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Structure of 4,5-Epoxy-3-methoxy-*N*, α , α -trimethylmorphinan-5,8-diene-7 α -methanol

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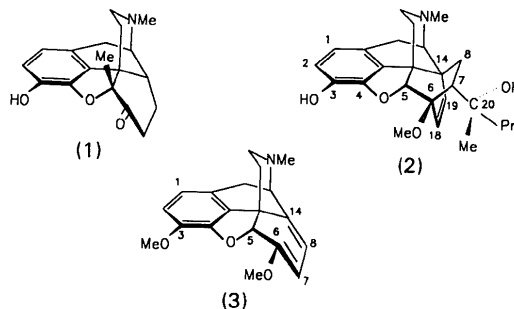
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Abstract. C₂₁H₂₅NO₃, *M_r* = 339.43, orthorhombic, *P*2₁2₁2₁, *a* = 9.830 (1), *b* = 10.878 (1), *c* = 16.781 (1) Å, *V* = 1794.4 (3) Å³, *Z* = 4, *D_x* = 1.256 g cm⁻³, λ(Cu Kα) = 1.54184 Å, μ = 6.3 cm⁻¹, *F*(000) = 728, *T* = 295 K, *R* = 0.046 for 2364 reflections [*I* > 2.5σ(*I*)]. The title compound is one of three isomeric morphinans, which were obtained from deprotonation of the 5-position of 6-dimethoxythebaine with butyllithium, followed by reaction of the resultant anion with acetone. The dimethylmethanol substituent is in the 7 α -position of the morphinan skeleton and its hydroxyl group forms an intermolecular hydrogen bond with the lone pair of the tertiary nitrogen, resulting in an infinite hydrogen-bonded chain running in the *b* direction. An interesting feature of the title compound is the C(5)—C(6) double bond that does not seem to limit the substitution possibilities on the ring.

Introduction. Metopon (1), a semisynthetic analgesic, exhibits remarkable pharmacological properties, namely an increase of antinociceptive action with a parallel decrease of unwanted side effects (Casy & Parfitt, 1986). Etorphine (2) is, like metopon (1), a

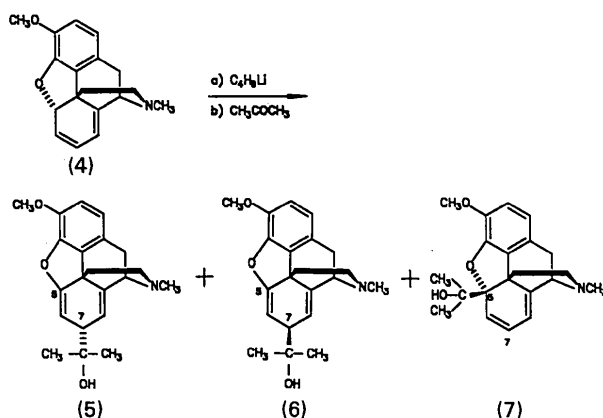
semisynthetic analgesic, but it shows an extraordinarily high analgesic activity (1000 × morphine) (Lewis, Bentley & Cowan, 1971). Therefore an interesting biological activity is expected with the introduction of an etheno bridge in metopon (Woudenberg, Lie & Maat, 1990) and analogues.



We have investigated the influence of substituents at the 5 β -position of thebaine (3) on its pharmacological characteristics and on the course of the Diels–Alder reaction, for which we introduced a dimethylmethanol group at the 5 β -position of thebaine (3) (Woudenberg, Lie & Maat, 1991) according to known procedures (Gates, Boden & Sundararaman, 1989).

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In order to extend the series of thebaine-5 β -(dimethylmethanol) derivatives, 6-demethoxythebaine (4) was deprotonated with butyllithium, followed by reaction with acetone, analogously to thebaine. Analysis of the reaction mixture showed that the 5 β -substituted product (7) was a minor product and that the major products were the 7 α - and the 7 β -substituted 4,5-epoxy-5,6,8,14-tetrahydromorphinans (5) and (6). A single-crystal X-ray analysis of the product (5) shows the position of all substituents, in agreement with the indications obtained from the mass spectrum and ¹H and ¹³C NMR spectra. A point of interest is the position of the dimethylmethanol group at C(7). To our knowledge, this is the first reported X-ray study of an unconjugated 4,5-epoxymorphinandiene.



