Communications to the Editor

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DESIGN AND SYNTHESIS OF SULFUR-CONTAINING MORPHINE AND AN OPIOID RECEPTOR PROBE

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Sulfur-containing morphine derivatives were synthesized and their pharmacological properties were evaluated.

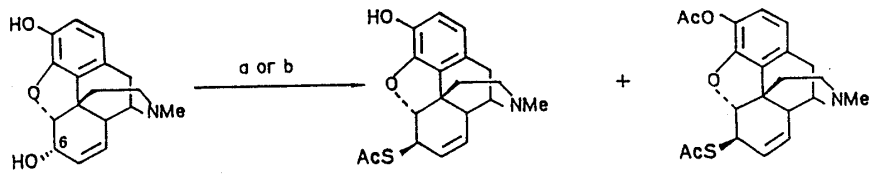
KEYWORDS——— sulfur-containing morphine; 6β-acetylthiomorphine; 6β-acetylthio-dihydromorphine; opioid receptor probe; analgesic activity; μ-opioid

The concept of multiplicity of opioid receptors, originally proposed by Martin to account for the different pharmacological effects of several opiates in spinal dogs, has received much support from binding and other pharmacological studies.[1)]

In the light of these problems, Bowen et al. have postulated a three-state allosteric model consisting of μ-agonist, μ-antagonist, and δ-agonist-preferring states, whose equilibrium may be regulated by a thiol-disulfide exchange mechanism.[2)]

On the basis of this working hypothesis, we now report the design and synthesis of sulfur-containing morphine. Indeed, this is an exciting area of research as other thiol-containing opioid peptides have proven to have interesting properties.[3)]

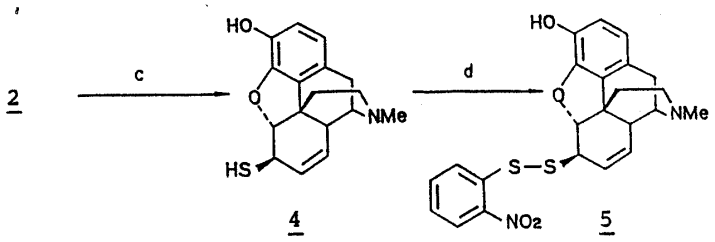
The introduction of the sulfhydryl group into the morphine skeleton was examined by two methods as shown in Chart 1.



1 2 3

a) AcSH/ $Me_2NCH(OR)_2$ /dry toluene/80°C

b) AcSH/iPrOCO-N=N-CO2iPr/PPh3 /dry THF/0°C



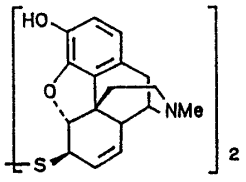
c) 0.2N KOH/EtOH/N2 (96%);

d)  /CH3CN/0°C (78%)

Chart 1

The reaction of morphine (1) with thioacetic acid in the presence of N,N-dimethylformamide dineopentyl acetal at 80°C in dry toluene[4] gave 6β-thioester (2) (mp 193.5-195°C)[5] and 3-acetyl-6β-thioester (3) in 30% and 59% yields, respectively. On the other hand, in dry THF the reaction of 1 with thioacetic acid in the presence of triphenylphosphine and diisopropylazodicarboxylate at 0°C[6] (the Mitsunobu reaction) gave 2 and 3 in 73% and 22% yields, respectively.

The stereochemistry of the C-6 thioester in 2 and 3 is assigned the β-orientation on the basis of ^{1}H-NMR analysis, since the coupling constant (J_{5-6}) for both compounds is 0.5 Hz. Compound 2 was hydrolyzed with ethanolic 0.2N KOH under nitrogen bubbling to afford 6β-thiomorphine (4) (mp 155-160°C, 66%), which was easily oxidized by O_2 in the medium, and generated disulfide compound (6). The reaction of 4 with 2-nitrobenzenesulfenyl chloride in acetonitrile at 0°C gave unsymmetrical disulfide (5) as yellow needles (mp 128.5-130°C, 79%).[7]



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Similar treatment of dihydromorphine (7) with thioacetic acid in the presence of triphenylphosphine and diisopropylazodicarboxylate gave 8, only in poor yield (7%), accompanied with 3-acetylmorphine (9) (93%). However, the Mitsunobu reaction of dihydrocodeine (10) afforded 6β-thioester (11) in almost quantitative yield. Thus, the unsymmetrical disulfide (14) was obtained by demethylation of 11 followed by hydrolysis and sulfenylation as described above.[8]

