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Acta Cryst. (1987). C**43**, 2384–2386

Structure of a New Deoxygenated Etorphine Analogue

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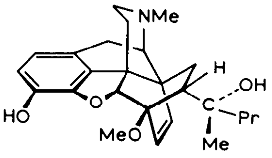
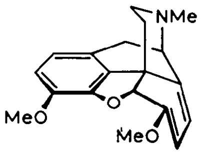
(*Received* 3 *June* 1987; *accepted* 15 *July* 1987)

Abstract. (+)-3-Hydroxy-α,α,17-trimethyl-6*β*,14*β*-ethenomorphinan-7*β*-methanol, $C_{22}H_{29}NO_2$, $M_r = 339{\cdot}5$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}810\,(2)$, $b = 14{\cdot}152\,(2)$, $c = 16{\cdot}705\,(4)$ Å, $V = 1846{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}23$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}083$ mm^{-1}, $F(000) = 736$, $T = 293$ K, $R = 0{\cdot}040$ for 2387 observed $[I > \sigma(I)]$ reflections. The etheno bridge is in the 6*β*,14*β* position and the dimethylmethanol substituent is in the 7*β* position of the morphinan skeleton, confirming that the title compound is a novel deoxygenated etorphine analogue.

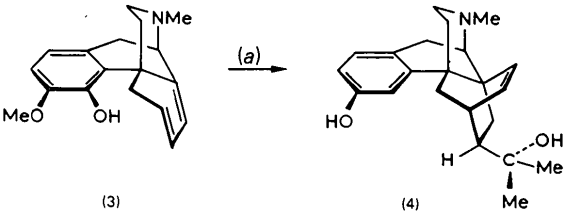
Introduction. Etorphine, (–)-(*R*)-4,5α-epoxy-3-hydroxy-6-methoxy-α,17-dimethyl-α-propyl-6α,14α-ethenomorphinan-7α-methanol (1) is a semisynthetic analgesic which is approximately 1000 times more potent than morphine; however, it has undesirable side effects. It is prepared from the opium alkaloid thebaine (2) (Lewis, Bentley & Cowan, 1971). In our search for the synthesis of etorphine analogues with fewer oxygen-containing substituents we started from 6-demethoxy-*β*-dihydrothebaine [6,7,8,14-tetradehydro-3-methoxy-17-methylmorphinan-4-ol, (3)]. Diels–Alder reaction with methyl vinyl ketone afforded 7*β*-acetyl-3-methoxy-17-methyl-6*β*,14*β*-ethenomorphinan-4-ol (van Koningsveld, Lie & Maat, 1984). In order to remove the hydroxyl group in position 4, it was converted into the phenyl ether through an Ullmann reaction with bromobenzene, followed by treatment with sodium in liquid ammonia. The methanol substituent on position 7*β* was obtained from the acetyl substituent by means of a Grignard reaction with methyl magnesium bromide. Finally, the methyl ether in position 3 was hydrolyzed with potassium hydroxide in boiling 1,2-ethanediol. It is plausible that during the Ullmann reaction or the treatment in liquid ammonia epimerization of the acetyl substituent in position 7*β* could occur. The single-crystal X-ray analysis of the end product (4), reported here, proved that the methanol substituent was still in the 7*β* position.



(1)
Etorphine



(2)
Thebaine



(3)
6-Demethoxy-β-dihydrothebaine

(4)

(*a*) (i) $CH_2 = CHCOCH_3$, (ii) PhBr, (iii) MeMgBr, (iv) KOH/CH_2OHCH_2OH

Experimental. Title compound was prepared in the Laboratory of Organic Chemistry (Linders, Kokje, Overhand, Lie & Maat, 1987). Crystals grown from hexane/diethyl ether, m.p. 457–459 K, $[\alpha]_D^{25\,^\circ\mathrm{C}} + 55^\circ$ [chloroform/ethanol 9:1, $0{\cdot}7$ g dm^{-3}]. D_m not

