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Crystal and Molecular Structures of two epimers of N-cyclopropylmethyl-[7,3′]-dihydro-2′-furanone-6, 14-*endo*-ethenotetrahydrothebaine

Key word : crystal structure, opioid, epimers

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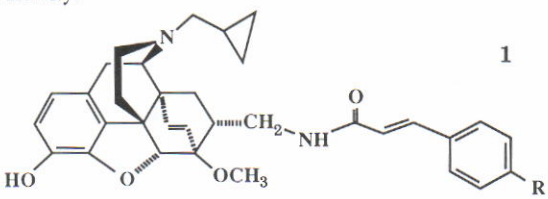
Abstract

The structures of two opioids derivatived from thebaine have been determined by single crystal X-ray crystallographic methods. Epimer **I** of N-cyclopropylmethyl-[7,3′]-dihydro-2′-furanone-6,14,-***endo***-ethenotetrahydrothebaine, crystallized in monoclinic system having space group $P2_1$ with a = 7.645(2), b = 9.349(14), c = 16.076(5) Å and β = 103.4(2)°. Epimer **II** crystallized in orthorhombic system having space group $P2_12_12_1$ with a = 7.948(1), b = 16.652(3), c = 16.661(3) Å . the two epimers have opposite stereochemistry at the spiro junction of ring H. In other respects the molecular structures are similar.

Introduction

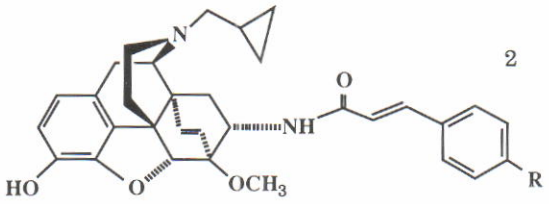
Morphine[1] has long been used in modern medicine as a treatment to relieve moderate to severe pain. However, it causes several undesirable effects such as respiratory depression, lowering of the blood pressure, some nausea, vomiting and constipation. The most serious disadvantage is that on continued administration of the drug, patients develop not only tolerance but also dependence.

Although a large number of selective compounds for the opioid receptors have been synthesised and evaluated, there is still a great deal to be learnt about how these compounds interact with the receptor at the molecular level. Recently it was discovered[2] that the 7 α - cinnamoaminomethyl derivatives of thebaine (1) were non-competitive, selective μ antagonists with an extremely long duration of activity.



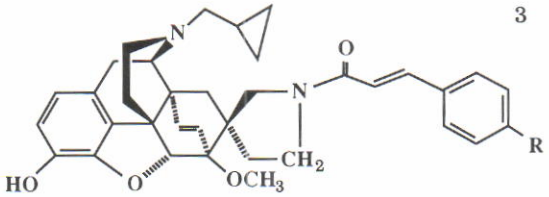
1

Since the colsely relatived 7α-cinnamoylamino derivatives of thebaine (2) were much less effective, it can be concluded that the location of the cinnamoylamino group is of major importance for the irreversible interaction of these derivatives with μ opioid receptors.



2

To the further explore this situation, we wished to constrain the aminomethyl group within a pyrolidine ring with spiro attachment to C(7) (3 and 4).