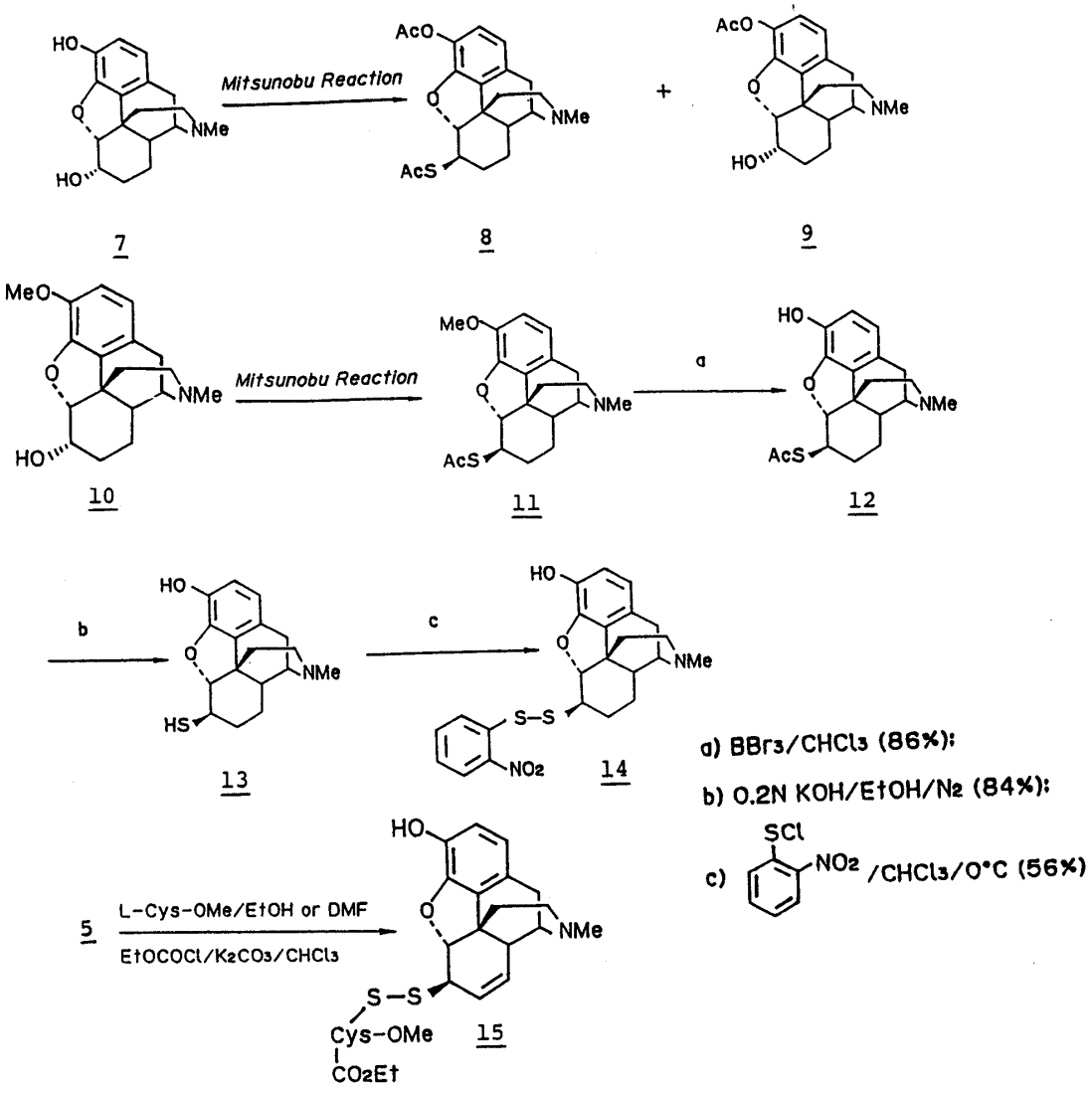

Chart 2

The thiol-disulfide exchange reaction of compound 5 with L-cysteine was also examined. Adding a dry-DMF solution of L-cysteine methyl ester to the dry-DMF solution of 5 smoothly afforded disulfide, which was identified as the corresponding carbamate 15 (ethyl chloroformate/ K_2CO_3, 40% from 5). It appears that compound 5 can react with the sulfhydryl groups on opioid receptors.

The analgesic activity was found by test drugs to be an inhibition of the twitch responses in guinea pig ileum: Compound 2 was about twice as potent as morphine. Compound 5 and morphine were equipotent. The concentration-inhibitory response curves of 2 and 5 were abolished by naloxone (10^{-7} M). This suugests that they were μ-opioid agonists. The analgesic activity of 2 was also measured in rats. It was about 5 times as potent as morphine. The analgesic effect of 2 (0.5 mg/kg, s.c.) was abolished by naloxone (1 mg/kg, s.c.) in a dose sufficient to abolish the analgesic action of morphine (2.5 mg/kg, s.c.). Apparently, compound 2 is a potent

narcotic analgesic drug.

