SYNTHESIS AND CRYSTAL STRUCTURE OF 17-ALLYL-4,5-ANHYDRO-7α-[(*R*)-1-HYDROXY-1-METHYL-3-(2-THIENYL)PROPYL]-6-METHOXY-6,14-ETHANOMORPHINAN-3,4,5-TRIOL

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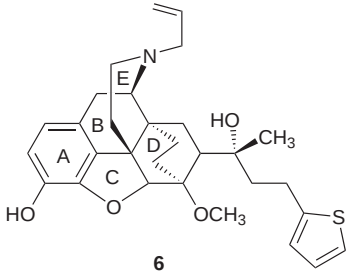
17-Allyl-4,5-anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6-methoxy-6,14-ethanomorphinan-3,4,5-triol (thienorphine **6**) was synthesized and structurally characterized by NMR spectra, ESI-MS and X-ray diffraction. The crystal structure indicates that thienorphine maintained the main rigid structure of morphine while containing the C6–C14 ethano bridge. The allyl group is located in the equatorial position as expected. The packing diagram of **6** showed the presence of intramolecular and intermolecular O–H···O hydrogen bonds linking the molecules into a zigzag infinite quasi-one-dimensional chain structure.
Keywords: Oripavine derivatives; Morphine; Opioids; Thienorphine; Alkaloids; Thiophenes; Grignard reagents; Analgesics.

Opioid analogues remain important drugs for the relief of severe pain and morphine is still the drug of choice in such situations. For many years, the search for new centrally acting opioid derivatives with pain-relieving properties and without undesired side effects, such as addiction, obstipation, etc., has been the goal of a large number of scientists[1]. Due to the high patient-to-patient variability in response to opioids, complete pain control is only achieved by doses, that cause side effects like nausea, respiratory depression and mood disturbance. This is further complicated by development of tolerance[2] which requires increasing doses of the drug. The abuse of cocaine and other stimulant drugs is becoming a significant social and public health concern all over the world[3]. Consequently, a wide variety of modifications of the well-known alkaloids morphine, codeine and oripavine have been described[4]. Synthesis and pharmacological effects of 6,14-endoethanomorphinan derivatives have been extensively studied. Typical examples of pharmacologically active compounds reported in the literature are buprenorphine (Temgesic)[5], etorphine (Immobilon)[6] and dihydroetorphine[7]. These compounds are characterized by the 6,14-ethano

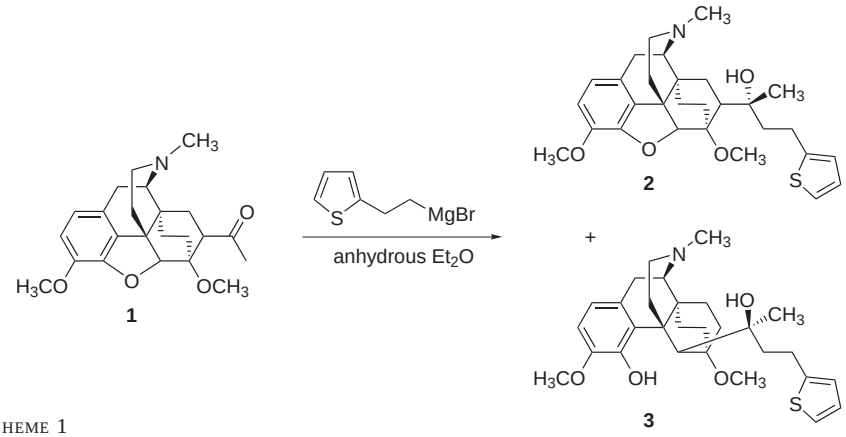
bridge and a lipophilic substituent in position 7α of the morphinan skeleton. We have been engaged in the synthesis and biological activity studies of oripavine derivatives for many years. As a result 17-allyl-4,5-anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6-methoxy-6,14-ethanomorphinan-3,4,5-triol (**6**), was found to be a very potent oripavine derivative with mixed agonist and antagonist opiate receptor activities. Compound **6** showed a very good analgesic activity and a strong morphine and heroin antagonistic effect. The biological results[8] showed that use of compound **6** for the maintenance treatment of opioid dependence is relatively safe and efficient, compared with buprenorphine.



