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Structure of a Diels–Alder Adduct at a 5,7-Disubstituted Thebaine Derivative

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(*Received* 11 *June* 1993; *accepted* 5 *October* 1993)

Abstract

The structure of (+)-ethyl 3,18-dimethoxy-5β,17-dimethyl-4,5α-epoxy-6β,14β-ethenomorphinan-8β-carboxylate (3), $C_{25}H_{31}NO_5$, is described. Diels–Alder reaction of the thebaine analogoue (−)-5β-methyl-7-methoxy-6-demethoxythebaine (2), with ethyl propenoate gives rise to anomalous α-face approach of the dienophile, yielding the title compound (3), in which the etheno bridge is at the 6β,14β position and the ethoxycarbonyl substituent is at the 8β position.

Comment

Diels–Alder reaction of the opium alkaloid (−)-thebaine (Bentley, 1971) with several dienophiles yields exclusively 7-substituted 6α,14α-ethenoisomorphinans, although this reaction of (−)-morphinan-6,8-dienes may yield, in principle, eight isomers. Two stereoisomeric structures, namely the 6β,14β-ethenomorphinan or 6α,14α-ethenoisomorphinan structure, are formed by α-face or β-face approach, respectively, from the diene system by the dienophile. The position of the new substituent (*R*) determines four regioisomers for each stereoisomer (Fig. 1).

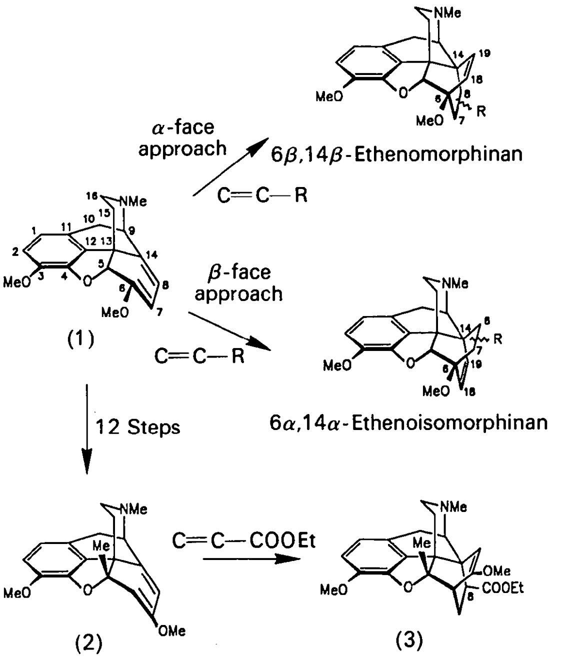

Fig. 1. Diels–Alder reactions forming 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans.

In our search for novel Diels–Alder adducts, in which the substituent is present at the 8 position, we (Meuzelaar, Woudenberg, Sinnema & Maat, 1993; Woudenberg, Meuzelaar & Maat, 1993) developed a route for the synthesis of 7-methoxy-5β-methyl-6-demethoxythebaine (2). Diels–Alder reaction of (2) with ethyl propenoate yielded one cycloadduct. In the ^{1}H NMR spectrum the signal of the vinyl proton H(19) was present at δ 5.09. This indicates a 6α,14α-ethenoisomorphinan structure, because in a series of 21 6α,14α-ethenoisomorphinans derived from thebaine, Fulmor *et al.* (1967) found H(18) at δ 5.91 ± 0.08 and H(19) at δ 5.48 ± 0.06, whereas Linders, Prazeres, Lie & Maat (1989) demonstrated downfield shifts for H(18) and H(19) from δ 6.0 and higher in a series of 6β,14β-ethenomorphinans. However, the presence of the methoxy group at the 18 position with its shielding effect makes the assignment of the 6α,14α-ethenoisomorphinan structure ambiguous. Neither the mass spectrum nor the ^{1}H and ^{13}C NMR spectra could give definitive proof of the structure. Therefore, we performed a single-crystal X-ray analysis of adduct (3), which gave the final proof for the 6β,14β-ethenomorphinan structure with the ethoxycarbonyl group at the 8β position. To our knowledge, this is the first reported single-crystal X-ray study of a 4,5α-epoxy-6β,14β-ethenomorphinan obtained by Diels–Alder reaction, in which the dienophile approached the diene system from the α face. This is in contrast to the case of thebaine (1) itself, where the Diels–Alder reaction takes place exclusively from the β face. The results can be explained by the electronic effect of the methoxy group combined with the steric hindrance of the