Experimental. The title compound (5) was prepared by deprotonation of 6-demethoxythebaine with butyllithium and reaction of the resultant anion with acetone, separated chromatographically, and crystallized as the free base from a solution of chloroform, after the addition of diethyl ether. Data were collected on an Enraf-Nonius CAD-4 diffractometer for a slightly coloured transparent crystal (0.35 × 0.35 × 0.35 mm) glued on top of a glass fibre. Unit-cell parameters and their e.s.d.'s were derived from a least-squares treatment of 25 SET4 reflections (23 < θ < 29°). Intensity data for 2526 reflections (h -8-12, k 0-13, l 0-21; θ < 75°; Ni-filtered Cu $K\alpha$ radiation) were collected in the $\omega/2\theta$ scan mode with $\Delta\omega = (0.60 + 0.15 \tan\theta)^\circ$. Three reference reflections (130, 023 and 30 $\bar{1}$) indicated no decay during 29.1 h of X-ray exposure. The intensity data were corrected for Lp but not for absorption. The variance $\sigma^2(I)$ was calculated based on counting statistics plus an instability constant term (0.0247 I^2) as derived from the excess variance in the reference reflections (McCandlish, Stout & Andrews, 1975). The space group was derived from the observed systematic absences. The structure was solved by direct methods (*SHELXS86*; Sheldrick, 1986) and refined on F by

full-matrix least squares with *SHELXL76* (Sheldrick, 1976). The H atoms bonded to O(3), C(7) and C(8) were located in a difference Fourier map and their positions refined. All other H atoms were introduced on calculated positions (C—H = 0.98 Å) and refined with fixed geometry with respect to the atoms they are attached to and with two common isotropic thermal parameters. Refinement with $w^{-1} = \sigma^2(F)$ converged at $R = 0.046$ [$wR = 0.070$; $S = 0.41$; 248 parameters; 2364 reflections; $(\Delta/\sigma)_{\max} = 0.1$]. An empirical extinction correction was applied: $F_{\text{corr}} = F_{\text{calc}}[1 - P(F_{\text{calc}})^2/\sin\theta]$ with $P = 1.9(2) \times 10^{-6}$. A final difference Fourier map did not show residual peaks outside -0.33 and 0.36 e \AA^{-3} . Scattering factors of Cromer & Mann (1968) and anomalous-dispersion terms from Cromer & Liberman (1970). Final parameters were given in Table 1.* The programs *PLATON* and *PLUTON* (Spek, 1982) were used for the calculation of geometrical data and the plot respectively. All calculations were performed on a MicroVAX-II cluster.

Discussion. The molecular structure of (5) is shown in Fig. 1, together with the atomic numbering scheme. Bond distances and angles are given in Table 2. The dimethylmethanol group is in the 7 α -position, consistent with the coupling constants of H(C6)—H(C7) and H(C7)—H(C8) in the ¹H NMR spectrum. From these constants we established that C(7) is not in the plane determined by C(5), C(6), C(8) and C(14). However the position of C(7) with respect to this plane could not be assigned. The position of C(7) is of critical importance to the assignment of the position of the dimethylmethanol group.

The torsion angle of the furan ring C(4)—C(12)—C(13)—C(5) is 20.7(2)° which falls into the range previously found for morphine and a codeine derivative [14.2(4)° (Bye, 1976) and 20.17° (Liebman, Malarek, Blount, Nelson & Delaney, 1978)].

The six-membered ring [C(5), C(6), C(7), C(8), C(14), C(13)] adopts the boat conformation as indicated by the puckering parameters (Cremer & Pople, 1975): $Q = 0.341(2) \text{ \AA}$, $\theta = 90.5(3)^\circ$, $\varphi = 301.4(4)^\circ$. The five-membered ring [O(2), C(4), C(12), C(13), C(5)] has puckering parameters [$Q = 0.278(2) \text{ \AA}$, $\varphi = 313.5(5)^\circ$] indicating a conformation intermediate between envelope and half-chair. A noncrystallographic mirror plane lies through C(5) according to the asymmetry parameter $C_s[C(5)] = 5.4(2)^\circ$ (Duax, Weeks & Rohrer, 1976). The plane of the hexadiene ring [C(5), C(6), C(7), C(8), C(14), C(13)] and the plane