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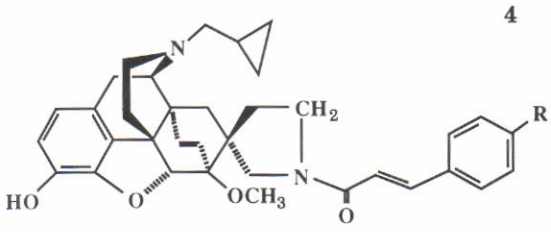
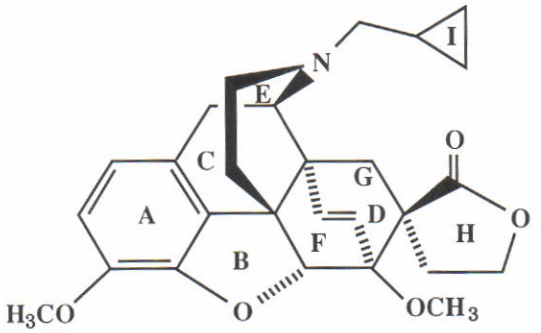
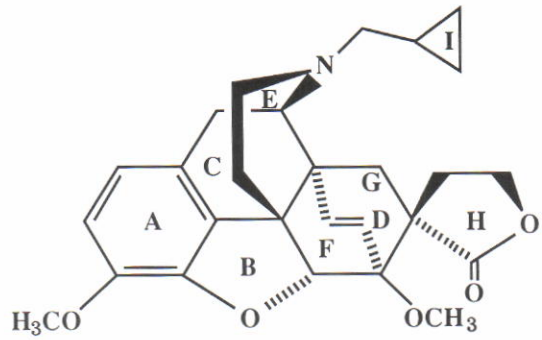


The preparation of these compounds involves a route through the corresponding lactones (compounds **I** and **II**), **3** being synthesised from the γ-lactone **I** and **4** from the epimeric γ-lactone **II**. Thus it was crucial that the stereochemistry about C(7) was known with certainty. Single crystal X-ray crystallographic methods were employed to achieve this aim.



I



II

Experimental

The structure determinations of **I** and **II** were carried out on block-like crystals chosen from samples recrystallized from methanol for **I** and dichloromethane/ methanol solutions for **II**. From these one single crystal was selected. Since the compounds were air stable the crystal was mounted on a glass fibre with silicone grease. For **I** all diffraction measurements were made at low temperature (173K) with a Siemens three-circle SMART[3] area detector diffractometer using graphite mono-chromated Mo-K_α radiation. The intensities in a hemisphere of reciprocal space for $2\theta<55^\circ$ were integrated using the SAINT[4] program. For **II** all diffreaction measurements were made at room temperature (293K) on a Siemens P4 diffractometer, using graphite monochromated Mo-K_α X-radiation. XSCANS[5] software was used for all data measurements. Diffracted intensities were measured in a unique octant of reciprocal space for $4.0<2\theta<55.0^\circ$ by $\theta/2\theta$ scans.

Lorentz and polarisation corections were applied. The structures were solved by direct methods and refined using full-matrix least-squares refinement on F^2 with the SHELXTL program[6] on a Silicon Graphics IRIS computer. All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. Hydrogen atoms were constrained to idealised positions. An isotropic extinction correction[7] was applied for **I**, parameter x refined to 0.0132(18) where $F_C = F_{uncorr}/(1+0.001xF_C^2/\sin\theta)^{1/4}$. The lattice of **I** is pseudo-orthorhombic C-centred (a = 7.645, b = 31.277, c = 9.349 Å and $\gamma = 90.35^\circ$) but Laue symmetry is clearly monoclinic (R_{int} orthorhombic 0.411, R_{int} monoclinc 0.040). The twin law, -1 0 0 0 -1 0 1 0 1, was applied for refinement and gave twin component values 0.9975(12) and 0.0025(12) indicating no significant pseudo-orthorhombic twinning. The Flack absolute structure parameters x[8] were used as the check on whether or not the absolute configuration could be determined from the experimental data, the values,-2(2) for **I** and -1(2) for **II**, for this parameter indicates there is no evidence for an incorrect assignment of chirality.

Table 1 lists pertinent physical data and details of the structure analyses.