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measured. Crystal: approximate size 0·50 × 0·50 × 0·15 mm. CAD-4 diffractometer. Graphite-monochromated Mo $K\alpha$ radiation. Unit cell: 25 reflections, $15{\cdot}0 < \theta < 17{\cdot}0°$. Data collected in $\omega/2\theta$ scan mode, $\theta_{\max} = 30{\cdot}0°$, width = $(0{\cdot}85 + 0{\cdot}35 \tan\theta)°$, max. recording time 90 s, $\sigma_{\rm count}(I)/I < 0{\cdot}02$ requested in a scan. Index range: $h\,0 \to 11$, $k\,0 \to 19$, $l\,0 \to 23$. Three standard reflections measured every 7200 s. Data corrected for 5% decay. No absorption or extinction corrections. 3032 unique reflections measured, 2388 observed $[I > \sigma(I)]$, one reflection omitted because of suspected extinction effect. Structure solved by *MULTAN* (Germain, Main & Woolfson, 1971). Absolute configuration chosen in accordance with the configuration of the morphinan skeleton from previous analysis (van Koningsveld, Jansen, Lie & Maat, 1986). Least-squares refinement minimized $\sum w(\Delta F)^2$, $w = 1$. All non-H atoms anisotropic. H atoms located from difference map and refined with fixed isotropic temperature factors. $R = 0{\cdot}040$, $wR = 0{\cdot}035$, $S = 0{\cdot}71$ for 314 variables and 2850 observations [2387 with $I > \sigma(I)$ plus those for which $F_c > F_o$]; $(\Delta/\sigma)_{\max} = 0{\cdot}75$ [yH(102)]. Final ΔF synthesis has $\rho < 0{\cdot}21$ e Å^{-3}. All calculations performed on the Delft University Amdahl 470/V7B computer using programs of the *XRAY72* (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) and *MULTAN* (Germain *et al.*, 1971) packages. Atomic scattering factors from *XRAY72*.

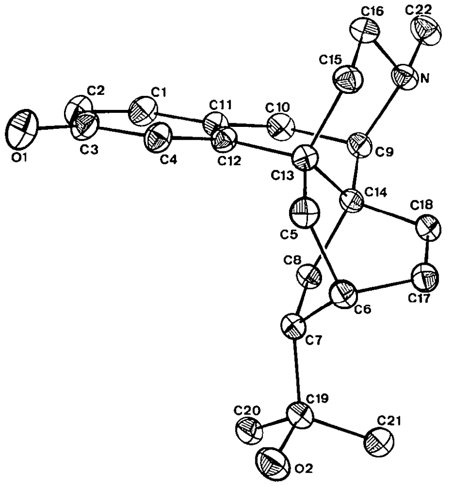

Fig. 1. *ORTEP* plot (Johnson, 1965) of the title compound. Boundary surfaces are drawn to enclose 50% probability.

Table 1. *Final coordinates* (× 10^4) *and equivalent isotropic temperature factors* (Å^2 × 10^3) *with e.s.d.'s in parentheses*

$$U_{\rm eq} = \tfrac{1}{3}(U_{11} + U_{22} + U_{33}).$$

	x	y	z	$U_{\rm eq}$
C(1)	1120 (5)	−1307 (2)	−279 (2)	49 (1)
C(2)	67 (5)	−1002 (2)	−884 (2)	53 (1)
C(3)	−15 (5)	−39 (2)	−1053 (2)	49 (1)
C(4)	991 (5)	577 (2)	−617 (2)	43 (1)
C(5)	2215 (4)	1968 (2)	577 (2)	39 (1)
C(6)	1630 (4)	2173 (2)	1444 (2)	39 (1)
C(7)	342 (3)	1374 (2)	1652 (2)	36 (1)
C(8)	1345 (4)	441 (2)	1732 (2)	35 (1)
C(9)	4171 (4)	−363 (2)	1361 (2)	36 (1)
C(10)	3165 (4)	−1092 (2)	862 (2)	43 (1)
C(11)	2115 (4)	−695 (2)	179 (2)	38 (1)
C(12)	2021 (4)	277 (2)	14 (2)	35 (1)
C(13)	3043 (4)	969 (2)	525 (2)	33 (1)
C(14)	3173 (3)	564 (2)	1395 (2)	31 (1)
C(15)	4878 (4)	1062 (2)	189 (2)	42 (1)
C(16)	5930 (5)	167 (3)	250 (2)	47 (1)
C(17)	3184 (4)	2110 (2)	1967 (2)	40 (1)
C(18)	3992 (4)	1292 (2)	1928 (2)	37 (1)
C(19)	−882 (4)	1576 (2)	2352 (2)	44 (1)
C(20)	−1987 (5)	2439 (3)	2172 (3)	61 (1)
C(21)	−22 (5)	1678 (4)	3161 (2)	65 (1)
C(22)	7059 (5)	−992 (3)	1172 (3)	58 (1)
N	5931 (3)	−172 (2)	1082 (2)	41 (1)
O(1)	−1049 (4)	339 (2)	−1621 (2)	66 (1)
O(2)	−1981 (3)	755 (2)	2424 (1)	48 (1)