Acta Crystallographica Section C
ISSN 0108-2701 ©1994

5β-methyl group. The 7-methoxy group contributes to the formation of only 8-substituted 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans (Fig. 1). Introduction of a 5β-methyl group blocks the formation of 8-substituted 6α,14α-ethenoisomorphinans, which can be explained *via* an asynchronous Diels–Alder mechanism (Woudenberg & Maat, 1993). The methyl-vinyl-ether moiety is practically planar: the maximum deviation from the plane through atoms C(6), C(14), C(18), C(19), O(3) and C(23) is 0.044 (6) Å for C(23), with a torsion angle C(19)—C(18)—O(3)—C(23) of −2.7 (5)°. This indicates that the 18-methoxy group with its two lone pairs contributes to an upfield shift for H(19). Apparently, the downfield shift of H(19) attributed to the anisotropy of the N-atom lone pair normally observed in 6β,14β-ethenomorphinans, is compensated by the shielding effect of the 18-methoxy group, which causes the signal of H(19) at δ 5.09 in the ^{1}H NMR spectrum.

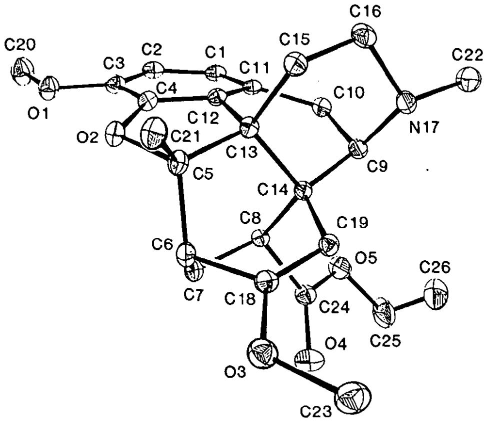

Fig. 2. *ORTEP* plot (Johnson, 1965) of the title compound. Boundary surfaces are drawn to enclose 50% probability.

Experimental

The title compound was synthesized in our laboratory starting from natural (−)-thebaine with known absolute configuration (Meuzelaar, Woudenberg, Sinnema & Maat 1993; Woudenberg, Meuzelaar & Maat, 1993). Crystals were grown from methanol; m.p. 425-426 K.

Crystal data

$C_{25}H_{31}NO_5$
M_r = 425.46
Orthorhombic
$P2_12_12_1$
a = 7.220 (2) Å
b = 9.528 (2) Å
c = 32.344 (7) Å
V = 2225.0 (9) Å^3
Z = 4
D_x = 1.27 Mg m^{-3}

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 9.25-13.05°
μ = 0.082 mm^{-1}
T = 293 K
0.65 × 0.40 × 0.25 mm
Transparent, colourless

Data collection

Enraf-Nonius CAD-4 diffractometer
$\omega/2\theta$ scans [width (0.30 + 0.35tanθ)°]
Absorption correction: none
3698 measured reflections
3698 independent reflections
2205 observed reflections [$I > 2.0\sigma(I)$]

$\theta_{\max}$ = 30°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 13$
$l = 0 \rightarrow 45$
3 standard reflections
frequency: 120 min
intensity variation: <2.0%

Refinement

Refinement on F
R = 0.056
wR = 0.053
S = 3.6
2205 reflections
280 parameters
H-atom parameters not refined
$w = 1/\sigma^2(F)$

$(\Delta/\sigma)_{\max}$ = 0.001
$\Delta\rho_{\max}$: $|\Delta\sigma|$ = 0.40 e Å^{-3}
$\Delta\rho_{\min}$: $|\Delta\sigma|$ = 0.40 e Å^{-3}
Atomic scattering factors from *Xtal*3.2 (Hall, Flack & Stewart, 1992) and *International Tables for X-ray Crystallography* (1974, Vol. IV, p. 149)