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53648 (20 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final coordinates and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq} (Å ²)
O(1)	0.9400 (2)	0.2039 (2)	0.0898 (1)	0.0682 (7)
O(2)	1.1210 (2)	0.3514 (2)	0.1854 (1)	0.0564 (6)
O(3)	1.5957 (2)	0.3896 (2)	0.2925 (1)	0.0600 (6)
N(1)	1.1740 (2)	0.8120 (2)	0.1173 (1)	0.0500 (6)
C(1)	1.0022 (3)	0.4828 (2)	-0.0347 (1)	0.0546 (8)
C(2)	0.9491 (3)	0.3697 (2)	-0.0100 (2)	0.0544 (8)
C(3)	0.9795 (3)	0.3180 (2)	0.0637 (2)	0.0507 (7)
C(4)	1.0617 (2)	0.3871 (2)	0.1131 (1)	0.0452 (7)
C(5)	1.2239 (2)	0.4408 (2)	0.1972 (1)	0.0471 (7)
C(6)	1.3443 (2)	0.4220 (2)	0.2291 (1)	0.0482 (7)
C(7)	1.4518 (2)	0.5230 (2)	0.2234 (1)	0.0407 (6)
C(8)	1.4244 (2)	0.6101 (2)	0.1535 (1)	0.0414 (6)
C(9)	1.2490 (2)	0.7224 (2)	0.0663 (1)	0.0419 (6)
C(10)	1.1634 (3)	0.6667 (2)	-0.0034 (1)	0.0506 (7)
C(11)	1.0821 (2)	0.5528 (2)	0.0163 (1)	0.0429 (6)
C(12)	1.1012 (2)	0.5031 (2)	0.0915 (1)	0.0393 (6)
C(13)	1.1838 (2)	0.5570 (2)	0.1568 (1)	0.0394 (6)
C(14)	1.3013 (2)	0.6265 (2)	0.1235 (1)	0.0381 (6)
C(15)	1.0997 (3)	0.6480 (3)	0.2081 (1)	0.0523 (8)
C(16)	1.0572 (2)	0.7574 (3)	0.1580 (2)	0.0559 (8)
C(17)	1.1319 (3)	0.9228 (2)	0.0733 (2)	0.072 (1)
C(18)	0.8430 (3)	0.1396 (3)	0.0443 (2)	0.077 (1)
C(19)	1.5959 (2)	0.4654 (2)	0.2223 (2)	0.0448 (7)
C(20)	1.6193 (3)	0.3841 (3)	0.1504 (2)	0.072 (1)
C(21)	1.7055 (3)	0.5628 (3)	0.2293 (2)	0.076 (1)

