	0.022(2)	0.024(2)	0.017(1)	–0.001(1)	0.000(1)	0.002(1)
C(17)	4*a*	0.4058(5)	0.2518(4)	0.1789(1)	0.021(2)	0.020(2)	0.026(2)	–0.003(1)	0.001(1)	0.002(1)
C(18)	4*a*	0.4040(5)	0.2071(4)	0.2292(1)	0.028(2)	0.027(2)	0.023(2)	–0.004(2)	–0.004(1)	0.001(1)
C(19)	4*a*	0.4264(7)	–0.3595(4)	0.0266(1)	0.069(3)	0.033(2)	0.032(2)	0.012(2)	–0.003(2)	–0.010(2)
C(20)	4*a*	0.0839(5)	0.2247(4)	0.0034(1)	0.043(2)	0.036(2)	0.018(2)	0.004(2)	–0.001(2)	–0.001(2)
C(21)	4*a*	–0.1399(5)	0.4665(4)	0.1023(1)	0.030(2)	0.025(2)	0.017(2)	0.006(2)	0.001(1)	–0.001(1)
C(22)	4*a*	–0.1085(6)	0.6155(4)	0.0792(1)	0.039(2)	0.027(2)	0.042(2)	0.006(2)	–0.001(2)	0.011(2)
C(23)	4*a*	0.2181(5)	0.1728(4)	0.2959(1)	0.035(2)	0.028(2)	0.019(2)	0.001(2)	–0.004(2)	–0.001(1)

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