6

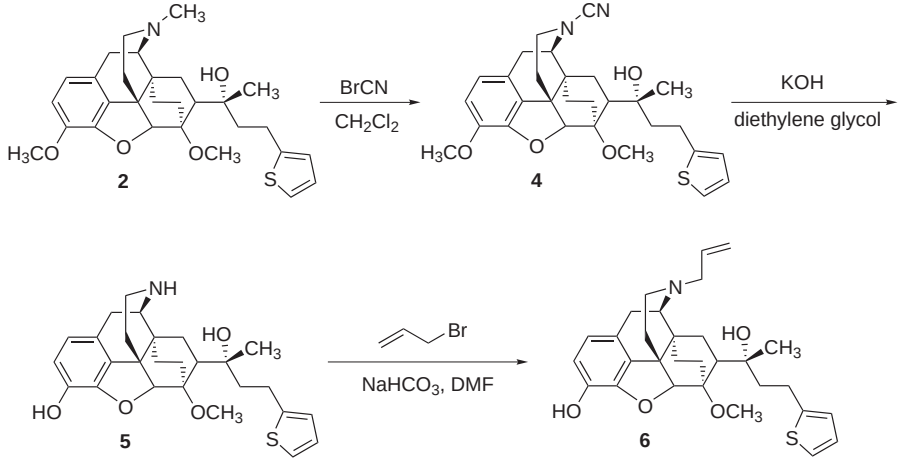
CHART 1
Structure of thienorphine (**6**)

17-Allyl-4,5-anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6-methoxy-6,14-ethanomorphinan-3,4,5-triol (**6**) was prepared by a modified method as described in the literature[9]. 7α-Acetyl-4,5-anhydro-3,6-dimethoxy-17- methyl-6,14-ethenomorphinan-4,5-diol (**1**) was coupled with 2-(2-thienyl)ethylmagnesium bromide to give 4,5-anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-17-methyl-6,14-ethanomorphinan-4,5-diol (**2**) and a by-product **3** (Scheme 1). Reactions of **1** with Grignard regents have been reported to produce many by-products[10]. In our studies, **1** treated with 2 molar equivalents of the Grignard reagent in anhydrous benzene/ether provided only one by-product, which was separated by column chromatography. Its structure was established by NMR spectroscopy and X-ray analysis. It is evident that dihydrofuran ring was opened forming a new phenolic hydroxy group and a three-membered ring structure[8].



SCHEME 1

A mixture of the intermediate **2** and cyanogen bromide in anhydrous CH_2Cl_2 was refluxed to obtain 4,5-anhydro-17-cyano-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6,14-ethanomorphinan-4,5-diol (**4**; Scheme 2). 4,5-Anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6,14-ethanomorphinan-4,5-diol (**5**) was obtained by treating **4** with KOH in diethylene glycol at 205–210 °C. *N*-Allylation of the compound **5** under usual conditions then provided **4**.



SCHEME 2

The single crystals suitable for the X-ray analysis of compound **6** was obtained by slow evaporation of its methanolic solution. The X-ray ORTEP structure of **6** with atomic labeling is shown in Fig. 1. The crystal structure of **5** maintains the main rigid structure of morphine as described in the

