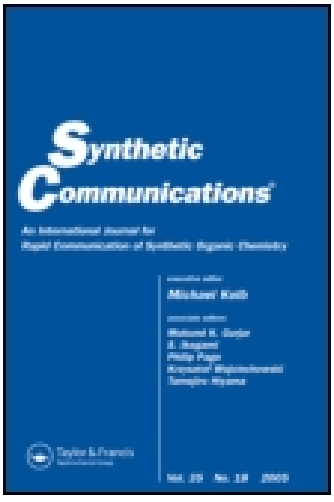

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Synthesis and Characterization of Thienorphine and Its Glucuronide Conjugate

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Synthesis and Characterization of Thienorphine and Its Glucuronide Conjugate

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Abstract: Thienorphine (**1**) is a very potent oripavine derivative with mixed agonist and antagonist opioid receptor activities. It was prepared with 7α-acetyl-6,14-endoethenotetrahydrothebaine as stated material by Grignard reaction, cyanidation, demethylation, and N-alkylation. The structure of **1** · HCl was elucidated by X-ray analysis. As part of a continuing program to define the metabolism and distribution of thienorphine in animals and man, the putative metabolite, 3-glucuronide, was synthesized.

Keywords: Thienorphine, X-ray analysis, glucuronide conjugate

Opioid analogues still remain important drugs for the relief of severe pain and morphine is still the drug of choice in such situations.[1–4] One to the high patient-to-patient variability in response to opioids, complete pain control is only achieved by increasing the dose, which causes side effects like nausea, respiratory depression, and mood disturbance. This is further complicated by development of tolerance to the analgesic effect.[5] The abuse of cocaine and other stimulant drugs is becoming a significant social and public health concern in the world. For many years, the search for new centrally acting opioid derivatives with pain-relieving properties and without undesired side

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effects, such as addiction, obstipation, etc., has been the goal of a large number of scientists. Consequently, a wide variety of modifications of the well-known alkaloids morphine, codeine, and thebaine were described.[6–8]

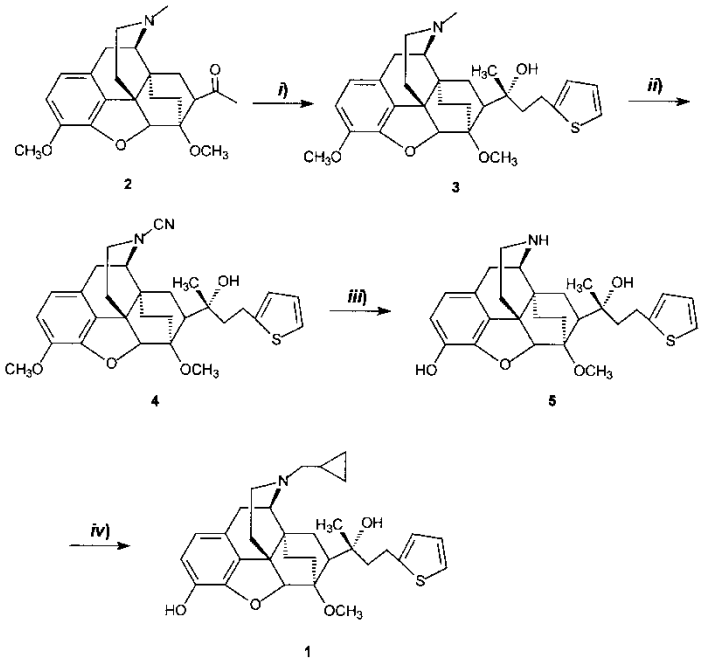
We have engaged in the synthesis and biological activity study of oripavine derivative for many years, as a result, N-cyclopropylmethyl-7α-[1-(*R*)-1-hydroxy-1-methyl-3-(thien-2-yl)propyl]-6,14-endoethanotetrahydronororipavine (thienorphine **1**), was found to be a very potent oripavine derivative with mixed agonist and antagonist opioid receptors activities. Compound **1** showed very good analgesic activity in the mouse using the acetic acid writhing model, mouse heat radiant tail-flick assay, and mouse heat plate test. The potent effect against morphine and heroin of thienorphine also was observed, and the effective duration was more 100 hours. Thus, thienorphine is on preclinic study as an analgesic and abstention drug.