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)	0.4996 (6)	0.4825 (4)	0.4677 (1)	0.060 (1)
C(2)	0.5301 (6)	0.6269 (5)	0.4719 (1)	0.065 (1)
C(3)	0.4392 (6)	0.7248 (4)	0.4479 (1)	0.060 (1)
C(4)	0.3065 (5)	0.6732 (4)	0.4207 (1)	0.049 (1)
C(5)	0.1200 (5)	0.6489 (4)	0.3634 (1)	0.049 (1)
C(6)	0.2136 (5)	0.6317 (3)	0.3214 (1)	0.048 (1)
C(7)	0.4187 (5)	0.5860 (4)	0.3269 (1)	0.051 (1)
C(8)	0.4267 (5)	0.4387 (4)	0.3466 (1)	0.044 (1)
C(9)	0.2294 (5)	0.2573 (4)	0.3857 (1)	0.052 (1)
C(10)	0.3445 (6)	0.2829 (4)	0.4261 (1)	0.057 (1)
C(11)	0.3639 (5)	0.4324 (4)	0.4407 (1)	0.048 (1)
C(12)	0.2638 (5)	0.5336 (4)	0.4200 (1)	0.042 (1)
C(13)	0.1311 (5)	0.5059 (4)	0.3861 (4)	0.043 (1)
C(14)	0.2220 (5)	0.3910 (3)	0.3584 (1)	0.040 (1)
C(15)	−0.0619 (5)	0.4529 (4)	0.4004 (1)	0.053 (1)
C(16)	−0.0587 (6)	0.3101 (4)	0.4204 (1)	0.064 (1)
N(17)	0.0372 (5)	0.2116 (3)	0.3935 (1)	0.056 (1)
C(18)	0.1147 (5)	0.5113 (4)	0.3002 (1)	0.048 (1)
C(19)	0.1169 (5)	0.3883 (4)	0.3186 (1)	0.045 (10)
C(20)	0.5960 (8)	0.9241 (5)	0.4747 (2)	0.108 (3)
C(21)	−0.0712 (5)	0.7150 (4)	0.3583 (1)	0.062 (1)
C(22)	0.0271 (7)	0.0684 (4)	0.4088 (1)	0.078 (2)
C(23)	−0.0486 (7)	0.4409 (5)	0.2408 (1)	0.077 (2)
C(24)	0.5118 (6)	0.3338 (4)	0.3173 (1)	0.057 (1)
C(25)	0.6627 (9)	0.1129 (5)	0.3142 (2)	0.124 (3)
C(26)	0.5606 (8)	−0.0142 (6)	0.3199 (2)	0.118 (3)
O(1)	0.4682 (5)	0.8669 (3)	0.4472 (1)	0.081 (1)
O(2)	0.2226 (4)	0.7489 (2)	0.3900 (1)	0.056 (1)
O(3)	0.0370 (4)	0.5508 (3)	0.2634 (1)	0.058 (1)
O(4)	0.5210 (5)	0.3438 (3)	0.2807 (1)	0.090 (1)
O(5)	0.5821 (5)	0.2260 (3)	0.3382 (1)	0.088 (1)

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

C(1)—C(2)	1.399 (6)	C(9)—N(17)	1.476 (5)
C(1)—C(11)	1.396 (5)	C(10)—C(11)	1.507 (5)
C(2)—C(3)	1.378 (6)	C(11)—C(12)	1.379 (5)
C(3)—C(4)	1.391 (6)	C(12)—C(13)	1.481 (5)
C(3)—O(1)	1.371 (5)	C(13)—C(14)	1.558 (5)
C(4)—C(12)	1.365 (5)	C(13)—C(15)	1.553 (5)
C(4)—O(2)	1.369 (6)	C(14)—C(19)	1.495 (5)

C(5)—C(6)	1.527 (5)	C(15)—C(16)	1.506 (5)
C(5)—C(13)	1.550 (5)	C(16)—N(17)	1.454 (5)
C(5)—C(21)	1.526 (5)	N(17)—C(22)	1.453 (5)
C(5)—O(2)	1.483 (4)	C(18)—C(19)	1.314 (5)
C(6)—C(7)	1.554 (5)	C(18)—O(3)	1.369 (4)
C(6)—C(18)	1.515 (5)	C(20)—O(1)	1.392 (6)
C(7)—C(8)	1.542 (5)	C(23)—O(3)	1.419 (5)
C(8)—C(14)	1.593 (5)	C(24)—O(4)	1.188 (5)
C(8)—C(24)	1.509 (5)	C(24)—O(5)	1.330 (5)
C(9)—C(10)	1.566 (5)	C(25)—C(26)	1.429 (8)
C(9)—C(14)	1.551 (5)	C(25)—O(5)	1.450 (6)

