Synthesis, crystal structure of 7α-[(*S*)-1-hydroxy-1-(2-thienyl)ethyl]-6, 14-endoethanotetrahydrothebaine

Chun-he Liu, He Liu*, Xiang-yu Han, Bo Wu, Xiao-Bo Zhang and Bo-hua Zhong

No. 7 Department, Institute of Pharmacology and Toxicology Academy, Beijing 100850, P. R. China

7α-[(*S*)-2-Hydroxy-2-(2-thienyl)ethyl]-6,14-endoethanotetrahydrothebaine was synthesised and studied by ^{1}H NMR and MS spectroscopy, its crystal structure was determined by X-ray diffraction.

Keywords: thebaine derivatives, X-ray diffraction, analgesic activity

Despite several analgesics, the opioid analogues still remain the main drug for the relief of the pain and morphine is still a drug of choice in such situations. For many years, the search for new opioid derivatives that act on the CNS and have pain-relieving properties and devoid of undesired side effects, such addiction, has been the goal of a large number of scientists.[1,2] The abuse of cocaine and other stimulant drugs is becoming a significant social and public health concern in the world.[3] Consequently, a wide variety of modifications of the well-known alkaloids morphine, codeine and oripavine have been described.[4] The synthesis and pharmacological of 6,14-endoethanomorphinan derivatives have been extensively studied. The typical examples of the pharmacological active compounds reported in the literature such as buprenorphine (Temgesic),[5] etorphine(Immobilon)[6] and dihydroetorphine.[7] These kinds of compounds are characterised by a 6,14-endoethano bridge and a lipophilic substituted in position 7α of the C-ring. We have engaged in the synthesis and biological activity study of opioid derivative for many years, have found some compounds are very potent opioid derivatives with mixed agonist and antagonist opiate receptor activities. We synthesised a buprenorphine derivative, 7α-[(*S*)-1-hydroxy-1-(2-thienyl)ethyl]-6,14-endoethano tetrahydrothebaine (**3**), which showed good analgesic activity in mouse using the acetic acid writhing model, mouse heat radiant tail-flick assay, and mouse heat plate test.

The X-ray ORTEP structure of **3** with atomic labelling is shown in Fig. 1. The crystal structure of **2** maintains the main rigid structure of morphine as described in the literature, such as morphine,[8] 3-methoxyetorphine,[9] and buprenorphine.[10] A rigid pentacyclic structure consisting of a benzene ring A, two partially unsaturated cyclohexane rings B and D, a piperidine ring E, a dihydrofuran ring C and the C_6–C_{14} enthano bridge. Rings A, B and D are the phenanthrene ring system that has little conformational flexibility. The title compound exhibits a three-dimentional "T" shape with rings A, B and C forming a near perfect vertical plane and rings E and D forming a more distorted horizontal plane. The piperidine ring E is in the chair conformation and the D ring is boat with the atoms

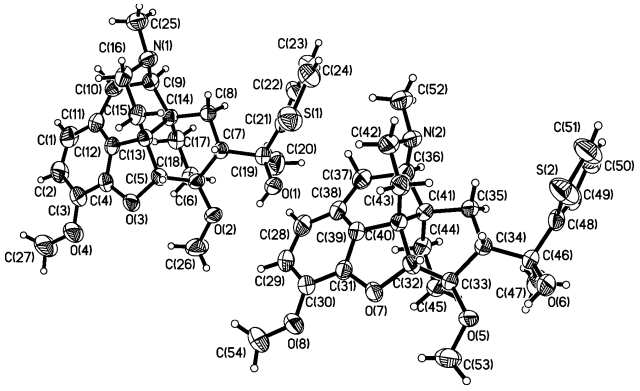
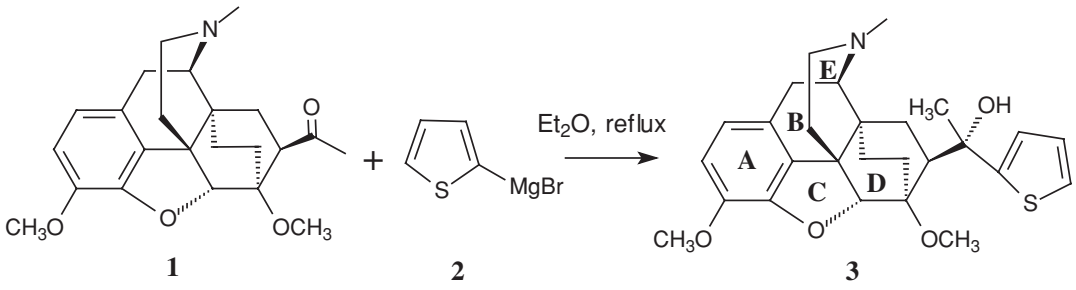


Fig. 1 The structure of the title compound, showing 50% thermal ellipsoid probability and the atom numbering scheme.