The metabolism of **1** was compared to that of the drugs containing the hydroxy group,[9–12] glycoconjugate is one of the major metabolites. As part of a continuing program to define the metabolism and distribution of **1** in animals and man, the putative metabolite, 3-glucuronide was required as a metabolic standard. This paper both describes the efficient syntheses 3-glucuronide of metabolite and presents a study of the scope of an inverse addition technique applied to glucuronidation.

1 was prepared by a modified method as described in the literature.[13–16] According to Scheme 1, **2** was coupled with Grignard reagent, 2-(thiophen-2-yl)ethylmagnesium bromide, to give **3**. This Grignard reaction shows a remarkably high degree of stereoselectivity. The *R* isomer was the almost sole product, whereas the *S* isomer was not afforded. A mixture of the intermediate **3** and cyanogens bromide in dried CH_2Cl_2 was refluxed to obtain **4**. **5** was obtained by treating **4** with KOH in diethylene glycol at 205–210°C. **1** was prepared by *N*-alkylation of **5**. The structure of **1** was established by nuclear magnetic resonance (NMR), mass (MS) spectroscopy, and elemental analysis.

The structure of thienorphine hydrochloride was confirmed by X-ray crystal-structure analysis. The ORTEP view of **1** · HCl with atom labeling is shown in Fig. 1. It consists of a protonated thienorphine cation, one Cl^- anion, and one H_2O molecule. The crystal structure of **1** reveals that it maintains the "T" shape of the morphine structure and contains a C_6–C_{14} enthano bridge.[17,18] The piperidine ring adopts a favored chair conformation and the cyclopropylmethyl group is located at the equatorial position as expected. The C_7 substituent is a 1-hydroxyl-1-methyl- 3-(thienyl-2-)propyl group adapting *R*-configuration.

The hydroxyl group O(4) is included by forming an intramolecular hydrogen bond with methyl ether oxygen O(3), and the distance between O(4) and O(3) is 2.675 Å with the H···O separation 1.989 Å, falling into the normal range of the O···O separation for hydrogen bonding,[19] the bond angle is 142.19°. The intermolecular hydrogen bonds, O–H···O, Cl···H–O, and Cl···H–N were formed by the O atoms of the water



Scheme 1. ***i)*** 2-(thien-2-yl)ethylmagnesium bromide, anhydrous Et_2O. ***ii)*** CNBr, CH_2Cl_2. ***iii)*** KOH, diethylene glycol. ***iv)*** Cyclopropylmethyl bromide, $NaHCO_3$, DMF.

molecule, hydroxyl group of aryl ring, protonated N atom of the piperidine ring and the Cl^- anion. The O···O, Cl···N, and Cl···O separations are in the range of 2.660∼3.193 Å with the H···O and H···Cl separations in the range of 1.857∼2.372 Å, the bond angles are 151.59∼171.24°.

Thienorphine-3-glucuronide **9** was synthesized by the additional of the solid bromo sugar **8** to a concentrated solution of a slight excess of the lithium salt of **1** in methanol at room temperature and hydrolysis with lithium hydroxide (Scheme 2).[20–22]

EXPERIMENTAL

General

Solvents were purified by standard procedures. Melting points were determined using a RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian UNITY INOVA 600 MHz and JNM-ECA-400 400 MHz instrument in the solvent indicated later. Chemical shift values are reported in parts per million (ppm) relative to that for tetramethylsilane used as an