Table 1 Summary of crystal parameters, data collection and refinement for the crystal structures

Compound	I	II
Empirical formula	$C_{27}H_{31}O_5N$	$C_{27}H_{31}O_5N$
Formular weight	449.53	449.53
Temperature/K	173(2)	293(2)
Wavelength/ Å	0.71073	0.71073
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a/ Å	7.645(2)	7.9482(11)
b/ Å	9.3486(14)	16.652(3)
c/ Å	16.076(5)	16.661(3)
β /°	103.4(2)	90.00
U/ Å^3	117.6(5)	2205.1(6)
Z	2	4
D_c /g/cm^{-3}	1.336	1.354
μ /mm^{-1}	0.092	0.093
F(000)	480	960
Crystal size/mm	0.4 x 0.2 x 0.2	0.4 x 0.3 x 0.2
Reflections collected	7111	3699
Independent reflections, R_{int}	4701, 0.0399	3491, 0.0297
Data/restraints/parameters	4700 / 1 / 301	3491 / 0 / 298
Goodness-of-fit on F^2	1.161	1.094
Final $R1^a$ and $wR2^b$	0.0748, 0.1454	0.0513, 0.1098
Absolute structure parameter	-2(2)	-1(2)
Weighting factors^b	0.0337, 1.7539	0.037, 1.2709
Largest diff. peak and hole/e. Å^{-3}	0.609, -0.422	0.221, -0.230

[a].Structure was refined on F_0^2 using all data; the value of R_1 is given for comparison with older refinements based on F_0^2 with a typical threshold of

$F \geq 4\sigma(F)$

[b] $wR_2 = [\Sigma w(F_0^2-F_C^2)^2 / \Sigma w(F_0^2)^2]^{1/2}$ where $w^{-1}=[\sigma^2(F_0^2)+(aP)^2+bP]$ and $P=[Max(F_0^2,0)+2F_C^2]/3$

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Results and Discussion

The molecular structures of **I** and **II** are illustrated in Fig. 1. The molecules are made up of five components; (i) the dihydrobenzofuran (A and B rings), (ii) C and E rings, (iii) the propalene (D, F and G rings), (iv) the γ-lactone (H ring), and (v) the cyclopropane (I ring). In general, for these compounds the absolute configuration known excepted for that of the spiro lactone ring.

The numbering of the caron atoms (Fig. 2 and 3) in the crystal structures correspond to the commonly accepted conventions for the morphine class of molecule. The T-shape[9] of the rigid morphine - like part is displayed in both compounds.

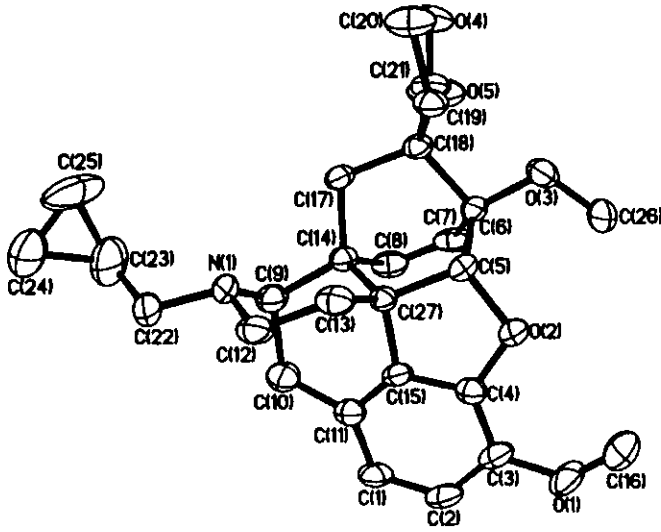

Fig.2 Structure and numbering scheme for **I**. Thermal ellipsoids are the 30% probability level and hydrogen atoms are omitted for clarity