literature for morphine[11], 3-methoxyetorphine[12] and buprenorphine[10b,13]. A rigid pentacyclic structure consisting of benzene ring A, partially unsaturated six-membered ring B and cyclohexane ring D, piperidine ring E, dihydrofuran ring C and the C6–C14 enthano bridge has been described for this skeleton. The shape of the title compound is a three-dimensional "T" with rings, A, B and C forming a nearly perfect vertical plane and rings E and D forming a more distorted horizontal plane. Piperidine ring E is in the chair and D ring is in the boat conformation. The new ethano bridge of the originally boat-shaped ring D forms the bicyclo[2,2,2]octane cage. The carbon in position 7 with the 1-hydroxy-1-methyl-3-(2-thienyl)propyl group has *R*-configuration. The Grignard reaction shows a remarkably high degree of stereoselectivity strictly obeying the Cram's rules[14]. As a result, the *R*-configuration was almost the sole product. Since the allyl group on N is larger than an electron pair or the proton on protonated N, it is predominantly equatorial. The stereostructure would be important in determining relative agonist potencies as discussed in the literature[1b,15]. The hydroxy group of C-4 is included by forming an intramolecular hydrogen bond with the methoxy oxygen O-3. The distance between O-4 and O-3 is 2.629 Å, with the H···O separation is 1.938 Å, falling into the normal range of the O···O separation for hydrogen bonding[16]; the bond angle is 141.42°.

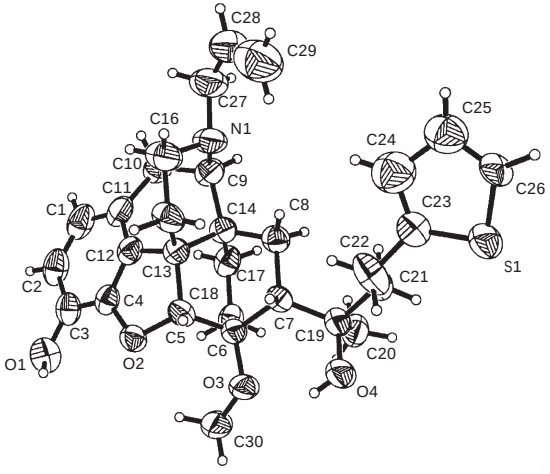


FIG. 1
ORTEP view of compound **6** with 50% thermal ellipsoid probability

As shown in Fig. 2, a zigzag infinite quasi-one-dimensional chain structure was formed through O···H–O intermolecular hydrogen bonds in which the O atoms of the hydroxy group links another hydroxy group of benzene ring in the neighboring molecule. The O···O separation is 2.734 Å with the O···H separation 1.936 Å; the bond angles are 163.90°.

EXPERIMENTAL

All the reagents were commercially available and were used without further purification or were purified by standard methods prior to use. Melting points were determined using an RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JNM-ECA-400 400 MHz instrument in the solvent indicated. Chemical shift δ values are reported in ppm relative to tetramethylsilane used as an internal reference standard, coupling constants *J* are given in Hz. Mass spectra were obtained using Micromass ZabSpec and API3000 instruments. Elemental analysis was carried at the Carlo Erba-1106. 7α-Acetyl-4,5-anhydro-3,6-dimethoxy-17-methyl-6,14-ethenomorphinan-4,5-diol (**1**) was synthesized by our group as described in the literature[9].

4,5-Anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-17-methyl-6,14-ethanomorphinan-4,5-diol (**2**)

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-4,5-anhydro-3,6-dimethoxy-17-methyl-6,14-ethenomorphinan-4,5-diol (**1**; 19.2 g,

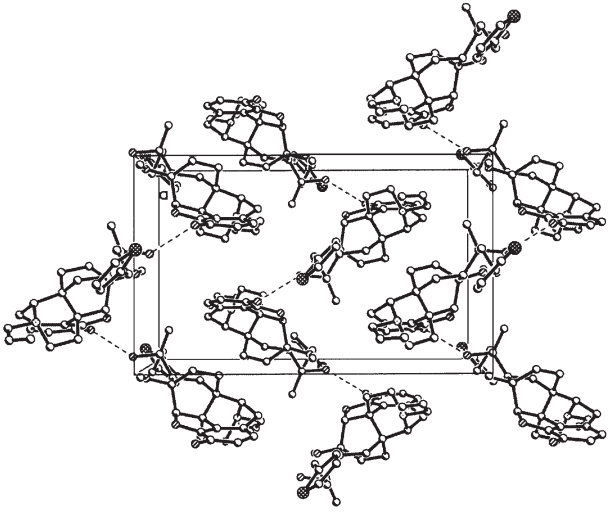


FIG. 2
Packing diagram of compound **6** showing hydrogen bonds

0.05 mol) in a mixture of 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 a saturated aqueous NH_4Cl solution (500 ml) was added. The mixture was extracted with ether (3 × 150 ml), the combined organic phase was washed with brine, dried with anhydrous Na_2SO_4 and evaporated to obtain a two-component product (TLC). The mixture was separated by column chromatography using CH_2Cl_2–MeOH (20:1) as eluent.