Table 2. *Bond distances (Å) and bond angles (°) for non-H atoms*

O(1)—C(3)	1.372 (3)	C(6)—C(7)	1.527 (3)
O(1)—C(18)	1.407 (4)	C(7)—C(8)	1.531 (3)
O(2)—C(4)	1.401 (3)	C(7)—C(19)	1.549 (3)
O(2)—C(5)	1.417 (3)	C(8)—C(14)	1.323 (3)
O(3)—C(19)	1.438 (3)	C(9)—C(10)	1.563 (3)
N(1)—C(9)	1.492 (3)	C(9)—C(14)	1.508 (3)
N(1)—C(16)	1.462 (3)	C(10)—C(11)	1.511 (3)
N(1)—C(17)	1.473 (3)	C(11)—C(12)	1.385 (3)
C(1)—C(2)	1.399 (3)	C(12)—C(13)	1.484 (3)
C(1)—C(11)	1.389 (3)	C(13)—C(14)	1.489 (3)
C(2)—C(3)	1.391 (4)	C(13)—C(15)	1.551 (4)
C(3)—C(4)	1.380 (3)	C(15)—C(16)	1.516 (4)
C(4)—C(12)	1.369 (3)	C(19)—C(20)	1.513 (4)
C(5)—C(6)	1.316 (3)	C(19)—C(21)	1.516 (4)
C(5)—C(13)	1.487 (3)		
C(3)—O(1)—C(18)	117.9 (2)	C(9)—C(10)—C(11)	116.0 (2)
C(4)—O(2)—C(5)	103.1 (2)	C(1)—C(11)—C(10)	127.8 (2)
C(9)—N(1)—C(16)	113.0 (2)	C(1)—C(11)—C(12)	115.1 (2)
C(9)—N(1)—C(17)	112.7 (2)	C(10)—C(11)—C(12)	116.6 (2)
C(16)—N(1)—C(17)	110.2 (2)	C(4)—C(12)—C(11)	124.2 (2)
C(2)—C(1)—C(11)	120.7 (2)	C(4)—C(12)—C(13)	108.9 (2)
C(1)—C(2)—C(3)	122.6 (2)	C(11)—C(12)—C(13)	126.3 (2)
O(1)—C(3)—C(2)	126.0 (2)	C(5)—C(13)—C(12)	98.4 (2)
O(1)—C(3)—C(4)	117.8 (2)	C(5)—C(13)—C(14)	113.4 (2)
C(2)—C(3)—C(4)	116.1 (2)	C(5)—C(13)—C(15)	115.5 (2)
O(2)—C(4)—C(3)	127.8 (2)	C(12)—C(13)—C(14)	110.4 (2)
O(2)—C(4)—C(12)	111.6 (2)	C(12)—C(13)—C(15)	111.7 (2)
C(3)—C(4)—C(12)	120.6 (2)	C(14)—C(13)—C(15)	107.3 (2)
O(2)—C(5)—C(6)	126.3 (2)	C(8)—C(14)—C(9)	130.4 (2)
O(2)—C(5)—C(13)	109.3 (2)	C(8)—C(14)—C(13)	119.9 (2)
C(6)—C(5)—C(13)	123.8 (2)	C(9)—C(14)—C(13)	109.0 (2)
C(5)—C(6)—C(7)	119.0 (2)	C(13)—C(15)—C(16)	109.9 (2)
C(6)—C(7)—C(8)	111.8 (2)	N(1)—C(16)—C(15)	111.2 (2)
C(6)—C(7)—C(19)	110.0 (2)	O(3)—C(19)—C(7)	102.8 (2)
C(8)—C(7)—C(19)	113.7 (2)	O(3)—C(19)—C(20)	108.5 (2)
C(7)—C(8)—C(14)	122.4 (2)	O(3)—C(19)—C(21)	109.8 (2)
N(1)—C(9)—C(10)	114.6 (2)	C(7)—C(19)—C(20)	112.6 (2)
N(1)—C(9)—C(14)	104.8 (2)	C(7)—C(19)—C(21)	111.5 (2)
C(10)—C(9)—C(14)	113.1 (2)	C(20)—C(19)—C(21)	111.2 (2)

through [C(7),O(3),C(19),C(8)] form an angle of 39.2 (2)°. The hydroxyl substituent of the dimethylmethanol group is in the 7 α -position of the morphinan skeleton. The molecule links *via* an intermolecular O(3)—H(3)···N(1) hydrogen bond [O···N 2.851 (3), O—H 0.87 (3), H···N 2.00 (3) Å, \angle O—H···N 166 (3)°] into infinite chains running in the *b* direction as depicted in Fig. 2.

In conclusion, the single-crystal X-ray analysis confirms that the previously mentioned conversion unexpectedly results in a novel type of morphinan-diene.

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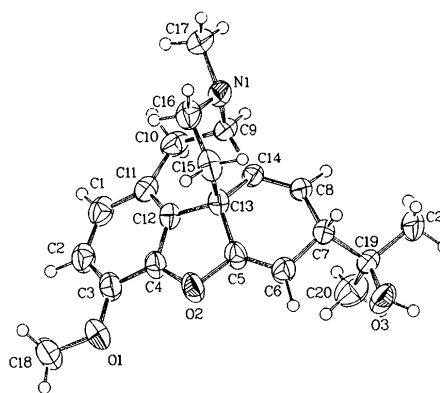
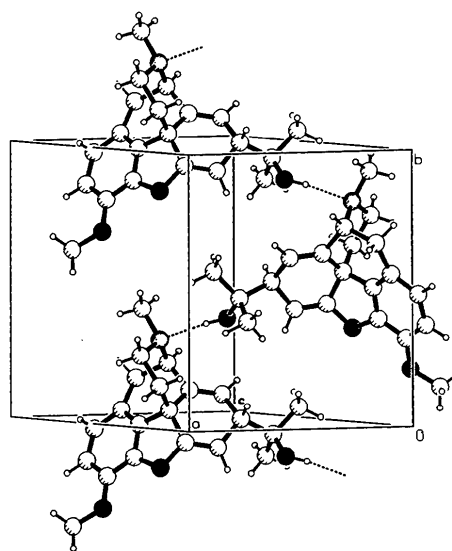