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

C(1)–C(2)	1·373 (5)	C(9)–N	1·476 (4)
C(1)–C(11)	1·393 (5)	C(10)–C(11)	1·513 (4)
C(2)–C(3)	1·393 (5)	C(11)–C(12)	1·405 (4)
C(3)–C(4)	1·381 (5)	C(12)–C(13)	1·524 (4)
C(3)–O(1)	1·356 (4)	C(13)–C(14)	1·566 (4)
C(4)–C(12)	1·392 (4)	C(13)–C(15)	1·544 (4)
C(5)–C(6)	1·546 (4)	C(14)–C(18)	1·504 (4)
C(5)–C(13)	1·558 (4)	C(15)–C(16)	1·514 (5)
C(6)–C(7)	1·553 (4)	C(16)–N	1·470 (4)
C(6)–C(17)	1·498 (4)	C(17)–C(18)	1·321 (4)
C(7)–C(8)	1·541 (4)	C(19)–C(20)	1·526 (5)
C(7)–C(19)	1·536 (4)	C(19)–C(21)	1·516 (5)
C(8)–C(14)	1·545 (4)	C(19)–O(2)	1·449 (4)
C(9)–C(10)	1·542 (4)	C(22)–N	1·464 (5)
C(9)–C(14)	1·527 (4)		

C(2)–C(1)–C(11)	122·9 (3)	C(5)–C(13)–C(14)	107·9 (2)
C(1)–C(2)–C(3)	119·0 (3)	C(5)–C(13)–C(15)	109·2 (2)
C(2)–C(3)–C(4)	119·0 (3)	C(12)–C(13)–C(14)	108·6 (2)
C(2)–C(3)–O(1)	123·7 (3)	C(12)–C(13)–C(15)	109·7 (2)
C(4)–C(3)–O(1)	117·3 (3)	C(14)–C(13)–C(15)	108·0 (2)
C(3)–C(4)–C(12)	122·4 (3)	C(8)–C(14)–C(9)	112·9 (2)
C(6)–C(5)–C(13)	110·2 (2)	C(8)–C(14)–C(13)	108·6 (2)
C(5)–C(6)–C(7)	105·3 (2)	C(8)–C(14)–C(18)	104·8 (2)
C(5)–C(6)–C(17)	107·2 (2)	C(9)–C(14)–C(13)	108·2 (2)
C(7)–C(6)–C(17)	110·6 (2)	C(9)–C(14)–C(18)	113·2 (2)
C(6)–C(7)–C(8)	108·3 (2)	C(13)–C(14)–C(18)	109·1 (2)
C(6)–C(7)–C(19)	116·0 (2)	C(13)–C(15)–C(16)	114·0 (3)
C(8)–C(7)–C(19)	114·2 (2)	C(15)–C(16)–N	109·7 (3)
C(7)–C(8)–C(14)	110·0 (2)	C(6)–C(17)–C(18)	114·3 (3)
C(10)–C(9)–N	115·2 (2)	C(14)–C(18)–C(17)	115·2 (3)
C(14)–C(9)–N	109·3 (2)	C(7)–C(19)–C(20)	110·6 (3)
C(10)–C(9)–C(14)	109·6 (2)	C(7)–C(19)–C(21)	114·8 (3)
C(9)–C(10)–C(11)	115·8 (2)	C(7)–C(19)–O(2)	106·4 (2)
C(1)–C(11)–C(10)	119·0 (3)	C(20)–C(19)–C(21)	110·5 (3)
C(1)–C(11)–C(12)	118·2 (3)	C(20)–C(19)–O(2)	108·8 (3)
C(10)–C(11)–C(12)	122·7 (3)	C(21)–C(19)–O(2)	105·4 (3)
C(4)–C(12)–C(11)	118·5 (3)	C(9)–N–C(16)	111·0 (2)
C(4)–C(12)–C(13)	122·1 (2)	C(9)–N–C(22)	112·5 (3)
C(11)–C(12)–C(13)	119·4 (2)	C(16)–N–C(22)	110·8 (3)
C(5)–C(13)–C(12)	113·4 (2)		

Discussion. The molecular structure is shown in Fig. 1 together with the atom numbering. The final least-squares structural parameters for the non-H atoms are given in Table1.* Bond lengths and bond angles are listed in Table 2.