C(2)—C(1)—C(11)	120.5 (4)	C(5)—C(13)—C(12)	103.2 (3)
C(1)—C(2)—C(3)	122.4 (4)	C(5)—C(13)—C(14)	111.6 (3)
C(2)—C(3)—C(4)	116.4 (4)	C(5)—C(13)—C(15)	112.4 (3)
C(2)—C(3)—O(1)	127.3 (4)	C(12)—C(13)—C(14)	106.1 (3)
C(4)—C(3)—O(1)	116.3 (3)	C(12)—C(13)—C(15)	114.7 (3)
C(3)—C(4)—C(12)	120.7 (3)	C(14)—C(13)—C(15)	108.7 (3)
C(3)—C(4)—O(2)	125.3 (3)	C(8)—C(14)—C(9)	109.8 (3)
C(12)—C(4)—O(2)	113.7 (3)	C(8)—C(14)—C(13)	109.2 (3)
C(6)—C(5)—C(13)	107.7 (3)	C(8)—C(14)—C(19)	105.6 (3)
C(6)—C(5)—C(21)	110.4 (3)	C(9)—C(14)—C(13)	105.4 (3)
C(6)—C(5)—O(2)	111.5 (3)	C(9)—C(14)—C(19)	119.6 (3)
C(13)—C(5)—C(21)	117.4 (3)	C(13)—C(14)—C(19)	107.0 (3)
C(13)—C(5)—O(2)	105.3 (3)	C(13)—C(15)—C(16)	114.1 (3)
C(21)—C(5)—O(2)	104.4 (3)	C(15)—C(16)—N(17)	109.5 (3)
C(5)—C(6)—C(7)	110.4 (3)	C(9)—N(17)—C(16)	111.0 (3)
C(5)—C(6)—C(18)	105.9 (3)	C(9)—N(17)—C(22)	112.4 (3)
C(7)—C(6)—C(18)	106.8 (3)	C(16)—N(17)—C(22)	112.3 (3)
C(6)—C(7)—C(8)	109.8 (3)	C(6)—C(18)—C(19)	117.7 (3)
C(7)—C(8)—C(14)	108.9 (3)	C(6)—C(18)—O(3)	112.2 (3)
C(7)—C(8)—C(24)	111.0 (3)	C(19)—C(18)—O(3)	130.1 (3)
C(10)—C(9)—C(14)	111.4 (3)	C(14)—C(19)—C(18)	112.4 (3)
C(10)—C(9)—N(17)	113.8 (3)	C(8)—C(24)—O(4)	126.5 (4)
C(14)—C(9)—N(17)	107.9 (3)	C(8)—C(24)—O(5)	110.3 (3)
C(9)—C(10)—C(11)	117.3 (3)	O(4)—C(24)—O(5)	123.1 (5)
C(1)—C(11)—C(10)	125.8 (3)	C(26)—C(25)—O(5)	110.7 (5)
C(1)—C(11)—C(12)	115.6 (3)	C(3)—O(1)—C(20)	118.5 (3)
C(10)—C(11)—C(12)	117.4 (3)	C(4)—O(2)—C(5)	107.7 (3)
C(4)—C(12)—C(11)	123.7 (3)	C(18)—O(3)—C(23)	115.1 (3)
C(4)—C(12)—C(13)	109.4 (3)	C(24)—O(5)—C(25)	117.1 (4)
C(11)—C(12)—C(13)	125.0 (3)		

Data were corrected for Lorentz and polarization effects. The structure was solved using direct methods (*Xtal*3.2; Hall, Flack & Stewart, 1992) with full-matrix least-squares refinement of anisotropic heavy atoms using *CRYLSQ* in *Xtal*3.2. H atoms were included in idealized positions (sp^2, C—H = 0.95 Å; sp^3, C—H = 1.00 Å] with isotropic displacement parameters [U(H) = $1.1U_{\rm eq}$(C)] and were allowed to ride on the parent C atoms.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71710 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AL1065]

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Acta Cryst. (1994). C**50**, 915–919

2,2′,3,3′-Tetra-*O*-acetyl-6,6′-dichloro-4,4′,6,6′-tetradeoxy-α,α-trehalose†

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(*Received* 16 *September* 1993; *accepted* 18 *November* 1993)

Abstract

The crystal structure of the title compound (2,3-di-*O*-acetyl-6-chloro-4,6-dideoxy-α-D-glucopyranosyl 2,3-di-*O*-acetyl-6-chloro-4,6-dideoxy-α-D-glucopyranoside, $C_{20}H_{28}Cl_2O_{11}$) has been determined by X-ray diffraction. The two symmetry-independent molecules have very similar molecular dimensions, except for minor variations in the orientations of the ring substituents. The hexopyranosyl residues have distorted chair $^4C_1$ conformations. As observed for α,α-trehalose [Taga, Senma & Osaki (1972). *Acta Cryst.* B**28**, 3258-3263; Brown, Rohrer, Berking, Beevers, Gould & Simpson (1972). *Acta Cryst.* B**28**, 3145-3158; Jeffrey & Nanni (1985). *Carbohydr. Res.* **137**, 21-30] and its derivatives [Lee & Koh (1994). *Carbohydr. Res.* In the press], the molecules have approximate C_2 symmetry, differing only in the orientation of the chloromethyl substituents, and in the torsion angles about the α 1 → 1 linkage.

Comment

The ubiquitous character of α,α-trehalose, also known as mycose or mushroom sugar, as a probable energy reserve in many organisms has stimulated much research on the sugar (Birch 1963; Lee, 1980). It has served as an ideal molecule for taste-structure studies (Lee, 1973; Birch & Lee, 1974) because the molecule contains two chemically equivalent glucopyranose residues in the most stable $^4C_1$

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† Crystal Structures of Trehalose Derivatives, Part 3. For Part 2, see Lee & Koh (1994).

Acta Crystallographica Section C
ISSN 0108-2701 ©1994