6 and 14 fore and aft. The new ethano bridge and the original boat-shape ring D form the bicycle[2,2,2]octane cage. The 1-hydroxy-1-(2-thienyl)ethyl group on C_7 position adapted *S*-configuration. The Grignard reaction shows a remarkably high degree of stereoselectivity and strictly obeyed the Cram's rules(Scheme 1),[11] as a result the *S*-configuration was almost the sole product. Since the methyl group on N is large than an electron pair or a protonated electron pair, it is predominantly equatorial (as shown), the stereostructure would be important in determining relative agonist potencies as discussed in the literature.

Experimental

All the reagents for syntheses were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on JNM-ECA-400 400 MHz instrument in the solvent indicated below. Chemical shift values are reported in parts per million (ppm) relative to that for tetramethylsilane used as an internal reference standard. Mass spectra were obtained from API3000 instruments. Elemental analysis was carried at the CarloErba-1106. Single-crystal X-ray diffraction measurement



Scheme 1 Synthesis of 7α-[(S)-1-Hydroxy-1-(2-thienyl)ethyl]-6,14-endoethanotetrahydrothebaine 3.

* Correspondent. E-mail: hliuarmms@yahoo.com

was carried out on a Bruker Smart 1000 CCD diffractometer. 7α-acetyl-6,14-endo-ethanotetrahydrothebaine (**1**) was prepared from thebaine as described in the literature.[12]

7α-[(S)-1-Hydroxy-1-(2-thienyl)ethyl]-6,14-endoethanotetrahydrothebaine (**3**): To the Grignard reagent **2** prepared from magnesium shavings (0.7g, 0.03mol) and 2-bromothiophene (1.63g, 0.01mol) in absolute ether (30 ml) a solution of 7α-acetyl-6,14-endoethenotetrahydrothebaine **1** (1.92g, 0.005mol) in anhydrous benzene (10 ml) and anhydrous ether (10 ml) was added dropwise over a period of 1 h. Then the solution was stirred under gentle reflux for 3 h, allowed to cool to room temperature, and the saturated aqueous ammonium chloride solution (50 ml) was added. The mixture was extracted with ether (3 × 20 ml), the combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated to obtain a crude product. The crude product was purified by re-crystallised from methanol to give colorless crystal **3** (1.8g). Yield: 77%. M.p. 216–218 °C. ^{1}H NMR (DMSO-d^6) (δ): 7.27(1H, m, Ar–H), 6.94(1H, m, Ar–H), 6.89(1H, m, Ar–H), 6.71(1H, d, *J*=8Hz, Ar–H), 6.56(1H, d, *J*=8Hz, Ar–H), 5.82(1H, s, OH), 4.44(1H, s, 5β-H), 3.89(3H, s, Ar-OCH_3), 3.61(3H, s, 6-OCH_3), 3.06(1H, d, *J*=10Hz), 2.55(1H, d, *J*=6Hz), 2.11–2.35(7H, m), 1.80–1.90(6H, m), 1.60(2H, m), 0.91–1.14(2H, m), 0.79(1H, m, CH). ESI-MS: 468.4(M+1). Anal. Calcd(%). for $C_{27}H_{33}NO_4S$: C, 69.35; H, 7.11; N, 3.00. Found: C, 69.16; H, 7.36; N, 3.11.

Crystal data: $C_{27}H_{33}NO_4S$, M*r* = 467.60, orthorhombic, $P2_12_12_1$, *a* = 12.840(3) Å, *b* = 15.845(5) Å, *c*=23.296(7) Å. *V* = 4740(2) Å^3, D_x = 1.311 g cm^{-3}, *Z* = 8, μ = 0.171 cm-1, *T* = 293(2)K. Crystals suitable for X-ray structure determination were obtained from the filtrate by slow evaporation of the solvent. A colourless crystal with dimensions of 0.32 mm × 0.20 mm × 0.20 mm was mounted on a Bruker Smart 1000 CCD diffractometer equipped with a graphite monochromator for data collection. The determination of unit cell parameters and data collection were performed with Mo Kα radiation (λ = 0.71073 Å) and unit cell dimensions were obtained with least-squares refinements. A total of 27762 reflections with 9740 independent ones with R_{int} = 0.0482 and 6261 observed reflections with $I > 2\sigma(I)$ were collected in the range of $1.55 < \theta < 26.472°$ by an ω/θ scan mode at 293(2) K. The structure was solved by direct methods with SHELXL-97 program[13] and all data were corrected by using semi-empirical absorption corrections (SADABS[14]) method. All the other non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was carried out by full matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were added theoretically, and riding on the concerned atoms and refined with fixed thermal factors. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0549P)^2 + 0.1599P]$, where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to the final R = 0.0510 and wR = 0.1010, R = 0.0968 and wR = 0.1172 for all data. S = 1.024. Molecular graphics were drawn with the program package XP.

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications (CCDC No. 212448). Copies of available materials can ben obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 int. code (+44)(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

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