The etheno bridge is in the 6β,14β position and the dimethylmethanol substituent is in the 7β position of the morphinan skeleton. This means that neither during the Ullmann reaction nor during the treatment in liquid ammonia has epimerization occurred. The synthetic pathway developed for the title compound is therefore applicable for the preparation of this novel class of deoxygenated etorphine analogues. These new etorphine analogues may contribute to the knowledge of structure–activity relationships of analgesics.

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* Lists of structure factors, anisotropic temperature factors, H-atom parameters and distances and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44251 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Acta Cryst. (1987). C**43**, 2386–2389

17-Oxosparteine *N*(1)-Oxide Hydrochloride

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(*Received* 22 *November* 1986; *accepted* 7 *July* 1987)

Abstract. $[C_{15}H_{25}N_2O_2]^+.Cl^-$, $M_r = 300{\cdot}7$, trigonal, $P3_2$, $a = 9{\cdot}365\,(1)$, $c = 15{\cdot}166\,(1)$ Å, $V = 1151{\cdot}9\,(4)$ Å^3, $Z = 3$, $D_x = 1{\cdot}301\,(1)$ g cm^{-3}, $\lambda(\mathrm{Cu}\,K\alpha) = 1{\cdot}54178$ Å, $\mu(\mathrm{Cu}\,K\alpha) = 21{\cdot}19$ cm^{-1}, $F(000) = 486$, $T = 292$ K, $R = 0{\cdot}051$ for 900 unique reflections. The piperidine rings *A, B, C* and *D* have chair, chair, sofa and chair conformations respectively. The quinolizidine and quinolizidone moieties have *trans* and quasi-*trans* configurations. A hydrogen bond of 2·873 (5) Å is observed between the chloride anion and oxygen atom O(1) of the cation.

Introduction. The present work is a continuation of detailed studies on the chemistry and structure of sparteine *N*-oxides (Skolik, Łangowska & Wiewiórowski, 1971, 1974; Bratek-Wiewiórowska, Skolik & Wiewiórowski, 1977; Bratek-Wiewiórowska, Skolik, Łangowska & Wiewiórowski, 1974; Łangowska & Wiewiórowski, 1977), which have included the X-ray investigations of a number of sparteine *N*-oxide derivatives: sparteine *N*(16)-oxide sesquiperchlorate (Srivastava & Przybylska, 1969), episparteine *N*(16)-oxide sesquiperchlorate (Małuszyńska & Okaya, 1977*a*), episparteine *N*(16)-oxide semiperchlorate (Małuszyńska, Kałuski & Wiewiórowski, 1987), sparteine *N*(16)-oxide monoperchlorate (Kałuski & Małuszyńska, 1978), 2-phenylsparteine *N*(16)-oxide monoperchlorate (Małuszyńska & Okaya, 1977*b*), episparteine *N*(16)-oxide dihydrochloride trihydrate (Katrusiak, Hoser & Kałuski, 1983) and lupanine *N*(16)-oxide monoperchlorate (Kałuski, Gusiev, Struchkov, Skolik, Baranowski & Wiewiórowski, 1972). 17-Oxosparteine *N*(1)-oxide hydrochloride [hereinafter referred to as (I)] is the first *N*(1)-oxide of sparteine and the second oxo-derivative of sparteine *N*-oxide investigated by X-rays so far; unlike lupanine *N*(16)-oxide perchlorate [hereinafter (II)] it has the oxo-substituent located in the inner ring of the sparteine skeleton, in ring *C*. The X-ray analysis of the title compound was undertaken to establish the conformation of the cation and the geometry of its intermolecular hydrogen bonding.

Experimental. Recrystallization from ethanol solution, colourless prisms, crystal fragment 0·40 × 0·35 × 0·30 mm, Syntex $P2_1$ diffractometer, graphite-monochromated Cu $K\alpha$ radiation. Unit cell from least-squares fit to 15 reflections ($12 \le 2\theta \le 25°$); 2θ–θ mode with variable scan speed depending on the reflection intensity: 2·0 to 29·3° min^{-1}, two control reflections monitored every 50 current measurements, 1108 reflections measured up to $2\theta = 115°$, index range

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