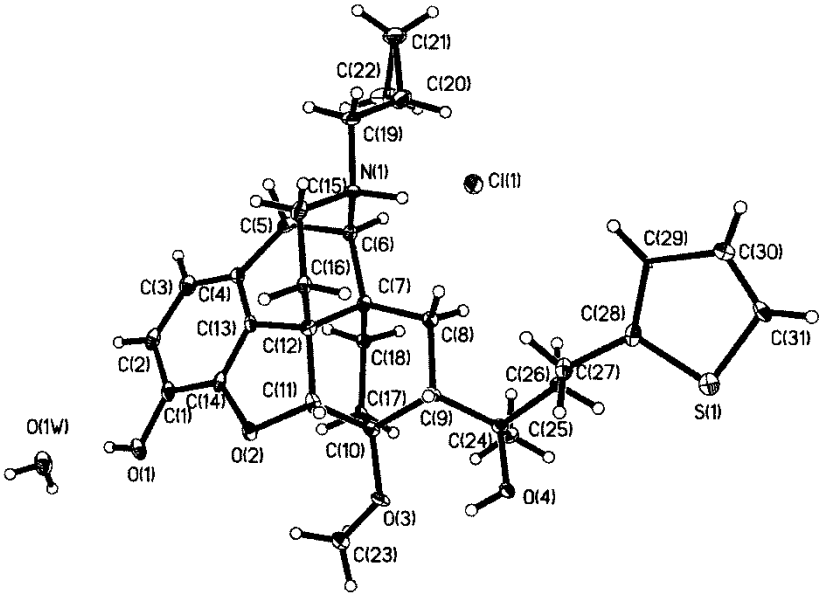
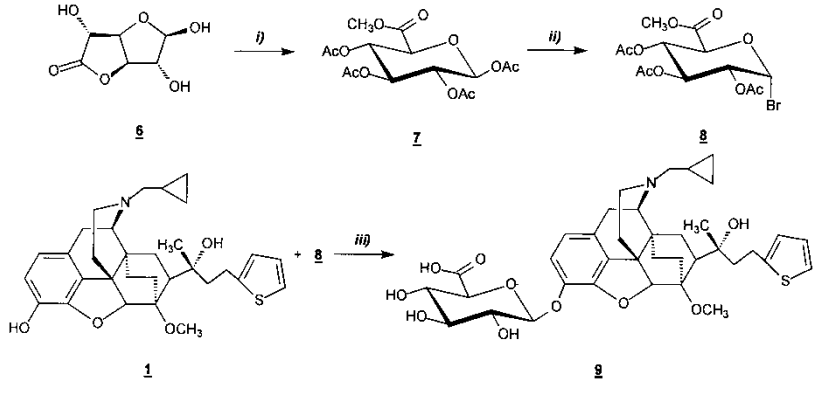


Figure 1. Crystal structure of N-cyclopropylmethyl-7α-[(R)-1-hydroxyl-1-methyl-3-(thieny-2-)propyl])-6,14-endoethano-6,7,8,9-trahydronororipavine **1**.

internal reference standard. Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; m, multiplet. Mass spectra were obtained using API3000 instruments. Elemental analysis was carried at the CarloErba-1106. Optical rotations were measured on a



Scheme 2. ***i)*** $NaOH/CH_3OH$; Ac_2O/Pyridine. ***ii)*** 30% HBr in AcOH. ***iii)*** $LiOH{\cdot}H_2O/CH_3OH$.

PE-243B instrument. Single-crystal X-ray diffraction measurement was carried out on a Bruker Smart 1000 CCD diffractometer.

All reactions were monitored by thin layer chromatography (TLC) on 25 × 75 mm glass sheets precoated with silica gel (GF254) to a thickness of 0.25 mm and viewed at 254 nm UV-light.

