MOLECULAR STRUCTURE OF (-)-3-ACETYL-6β-(ACETYLTHIO)-*N*-(CYCLOPROPYLMETHYL) NORMORPHINE AND ITS 14-HYDROXY CONGENERS

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The stereochemistry of the title compound **3** was confirmed by X-ray analysis. The 6-acetylthio derivatives with an OH group at C-14 were also designed and synthesized.

KEYWORDS sulfur-containing morphine; opioid receptor probe; X-ray analysis; 6β-(acetylthio)normorphine; 6α-(acetylthio)-14-hydroxymorphine; 6β-(acetylthio)-14-hydroxymorphine

The design of clinical analgesics of low side-effect liability or without producing physical dependence remains a goal of the medicinal chemist in spite of the range of such agents as pentazocine and buprenorphine already in general use. Also, the existence of multiple opioid receptors in the brain and the peripheral tissues has been documented on the basis of biochemical and pharmacological studies. The affinity of the opioid agonists and antagonists for their receptors is influenced by the reagents for the SH group such as *N*-ethylmaleimide (NEM).[1)]

As a part of our research programs on the design of the opioid receptor probes, we describe here the synthesis of (-)-3-acetyl-6ß-(acetylthio)-*N*-(cyclopropylmethyl)normorphine (**3**), in which the narcotic opiate, morphine (**1**) is free from undesirable physical and psychic dependence liabilities.[2)]

As shown in Chart 1, testing *N*-(cyclopropylmethyl)normorphine (**2**) with thioacetic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate at 0°C (Mitsunobu reaction[3)]) followed by acetylation with acetic anhydride afforded the title compound **3** in good yield [*Anal.* Calcd for $C_{24}H_{27}NO_4S$ HCl (462.007) : C, 62.39 : H, 6.11 : N, 3.03 . Found : C, 62.12 : H, 6.25 : N, 2.87 . mp 200°C (dec.), $[\alpha]_D^{20}$ -260.2° (c = 0.327, H_2O)].

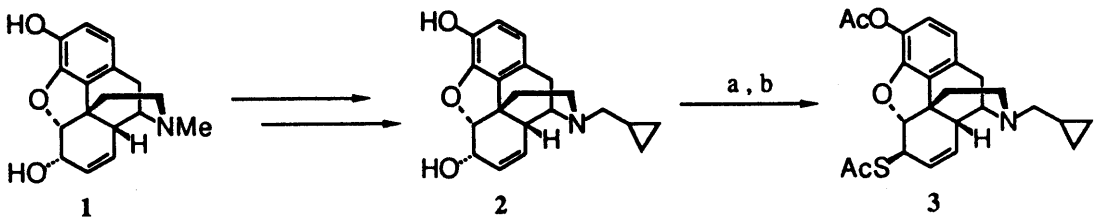
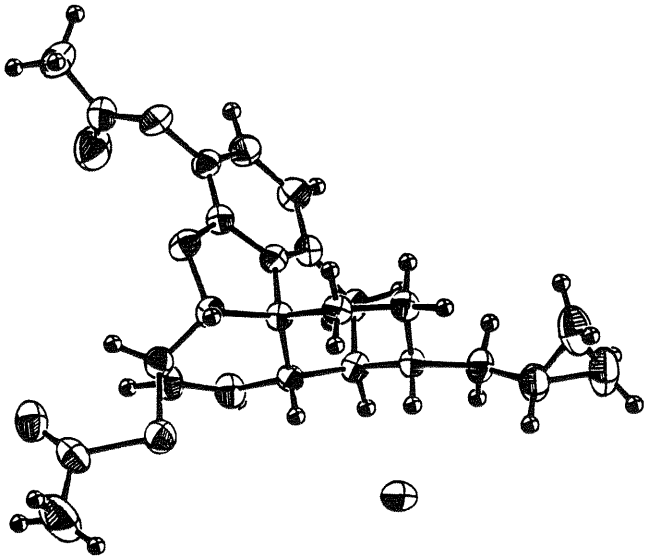


Chart 1 . Reagents and conditions : (a) Ph_3P, diisopropyl azodicarboxylate, AcSH, THF, 0°C ; (b) Ac_2O.

The stereochemistry of the C-6 thioester was assigned the β-orientation on the basis of ^{1}H-NMR analysis ($J_{5\beta-6\alpha}$ = 0.5Hz). Unequivocal support for the 6β-configuration of the acetylthio group in compound **3** was obtained by single-crystal X-ray analysis as shown in Fig. 1.

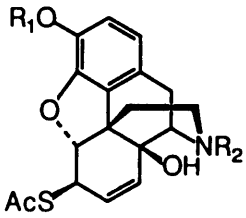
We also designed with compounds having a higher affinity to the opioid receptor than **3**. All of them were 6β-acetylthio derivatives having an OH group at C-14 in the morphine skeleton for that purpose. They were representative compounds of μ-agonist type ligands (R_2= Me) and μ-antagonist type ligands (R_2= cyclpropylmethyl) as shown in Chart 2.