Compound **2** was purified by crystallization from methanol to give colorless crystals of **2**; yield 18.6 g (75%); m.p. 183–185 °C. For $C_{29}H_{37}NO_4S$ (495.7) calculated: 70.30% C, 7.47% H; found: 70.18% C, 7.56% H. ^{1}H NMR (DMSO-d_6): 7.29 d, J = 5.0, 1 H (ArH); 6.93 m, 1 H (ArH); 6.85 m, 1 H (ArH); 6.73 d, J = 8, 1 H (ArH); 6.55 d, J = 8, 1 H (ArH); 4.61 s, 1 H (OH); 4.39 s, 1 H (5β-H); 3.77 s, 3 H (Ar-OCH_3); 3.41 s, 3 H (6-OCH_3); 2.82–2.94 m, 4 H; 2.58–2.76 m, 2 H; 2.10–2.27 m, 4 H; 1.80–2.05 m, 4 H; 1.66–1.76 m, 2 H (CH_2); 1.45–1.55 m, 2 H (CH_2); 1.30 s, 3 H (20-CH_3); 1.18–1.24 m, 1 H (CH); 1.07 m, 1 H (CH); 0.58 m, 1 H. ESI-MS: 496.1 $(M + 1)^+$.

Compound **3**. Yield 8%; m.p. 196–198 °C. For $C_{29}H_{37}NO_4S$ (495.7) calculated: 70.30% C, 7.47% H; found: 70.21% C, 7.53% H. ^{1}H NMR ($CDCl_3$): 7.09 dd, J = 1.0, J = 5.0, 1 H (ArH); 6.92 dd, J = 3.0, J = 1.7, 1 H (ArH); 6.82 d, J = 3.0, 1 H (ArH); 6.66 d, J = 8, 1 H (ArH); 6.61 d, J = 8, 1 H (ArH); 5.80 s, 1 H (ArOH); 5.01 s, 1 H (OH); 3.87 s, 3 H (Ar-OCH_3); 3.36 s, 3 H (6 × OCH_3); 2.95–3.02 m, 3 H; 2.80 s, 1 H; 2.53–2.64 m, 3 H; 2.31 m, 1 H; 2.28 s, 3 H (N-CH_3); 1.88–2.06 m, 5 H; 1.51–1.67 m, 3 H; 1.48 s, 3 H (20-CH_3); 1.29–1.32 m, 1 H (CH); 1.08–1.15 m, 1 H (CH). ESI-MS: 496.4 $(M + 1)^+$.

4,5-Anhydro-17-cyano-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6,14-ethanomorphinan-4,5-diol (**4**)

A solution of cyanogen bromide (12.2 g, 0.1 mol) and **2** (13.6 g, 0.027 mol) in dry CH_2Cl_2 (108 ml) was stirred under reflux for 5 h. The solution was evaporated to dryness and the residue was purified by recrystallization from ethanol to give colorless crystals of **4**; yield 12.5 g (91%); m.p. 171–173 °C. For $C_{29}H_{34}N_2O_4S$ (506.7): calculated: 68.77% C, 6.72% H; found: 68.81% C, 6.72% H. ESI-MS: 507.0 $(M + 1)^+$.

4,5-Anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6,14-ethanomorphinan-4,5-diol (**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 for 2 h. The mixture was then poured into stirred water (500 ml) containing crushed ice and adjusted pH to 8–9 with a saturated aqueous ammonium chloride solution. The precipitated solid was collected and crystallized from methanol to give colorless crystals of **5**; yield 9.7 g (86%); m.p. 268–270 °C. For $C_{27}H_{33}NO_4S$ (467.6) calculated: 69.38% C, 7.07% H; found: 69.30% C, 6.87% H. ESI-MS: 468.2 $(M + 1)^+$.