7α-[(R)-1-Hydroxy-1-methyl−3-(thien-2-yl)propyl]-6,14-endoethanotetrahydro- thebaine (**3**)

To the Grignard reagent prepared from magnesium shavings (7.2 g, 0.3 mol) and 2-(2-bromoethyl)thiophene (19.1 g, 0.1 mol) in absolute ether (300 mL) a solution of 7α-acetyl-6,14-endo-ethenotetrahydrothebaine **2** (19.2 g, 0.05 mol) in absolute benzene (100 mL) and absolute ether (100 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 (500 mL) was added. The mixture was extracted with ether (3 × 150 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 crystallization from methanol to give colorless crystal **3** (18.6 g). Yield: 75%. M.p. 183–185°C. ^{1}H-NMR (DMSO-d^6) (δ): 7.29(1H, d, J = 5.0 Hz, ArH), 6.93(1H, m, ArH), 6.85(1H, m, ArH), 6.73(1H, d, J = 8.2 Hz, ArH), 6.55(1H, d, J = 8.2 Hz, ArH), 4.61(1H, s, OH), 4.39(1H, s, 5β-H), 3.77(3H, s, Ar-OCH_3), 3.41(3H, s, 6-OCH_3), 2.82–2.94(4H, m), 2.58–2.76(2H, m), 2.10–2.27(4H, m), 1.80–2.05(4H, m), 1.66–1.76(2H, m, CH_2), 1.45–1.55(2H, m, CH_2), 1.30(3H, s, 20-CH_3), 1.18–1.24(1H, m, CH), 1.07(1H, m, CH), 0.58(1H, m). ESI-MS: 496.1(M + 1). $[\alpha]_D^{20} = -79.0$ (c = 0.50, CH_2Cl_2). Anal. calc. For $C_{29}H_{37}NO_4S$ (495.68): C 70.30, H 7.47; found: C 70.18, H 7.56.

N-Cyano-7α-[1-(R)-1-hydroxy-1-methyl−3-(thien-2-yl)propyl]-6,14-endoethano tetrahydronorthebaine (**4**)

A solution of cyanogens bromide (12.2 g, 0.11 mol) and **3** (13.6 g, 0.027 mol) in dry methylene chloride (108 mL) was stirred under reflux for 5 h. The solution was evaporated to dryness. The residue was purified by re-crystallization from ethanol to give colorless crystal **4** (12.7 g). Yield: 91%. M.p. 171–173°C. ESI-MS: 507.0(M + 1). Anal. calc. For $C_{29}H_{34}N_2O_4S$ (506.66): C 68.77, H 6.72; found: C 68.81, H 6.72.

7α-[1-(R)-1-Hydroxy-1-methyl−3-(thien-2-yl)propyl]-6,14-endoethanoetrahydro-nororipavine (**5**)

A mixture of **4** (12 g, 0.024 mol) and potassium hydroxide (30 g, 0.54 mol) in diethylene glycol (150 g) was vigorously stirred at 205–210°C under nitrogen

gas for 2 h. The mixture was then poured into stirred water (500 mL) containing crushed ice, adjusted pH to 8–9 with the saturated aqueous ammonium chloride solution. The precipitated solid was collected and recrystallized from methanol to give colorless crystal 5 (8.7 g). Yield: 91%. M.p. 268–270°C. ESI-MS: 468.2(M + 1). Anal. calc. For $C_{27}H_{33}NO_4S$ (467.62): C 69.38, H 7.07; found: C 69.30, H 6.87.

N-Cyclopropylmethyl-7α-[1-(R)-1-hydroxy-1-methyl–3-(thien-2-yl)propyl]-6,14-endoethanoetrahydronororipavine (**1**)