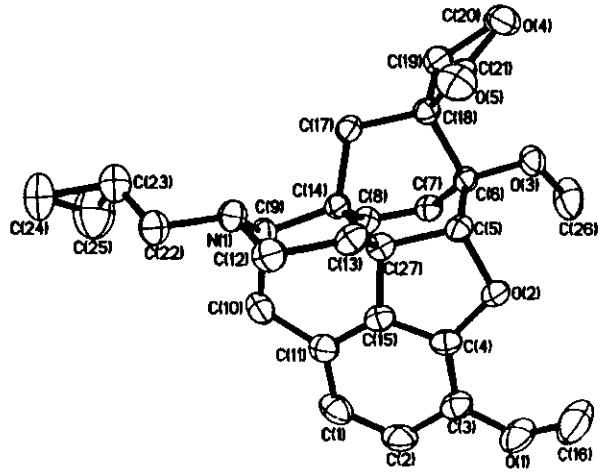

Fig. 3 Structure and numbering scheme for **II**. Thermal ellipsoids are the 30% probability level and hydrogen atoms are omitted for clarity

The atoms of the benzene ring, A, are essentially coplanar whereas the dihydrofuran ring, B, adopts a somewhat twisted envelope conformation as are those found in morphine derivatives[10,12-19,21]

The carbocylcic ring, C:[C(14)-C(27)-C(15)-C(11)-C(10)-C(9)], having five atoms roughly in a plane with C(14) out of plane (-0.51 Å in **I** and 0.46 Å in **II**), is in a sofa conformation[11] whereas the E, piperidine ring [N(1)-C(12)-C(13)-C(27)-C(14)-C(9)], assumes a chair conformation in both **I** and **II**. The substituent group at nitrogen atom is in the equatorial conformation, leaving the lone pair at nitrogen axial. The nitrogen atom does not participate in any hydrogen bonding, in contrast, the corresponding nitrogen is hydrogen bonded in the crystal structure of morphine monohydrate[12].

The fused ring system, propalene, contains rings D, F and G. the three carbocyclic rings, D: [C(5)-C(6)-C(18)-C(17)-C(14)-C(27)] and G: [C(6)-C(7)-C(8)-C(14)-C(17)-C(18)], all adopt the boat conformations and the conformation of the fused ring is as those found in other thebaine derivatives[20].

The γ-lactone, H ring, in both compounds has an envelope conformation. The compounds have opposite stereochemistry at the spiro ring junction, as shown in Fig. 4, with torsion angles [C(17)-C(18)-C(19)-C(20)] -89.5° in **I** and [C(17)-C(18)-C(19)-C(20)] -146.7° in **II** (see Table 2).

The cyclopropylmethyl side-chains (ring I) have different conformations (see in Fig. 4) in **I** and **II**. In **I**, it has a gauche$^-$ conformation with torsion angle [N(1)-C(22)-C(23)-C(25)] -80.0° and in **I** a gauche$^+$ conformation with torsion angle [N(1)-C(22)-C(23)-C(25)] 101.4°

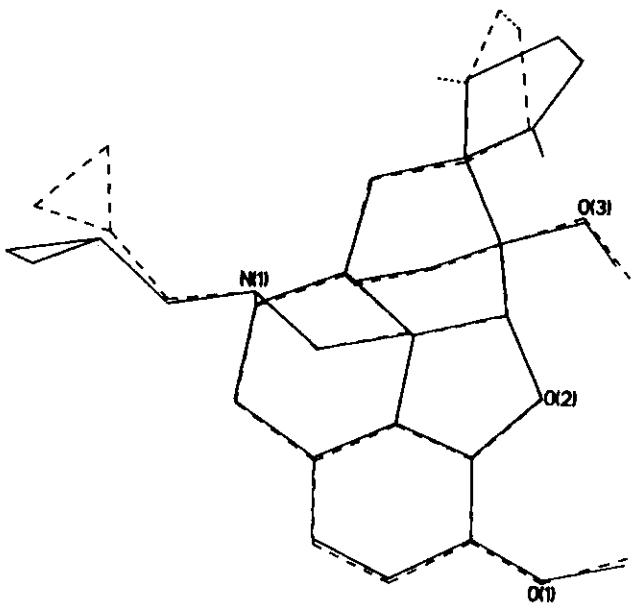

Fig. 4 The least square fit of **I** (broken line) to **II** (solid line) the oxygen and nitrogen atoms were used to perform the fit are labelled. The hydrogen atoms were omitted for clarity.