17-Allyl-4,5-anhydro-7α-[(*R*)-1-hydroxy-1-methyl-3-(2-thienyl)propyl]-6-methoxy-6,14-ethanomorphinan-3,4,5-triol (**6**)

A mixture of **5** (7.0 g, 0.015 mol), allyl bromide (3.6 g, 0.03 mol) and dry $NaHCO_3$ (4.0 g, 0.048 mol) in dimethylformamide (200 ml) was vigorously stirred at 70–80 °C under nitro-

gen for 16 h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in CH_2Cl_2, dried with anhydrous Na_2SO_4 and evaporated. Chromatography of the crude product on a silica gel column, eluting with a CH_2Cl_2–MeOH mixture (20:1) gave a white solid, which was crystallized from methanol to give colorless crystals of **6**; yield 3.8 g (31.2%); m.p. 198–200 °C. For $C_{30}H_{37}NO_4S$ (507.7) calculated: 70.97% C, 7.35% H, 2.76% N; found: 71.13% C, 7.21% H, 2.61% N. ^{1}H NMR ($CDCl_3$): 9.24 s, 1 H (Ar-OH); 7.41 m, 1 H (ArH); 7.12 m, 1 H (ArH); 7.02 m, 1 H (ArH); 6.68 d, J = 8, 1 H (ArH); 6.58 d, J = 8, 1 H (ArH); 5.96 m, 1 H (=CH); 5.60 d, J = 16.8, 1 H (=CH_2); 5.52 d, J = 10.3, 1 H (=CH_2); 4.59 s, 1 H (OH); 4.55 s, 1 H (5β-H); 3.80–3.97 m, 2 H (CH_2); 3.41 s, 3 H (6-OCH_3); 3.17 m, 1 H; 2.65–2.90 m, 5 H; 2.15–2.22 m, 1 H; 1.74–2.02 m, 4 H; 1.60–1.72 m, 1 H; 1.20–1.51 m, 7 H; 1.07 m, 1 H; 0.63 m, 1 H. ESI-MS: 508.4 $(M + 1)^+$.

TABLE I
Crystallographic data and structure refinement summary for compound **6**

Empirical formula	$C_{30}H_{37}NO_4S$
Molecular weight	507.6
Measured temperature, K	293(2)
Crystal size, mm^3	0.32 × 0.25 × 0.20
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions, Å	
a	10.984(3)
b	13.514(4)
c	17.975(6)
Volume *V*, $Å^3$	2668.1(4)
Z	4
D_{calcd}, g cm^{-3}	1.264
μ, mm^{-1}	0.157
F(000)	1088
θ range, °	1.89–26.39
Completeness to θ, %	97.8
h, *k*, *l*	–11/13, –16/9, –10/22
Reflection collected/unique	9671/5200
Parameters refined	403
R_{int}	0.0349
Final *R* indices [$I \geq 2\sigma(I)$]	$R1$ = 0.0495, $wR2$ = 0.0886
Goodness of fit	1.008
Residual electron densities, e $Å^{-3}$	0.162, –0.217

TABLE II
Bond lengths (in Å), angles (in °) and torsion angles (in °) of compound **6**