A mixture of **5** (7.0 g, 0.015 mol), cyclopropylmethyl bromide (4.1 g, 0.030 mol), and dried sodium bicarbonate (4.0 g, 0.048 mol) in *N,N*-dimethylformamide (200 mL) was vigorously stirred at 70–80°C under nitrogen gas for 16 h. The mixture was filtered. The filtrate was evaporated to dryness. The residue was dissolved with CH_2Cl_2, dried (Na_2SO_4) and evaporated to obtain a crude product. The crude product was purified by chromatography on silica gel column, eluting with a CH_2Cl_2/MeOH mixture (20:1) to give white solid, then crystallized from methanol to give colorless crystal 1 (3.8 g). Yield: 48%. M.p. 170–172°C. IR (KBr): 3406, 3224, 2989, 2926, 1634, and 1609. ^{1}H-NMR ($CHCl_3$-d) (δ): 8.98(1H, s, Ar-OH), 7.29(1H, d, J = 5.0 Hz, ArH), 6.93(1H, m, ArH), 6.85(1H, m, ArH), 6.73(1H, d, J = 7.9 Hz, ArH), 6.55(1H, d, J = 7.9 Hz, ArH), 4.61(1H, s, OH), 4.39(1H, s, 5β-H), 3.41(3H, s, 6-OCH_3), 2.85–2.98(4H, m), 2.58–2.76(2H, m), 2.10–2.27(4H, m), 1.80–2.05(4H, m), 1.66–1.76(2H, m, CH_2), 1.45–1.55(2H, m, CH_2), 1.30(3H, s, 20-CH_3), 1.18–1.24(1H, m, CH), 1.07(1H, m, CH), 0.75(1H, m, Cprop-CH), 0.58(1H, m), 0.44(2H, m, Cprop-CH2), 0.08(2H, m, Cprop-CH2). ^{13}C-NMR ($CHCl_3$-d) (δ): 3.48, 3.97, 9.39, 17.7, 23.2, 23.9, 29.8, 31.6, 35.6, 35.9, 43.5, 43.6, 45.7, 47.2, 52.8, 58.3, 59.8, 75.8 (C16, C19), 80.5, 97.4, 116.5, 117.4, 119.5, 122.7, 123.9, 126.7, 128.1, 132.2, 145.5, 146.0. ESI-MS: 522.1(M + 1). $[\alpha]_D^{20} = -81.2$ (c = 0.50, CH_3OH). Anal. calc. For $C_{31}H_{39}NO_4S$ (521.64): C 71.37, H 7.53, N 2.68, S 6.15; found: C 71.17, H 7.63, N, 2.46, S 6.01.

Hydrochloride **1** · HCl: M.p. 255–257°C. Anal. calc. For $C_{31}H_{39}NO_4S \cdot HCl$(558.18): C 66.71, H 7.22, N 2.51; found: C 66.59, H 7.43, N, 2.46.

Methyl (Tri-O-acetyl-α-D-glucopyranosyl bromide)uronate (**8**)

The compound was prepared by treating D-glucurono-3,6-lactone **6** with a methanolic solution of sodium hydroxide and acetylation of the resulting crude product mixture with acetic anhydride and perchloric acid as described previously. The β anomer **7** was crystallized from 2-propsnol. M.p. 154–158°C. ESI-MS: 377.0(M + 1).

A solution of **7** (1.5 g, 4 mmol) in 27% hydrobromic acid in acetic acid (20 mL) was stirred at room temperature for 12 h. The solution allowed to stand in the refrigerator overnight. The mixture was evaporated to dryness. The residue was dissolved with chloroform, washed with cold saturated aqueous sodium bicarbonate and water. After drying the chloroform solution, the solvent was removed under reduced pressure. The residual syrup was recrystallized from ethanol to give yellow crystal **8**. Yield: 65%. M.p. 74–76°C. ^{1}H-NMR (DMSO-d^6) (δ): 6.94(1H, d, J = 4 Hz). 5.42(1H, t, J = 9.4 Hz), 5.28(1H, t, J = 9.4 Hz), 5.14(1H, dd, J = 4 Hz, J = 9.2 Hz), 4.47(1H, d, J = 9.4 Hz), 3.67(3H, s, OCH_3), 2.05(3H, s, CH_3), 2.02(6H, s, $2CH_3$). ESI-MS: 397.0(M + 1).