Table 2 Selected torsion angles for I and II

torsion angles	I /°	I /°	torsion angles	I /°	I /°
C(12)-N(1)-C(9)-C(10)	56.6	56.6	C(6)-C(18)-C(19)-C(20)	144.0	-90.2
C(12)-N(1)-C(9)-C(14)	-68.4	-68.4	C(17)-C(18)-C(19)-C(20)	-89.5	146.7
C(22)-N(1)-C(9)-C(10)	-68.7	-68.7	C(21)-C(18)-C(19)-C(20)	27.2	25.2
C(12)-N(1)-C(9)-C(14)	166.4	166.4	C(18)-C(19)-C(20)-O(4)	-30.3	26.1
N(1)-C(9)-C(10)-C(11)	-93.6	-93.6	C(6)-C(18)-C(21)-O(4)	-135.5	-99.9
C(14)-C(9)-C(10)-C(11)	29.6	29.6	C(6)-C(18)-C(21)-O(5)	49.3	80.3
C(9)-N(1)-C(12)-C(13)	60.3	60.3	C(17)-C(18)-C(21)-O(4)	105.2	138.9
C(22)-N(1)-C(12)-C(13)	-172.9	-172.9	C(17)-C(18)-C(21)-O(5)	-70.1	-40.9
N(1)-C(12)-C(13)-C(27)	-51.5	-51.5	C(19)-C(18)-C(21)-O(4)	-15.3	16.6
C(7)-C(8)-C(14)-C(9)	-171.6	-171.6	C(19)-C(18)-C(21)-O(5)	169.5	-163.3
C(7)-C(8)-C(14)-C(27)	-55.6	-55.6	C(9)-N(1)-C(22)-C(23)	-74.6	63.1
N(1)-C(9)-C(14)-C(8)	-179.1	-179.1	C(12)-N(1)-C(22)-C(23)	159.8	-171.0
N(1)-C(9)-C(14)-C(17)	-56.4	-56.4	N(1)-C(22)-C(23)-C(24)	-154.5	171.9
N(1)-C(9)-C(14)-C(27)	63.8	63.8	N(1)-C(22)-C(23)-C(25)	-80.0	101.4
C(10)-C(9)-C(14)-C(8)	54.1	54.1	C(22)-C(23)-C(24)-C(25)	115.9	-110.5
C(10)-C(9)-C(14)-C(17)	176.8	176.8	C(25)-C(23)-C(24)-C(25)	0.0	0.0

Table 3. Selected bond distances for I and II

Bond	I	II	Bond	I	II
O(4)-C(21)	1.345(5)	1.342(4)	C(9)-C(10)	1.564(6)	1.581(4)
O(4)-C(20)	1.459(6)	1.453(4)	C(12)-C(13)	1.504(7)	1.512(5)
O(5)-C(21)	1.190(6)	1.201(4)	C(13)-C(27)	1.546(6)	1.540(4)
N(1)-C(12)	1.441(7)	1.474(4)	C(14)-C(27)	1.537(6)	1.545(4)
N(1)-C(22)	1.465(6)	1.466(4)	C(14)-C(17)	1.540(5)	1.538(4)
N(1)-C(9)	1.489(7)	1.474(4)	C(15)-C(27)	1.497(5)	1.483(4)
C(4)-C(15)	1.373(6)	1.373(4)	C(17)-C(18)	1.566(6)	1.557(4)
C(5)-C(27)	1.537(6)	1.533(4)	C(18)-C(19)	1.540(6)	1.539(4)
C(5)-C(6)	1.543(6)	1.548(4)	C(18)-C(21)	1.531(6)	1.534(4)
C(6)-C(7)	1.505(7)	1.507(4)	C(19)-C(20)	1.503(7)	1.521(5)
C(6)-C(18)	1.573(6)	1.593(4)	C(22)-C(23)	1.378(10)	1.493(5)
C(7)-C(8)	1.317(7)	1.314(4)	C(23)-C(25)	1.475(9)	1.471(7)
C(8)-C(14)	1.517(6)	1.512(4)	C(23)-C(24)	1.501(9)	1.499(6)
C(9)-C(14)	1.546(6)	1.545(5)	C(24)-C(25)	1.444(10)	1.489(7)