		Bond lengths	
O1–C3	1.371(3)	C11–C12	1.390(4)
O2–C4	1.387(3)	C12–C13	1.484(4)
O2–C5	1.467(3)	C13–C15	1.533(4)
O3–C30	1.415(3)	C13–C14	1.547(4)
O3–C6	1.438(3)	C14–C17	1.540(4)
O4–C19	1.452(3)	C15–C16	1.517(4)
N1–C27	1.456(9)	C17–C18	1.538(4)
N1–C16	1.468(4)	C19–C20	1.518(4)
N1–C9	1.474(4)	C19–C21	1.536(4)
N1–C27	1.481(6)	C21–C22	1.522(4)
C1–C2	1.373(4)	C22–C23	1.497(7)
C1–C11	1.400(4)	S1–C23	1.658(8)
C2–C3	1.405(4)	S1–C26	1.688(8)
C3–C4	1.378(4)	C23–C24	1.401(9)
C4–C12	1.380(4)	C24–C25	1.521(9)
C5–C6	1.531(4)	C25–C26	1.373(8)
C5–C13	1.557(3)	C8–C14	1.527(4)
C6–C18	1.532(4)	C9–C14	1.546(4)
C6–C7	1.569(3)	C9–C10	1.576(4)
C7–C19	1.551(4)	C10–C11	1.517(4)
C7–C8	1.557(4)		
		Bond angles	
C4–O2–C5	107.23(19)	C4–C12–C11	122.7(3)
C30–O3–C6	118.7(2)	C4–C12–C13	110.8(2)
C16–N1–C9	111.1(2)	C11–C12–C13	124.7(3)
C16–N1–C27	111.8(6)	C12–C13–C15	113.9(2)
C9–N1–C27	109.3(4)	C12–C13–C14	106.1(2)
C2–C1–C11	121.0(3)	C15–C13–C14	111.0(2)
C1–C2–C3	123.0(3)	C12–C13–C5	101.4(2)
O1–C3–C4	125.1(3)	C15–C13–C5	111.9(2)
O1–C3–C2	119.4(3)	C14–C13–C5	112.1(2)
C4–C3–C2	115.4(3)	C8–C14–C17	105.4(2)
C3–C4–C12	121.7(2)	C8–C14–C9	115.0(2)
C3–C4–O2	125.6(3)	C17–C14–C9	112.2(2)
C12–C4–O2	112.3(2)	C8–C14–C13	109.2(2)
O2–C5–C6	114.8(2)	C17–C14–C13	110.3(2)
O2–C5–C13	107.3(2)	C9–C14–C13	104.8(2)
C6–C5–C13	108.1(2)	C16–C15–C13	113.0(3)

TABLE II
(*Continued*)

Bond angles			
O3–C6–C5	110.4(2)	N1–C16–C15	109.2(3)
O3–C6–C18	113.4(2)	C18–C17–C14	110.3(2)
C5–C6–C18	109.2(2)	C6–C18–C17	110.6(2)
O3–C6–C7	106.0(2)	O4–C19–C20	109.4(3)
C5–C6–C7	104.0(2)	O4–C19–C21	104.4(2)
C18–C6–C7	113.3(2)	C20–C19–C21	109.4(3)
C19–C7–C8	113.4(2)	O4–C19–C7	108.8(2)
C19–C7–C6	117.7(2)	C20–C19–C7	113.8(2)
C8–C7–C6	109.3(2)	C21–C19–C7	110.6(2)
C14–C8–C7	109.7(2)	C22–C21–C19	115.6(3)
N1–C9–C14	108.5(2)	C23–C22–C21	109.9(6)
N1–C9–C10	114.4(3)	C23–S1–C26	90.4(5)
C14–C9–C10	111.9(3)	C24–C23–C22	119.1(9)
C11–C10–C9	115.2(2)	C24–C23–S1	116.1(6)
C12–C11–C1	115.5(3)	C22–C23–S1	124.7(7)
C12–C11–C10	118.2(3)	C23–C24–C25	108.8(8)
C1–C11–C10	125.2(3)	C26–C25–C24	107.0(10)
C25–C26–S1	117.6(9)		

X-ray Crystallography

Single-crystal X-ray diffraction measurement was carried out on a Bruker Smart 1000 CCD diffractometer. The determination of unit cell parameters and data collections was performed with MoKα radiation (λ = 0.71073 Å) and unit cell dimensions were obtained using least-squares refinements. The structure was solved by direct methods with SHELX97 programs[17] and all data were corrected by using the semiempirical absorption corrections (SADABS) 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, riding on the concerned atoms and refined with fixed thermal factors. Further details of the structure analyses are given in Table I. Bond distances and angles are listed in Table II. CCDC 237617 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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