Thienorphine-3-glucuronide (**9**)

A solid of **8** (1 g, 2.5 mmol) was added into a solution of **1** (1.5 g, 2.9 mmol) and $LiOH \cdot H_2O$ (0.12 g, 2.8 mmol) in MeOH (15 mL). After the addition, the mixture was allowed to stand at room temperature for 2 h. Then a solution of $LiOH \cdot H_2O$ (0.36 g, 8.4 mmol) was added with stirring for 2 h. The mixture was evaporated to dryness. The residue was dissolved with CH_2Cl_2, purified by chromatography on silica gel column, eluting with a CH_2Cl_2/MeOH mixture (4 : 1) to give yellow solid: **9** (720 mg, 41%). M.p. 268–240°C. ^{1}H NMR (DMSO-*d*^{6}) (δ): 7.29(1H, d, J = 5.0 Hz, ArH), 6.93(1H, m, ArH), 6.83–6.88(2H, m, ArH), 6.53(1H, d, J = 8.1 Hz, ArH), 5.22(1H, br, OH), 5.04(1H, br, OH), 4.93(1H, d, J = 6.5 Hz, CH), 4.65(1H, s, OH), 4.39(1H, s, 5β-H), 3.43(3H, s, 6-OCH_3), 3.20(3H, m, 3CH), 2.89–2.97(4H, m), 2.73(1H, t, J = 8.9 Hz), 2.60(1H, d, J = 7 Hz), 2.20–2.27(4H, m), 1.80–2.01(5H, m), 1.70–1.75(2H, m, CH_2), 1.54 (2H, d, J = 10Hz, CH_2), 1.30(3H, s, 20-CH_3), 1.19–1.23(1H, m, CH), 1.07(1H, m, CH), 0.75(1H, m, Cprop-CH), 0.58(1H, m), 0.44(2H, m, Cprop-CH2), 0.08(2H, m, Cprop-CH2). ^{13}C NMR ($CHCl_3$-*d*) (δ): 3.44, 3.65, 9.29, 18.2, 22.4, 23.4, 24.3, 29.1, 30.8, 35.1, 35.3, 43.0, 43.1, 44.5, 45.8, 52.1, 58.0, 59.0, 71.9, 73.3, 74.7(C16, C19), 76.5, 79.4, 95.4, 101.5, 118.2, 118.9, 123.1, 124.0, 126.8, 130.1, 132.7, 138.6, 145.7, 147.0, 172.9. ESI-MS: 698.4(M + 1), 522.1. $[\alpha]_D^{20} = -42.0$ (c = 0.5, CH_3OH).

X-ray Crystal-Structure Analysis of **1** · *HCl*

Crystals suitable for X-ray structure determination were obtained from the filtrate by slow evaporation of the solvent. The determination of unit cell parameters and data collections was performed with Mo Kα radiation ($\lambda = 0.71073$ Å) and unit cell dimensions were obtained with least-squares refinements. The structure was solved by direct methods with SHELXL-97 program[23] and all data were corrected by using semi-empirical absorption corrections (SADABS) method. All the other nonhydrogen 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 nonhydrogen atoms on F^2. The hydrogen atoms were added

Table 1. Crystallographic data and structure refinement summary for **1**

Empirical formula	$C_{31}H_{42}NO_5S$
Molecular weight	576.17
Measured temperature	293(2) K
Crystal size (mm^3)	0.47 × 0.42 × 0.10
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
	a = 10.4168(4) Å
	b = 13.1207(7) Å
	c = 21.1964(9) Å
Volume V ($Å^3$)	2897.0(2)
Z	4
D_{calcd} ($g\,cm^{-3}$)	1.321
μ (mm^{-1})	0.245
F (000)	1232
θ range (°)	2.50–27.48°
Completeness to θ	99.5%
$h/k/l$	−13/13, −16/17, −27/27
Reflection unique	6594
Parameters refined	373
Final R indices [$I \geq 2\sigma(I)$]	$R1 = 0.0297$,
	$wR2 = 0.0463$
Absolute structure parameter	0.00
Goodness of fit	0.00033(11)
Residual electron densities ($e\,Å^{-3}$)	0.276 and −0.254

theoretically, and riding on the concerned atoms and refined with fixed thermal factors. Further details of the structure analyses are given in Table 1.

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 be 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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