Further studies of the opioid receptor system using the new 6β-thiomorphine congeners are in progress and preliminary results will be reported elsewhere.

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6) Compound 2; ^{1}H-NMR ($CDCl_3$) δ: 1.74-1.88 (m, 1H), 1.94-2.11 (m, 1H), 2.18-2.74 (m, 3H), 2.35 (s, 3H, NMe), 2.93-3.04 (m, 1H, H-14), 3.07 (d, J= 18.3 Hz, 1H, H-10β), 3.99 (dd, J= 7.5, 3.7 Hz, 1H, H-9), 3.39 (br s, 1H, OH, D_2O disappear), 4.17 (dd, J= 5.9, 0.5 Hz, 1H, H-6), 4.75 (d, J= 0.5 Hz, 1H, H-5), 5.55 (dd, J= 9.6, 1.7 Hz, 1H, H-8), 5.69-5.83 (m, 1H, H-7), 6.50 (d, J= 8.0 Hz, 1H, H-1), 6.67 (d, J= 8.0 Hz, 1H, H-2). IR ($CHCl_3$) cm^{-1}: 2900, 1680, 1450. MS m/z(%): 343 (M^+)(6), 268 (100). $[\alpha]_D^{27}$ -356° (c= 0.5, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.16; H, 6.15; N, 4.08.

7) Compound 5; ^{1}H-NMR ($CDCl_3$) δ: 1.67-1.78 (m, 1H), 1.90-2.67 (m, 4H), 2.44 (s, 3H, NMe), 3.02 (d, J= 18.0 Hz, 1H, H-10β), 3.22-3.80 (m, 2H, H-14 and H-9), 3.60 (dd, J= 7.0, 0.5 Hz, 1H, H-6), 4.94 (d, J= 0.5 Hz, 1H, H-5), 5.63 (dd, J= 10.0, 1.5 Hz, 1H, H-8), 5.75-5.93 (m, 1H, H-7), 6.49 (d, J= 8.0 Hz, 1H, H-1), 6.55 (d, J= 8.0 Hz, 1H, H-2), 7.36 (ddd, J= 8.0, 8.0, 1.5 Hz, 1H, ArH), 7.70 (ddd, J= 8.0, 8.0, 1.5 Hz, 1H, ArH), 8.20-8.30 (m, 2H, ArH). IR ($CHCl_3$) cm^{-1}: 2920, 1590, 1510, 1450. MS m/z (%): 455 $(M+H)^+$ (18). $[\alpha]_D^{26}$ -143° (c= 0.5, $CHCl_3$). Anal. Calcd for $C_{23}H_{22}N_2O_4S_2$: C, 60.77; H, 4.88; N, 6.16. Found: C, 60.83; H, 4.92; N, 6.07.

8) Compound 14; ^{1}H-NMR ($CDCl_3$) δ: 0.92 (ddd, J= 26.0, 13.2, 2.6 Hz, 1H), 1.45 (ddd, J= 26.1, 14.7, 2.6 Hz, 1H), 1.52-1.61 (m, 1H), 1.63-1.68 (m, 1H), 1.87 (ddd, J= 12.2, 12.0, 4.8 Hz, 1H), 1.96-2.04 (m, 1H), 2.12-2.25 (m, 2H), 2.31 (dd, J= 18.4, 5.3 Hz, 1H, H-10α), 2.40 (s, 3H, NMe), 2.55-2.65 (m, 2H, H-6 and H-14), 2.98 (d, J= 18.4 Hz, 1H, H-10β), 3.09-3.12 (m, 1H, H-9), 4.43 (d, J= 8.7 Hz, H-5), 6.57 (d, J= 8.1 Hz, 1H, H-1), 6.67 (d, J= 8.1 Hz, H-2), 7.35 (ddd, J= 8.7, 7.1, 1.3 Hz, 1H, ArH), 7.75 (ddd, J= 8.3, 7.1, 1.3 Hz, 1H, ArH), 8.25 (dd, J= 8.3, 1.3 Hz, 1H, ArH), 8.39 (dd, J= 8.3, 1.3 Hz, 1H, ArH). IR ($CHCl_3$) cm^{-1}: 3000, 2920, 1580, 1435. MS m/z (%): 456 [M^+] (24), 302 (100), 270 (13), 211 (16), 154 (17). $[\alpha]_D^{27}$ -293° (c= 1.0, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}N_2O_4S_2 \cdot CH_3OH$: C, 59.00; H, 5.78; N, 5.73. Found: C, 58.89; H, 5.70; N, 5.87.

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