Crystal Data for **3**

Formula	$C_{24}H_{28}NO_4SCl$
F_W	462.007
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	11.906 (3)
b (Å)	8.8224 (8)
c (Å)	12.115 (2)
β (deg)	115.52 (1)
V (Å)^3	1148.5 (4)
Z value	2
D (Calcd) (g cm^{-3})	1.34
μ (Cu Kα) (cm^{-1})	25.65
F (000)	488
R_F (R_{WF})	0.029 (0.040)

Fig. 1. Molecular Structure of **3** by an ORTEP Drawing



R_1 : H or Ac

R_2 : Me or cyclopropylmethyl

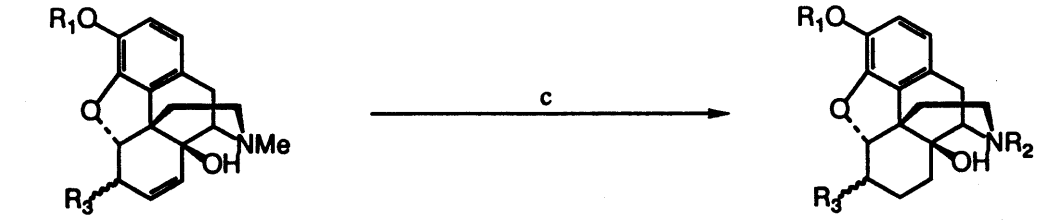
Chart 2

The Mitsunobu reaction with thioacetic acid of alcohol **4** gave the 6β-acetylthioester **5** in 89% yield; the stereochemistry of the C-6 thioester group was decided on the basis of ^{1}H-NMR analysis ($J_{5\beta-6\alpha}$ = 1.0Hz). Demethylation of **5** with boron tribromide gave 6β-(acetylthio)-14-hydroxymorphine (**6**) (mp 171-172°C, $[\alpha]_D^{26}$ -180° (c = 1.0, $CHCl_3$), 76%). In the same way, the Mitsunobu reaction of the dihydroalcohol **7** obtained by the hydrogenation of **4** with 10% Pd-C in 10% acetic acid afforded the 6β-acetylthioester **8** in quantitative yield ($[\alpha]_D^{24}$ -320° (c = 1.0, $CHCl_3$)). The demethylation of **8** followed by acetylation gave **10** (57% by two steps).

Similarly, the μ-antagonist type ligand of compound **14** was also synthesized. *N*-Cyclopropylmethyl derivative **11** was obtained from **7** in 68% yield in four steps. The Mitsunobu reaction of **11** gave 6β-acetylthioester **12**, followed by demethylation and acetylaton with acetic anhydride in the presence of triethylamine leading to 3-acetyl-6β-(acetylthio)-*N*-(cyclopropylmethyl)-14-hydroxynormorphine (**14**) (mp 125-126°C, $[\alpha]_D^{26}$ -165° (c = 1.1, $CHCl_3$), 46% yield from **11**).

It is difficult to introduce the acetylthio group to the C-6α in the morphine skeleton due to the hindered side of the molecule. Indeed, the Mitsunobu reaction of the 6β-dihydroalcohol **16** afforded the thioacetylated derivative **17** at the C-6α in poor yield (7%). The characteristic spectral feature was

diagnostic in the conformational analysis. The C-ring conformation of **17** was found to be the twist-boat form by the ^{1}H-NMR spectral inspection ($J_{5\beta\text{-}6\beta}$ = 4 Hz)[4] in contrast to compound **8** ($J_{5\beta\text{-}6\alpha}$ = 8.9Hz) which has the chair form as shown in Chart 4 .



g (a, b): **4** : R_1=Me, R_3=α-OH; **5** : R_1=Me, R_3=β-SAc; **6** : R_1=H, R_3=β-SAc; **15** : R_1=Me, R_3=β-OH

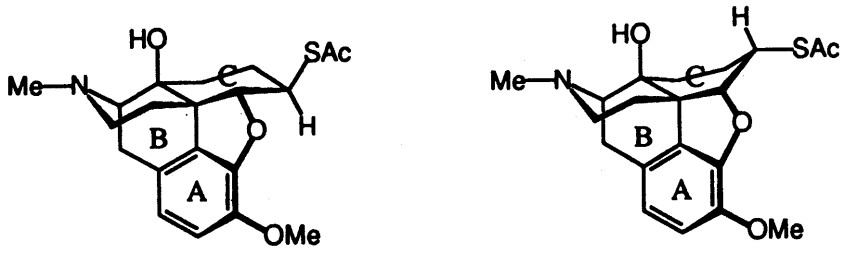
e (a, b, d): **7** : R_1=R_2=Me, R_3=α-OH (from **4**); **8** : R_1=R_2=Me, R_3=β-SAc; **9** : R_1=H, R_2=Me, R_3=β-SAc; **10** : R_1=Ac, R_2=Me, R_3=β-SAc

11 : R_1=Me, R_2=cyclopropylmethyl, R_3=α-OH

f (a, b): **12** : R_1=Me, R_2=cyclopropylmethyl, R_3=β-SAc; **13** : R_1=H, R_2=cyclopropylmethyl, R_3=β-SAc; **14** : R_1=Ac, R_2=cyclopropylmethyl, R_3=β-SAc

a: **16** : R_1=R_2=Me, R_3=β-OH (from **15**); **17** : R_1=R_2=Me, R_3=α-SAc

Chart 3 . Regents and conditions : (a) Ph_3P, diisopropyl azodicarboxylate, AcSH, THF, 0°C ; (b) BBr_3, $CHCl_3$, 20°C ; (c) H_2, 10% Pd-C, 10% AcOH ; (d) Ac_2O, CH_2Cl_2 ; (e) Ac_2O, 100°C ; BrCN, $CHCl_3$, reflux ; 25% H_2SO_4, reflux ; (bromomethyl)cyclopropane, K_2CO_3, DMF,100°C ; (f) Ac_2O, Et_3N, CH_2Cl_2; (g) Ph_3P, diisopropyl azodicarboxylate, AcOH, THF, 0°C ; 1N KOH, MeOH.



8 chair form **17** twist boat form

Chart 4

The 14-hydroxy derivatives served as opioid receptor probes to determine the action of the opiates. The results will be reported elsewhere.

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(Received March 19, 1990)