Fig. 1. Thermal ellipsoid plot of the title compound with numbering scheme (50% probability level).

Fig. 2. Intermolecular hydrogen bonding linking molecules into infinite chains in the *b* direction.

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Structures of Two Modifications of Bis(dicyclohexylthiophosphoryl) Disulfide. Evidence for $p\pi-d\pi$ Contribution to P—S Single Bonds

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Abstract. The crystal modification of the title compound is solvent dependent. Crystallization from 2-propanol/CH₂Cl₂ produces a monoclinic CH₂Cl₂ solvate, (I). Crystallization from a number of other solvent systems produces a triclinic form, (II). (I): C₂₄H₄₄P₂S₄·CH₂Cl₂, *M_r* = 607.76, monoclinic, *C2/c*, *a* = 16.887 (3), *b* = 14.860 (3), *c* = 12.574 (3) Å, β = 100.22 (2)°, *V* = 3105.2 Å³, *Z* = 4, *D_x* = 1.30 g cm⁻³, Mo *K*α, λ = 0.71073 Å, μ = 5.8 cm⁻¹, *F*(000) = 1296, *T* = 294 (1) K, *R* = 0.046 for 1320 unique observed reflections with $F_o^2 > 3.0\sigma(F_o^2)$. (II): C₂₄H₄₄P₂S₄, *M_r* = 522.82, triclinic, *P* $\bar{1}$, *a* = 20.392 (3), *b* = 12.302 (3), *c* = 12.749 (2) Å, α = 68.66 (2), β = 103.25 (1), γ = 107.26 (2)°, *V* = 2818.2 Å³, *Z* = 4, *D_x* = 1.23 g cm⁻³, Mo *K*α, λ = 0.71073 Å, μ = 4.5 cm⁻¹, *F*(000) = 1128, *T* = 294 (1) K, *R* = 0.034 for 6551 unique observed reflections with $F_o^2 > 3.0\sigma(F_o^2)$. In (I) the molecule has twofold molecular and crystallographic symmetry. The two independent molecules in (II) have essentially the same geometry but different from that of (I). The P—S—S—P skeleton is skewed with a torsion angle of 106.35 (7)° in (I) and 129.8 (3)° (ave) in (II). In (I) the configurations of the two ends are identical with S—P—S—S = 24.7 (1)°, but in (II) the two ends are different with S—P—S—S = 173.2 (2) and 21.4 (6)° (ave). The approach to planarity of the S—P—S—S unit (*cis* or

trans) is interpreted as evidence of a $p\pi-d\pi$ interaction in the P—S 'single' bond.

Introduction. The disulfide bond in chemical systems has been widely studied both experimentally and theoretically. Apart from the intrinsic chemical value of these studies they also help to shed light on the behavior of many biologically important molecules that contain disulfide links. Recently there have been a number of in depth theoretical studies on the prototype molecules H₂S₂ (Marsden & Smith, 1988; Rauk, 1984), MeSSMe (Rauk, 1984) and EtSSMe (Ohsaku & Allinger, 1988). These studies confirm that the preferred S—S torsion angle, θ , is close to 90°. Previous studies suggest that this may increase with large substituents (Jørgensen & Snyder, 1980). It is well known that there is observable restriction to rotation about the disulfide bond [experimental results to compare with theoretical calculations are referenced by Marsden & Smith (1988), Rauk (1984) and Ohsaku & Allinger (1988)]. The calculations all indicate that the *trans* barrier is lower than the *cis* barrier by a factor of 2–3. There is, however, a significant energy maximum at $\theta = 180^\circ$.

We have been interested in disulfides where the substituents are not alkyl, but dialkylthiophosphoryl groups. Recently we realized that our assumptions