Table 4 Selected bond angles for I and II

Angles	I	II	Angles	I	II
C(21)-O(4)-C(20)	110.4(4)	111.4(3)	C(21)-C(18)-C(19)	101.3(3)	101.0(2)
C(12)-N(1)-C(9)	111.2(4)	112.2(3)	C(19)-C(18)-C(17)	114.0(3)	114.1(2)
C(22)-N(1)-C(9)	113.4(5)	114.9(3)	C(21)-C(18)-C(6)	109.1(3)	109.1(2)
C(27)-C(5)-C(6)	108.0(3)	208.8(2)	C(19)-C(18)-C(6)	113.7(4)	110.5(2)
C(7)-C(6)-C(18)	107.5(4)	105.5(2)	C(20)-C(19)-C(18)	103.7(4)	104.6(3)
C(7)-C(8)-C(14)	114.7(4)	115.9(3)	O(5)-C(21)-C(18)	128.7(4)	128.0(3)
N(1)-C(9)-C(14)	108.2(3)	108.9(2)	O(4)-C(21)-C(18)	110.5(4)	111.0(3)
N(1)-C(12)-C(13)	110.1(4)	111.6(3)	C(22)-C(23)-C(25)	127.6(8)	120.5(4)
C(12)-C(13)-C(27)	112.6(4)	112.5(3)	C(22)-C(23)-C(24)	125.9(8)	119.1(4)
C(8)-C(14)-C(27)	107.2(4)	106.6(2)	C(25)-C(23)-C(24)	58.1(5)	60.1(3)
C(8)-C(14)-C(17)	105.6(3)	105.6(2)	C(15)-C(27)-C(14)	106.1(4)	106.7(2)
C(27)-C(14)-C(17)	108.7(4)	108.6(2)	C(15)-C(27)-C(5)	102.3(4)	101.9(2)
C(8)-C(14)-C(9)	113.8(4)	112.6(3)	C(14)-C(27)-C(5)	112.3(3)	111.6(2)
C(27)-C(14)-C(9)	105.3(3)	105.6(2)	C(15)-C(27)-C(13)	111.7(3)	112.7(3)
C(17)-C(14)-C(9)	115.9(4)	117.3(2)	C(14)-C(27)-C(13)	111.4(4)	111.2(2)
C(14)-C(17)-C(18)	109.1(1)	110.1(2)	C(5)-C(27)-C(13)	112.6(4)	112.4(3)

The crystal packing in both compounds showed weak intermolecular interactions dominated by normal Van der Waals contacts.

The selected bond lengths and bond angles for the non-hydrogen atoms are shown in Table 3 and 4. In general the bond lengths and bond angles are not significantly different. The three C-N bonds have an average length of 1.465(4) Å as is normal and as seen in morphine derivatives[13]. Similar lengths are seen in opiate alkaloids[16], morphine derivatives[17], dihydromorphine-6-*O*-sulfate[18], and in naltrexone hydrochloride[19]

The bond distances of **I** and **II** in the 6,14 ***endo*** -etheno bridge are similar to those in the other opioids, such as morphine and various of its derivatives[17]

Conclusion

Valuable information has been gained from X-ray studies of these compounds identifying the stereochemistry of epimers **I** and **II** and hence of **3** and **4**.

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