Communications to the Editor

[Chem. Pharm. Bull. 32(3)1268—1271(1984)]

SYNTHESIS OF THE NOVEL SULFUR-CONTAINING ANALGESIC S-ETORPHINE

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A novel etorphine analog, 3-benzoylthio-4,5α-epoxy-7α-[1(R)-hydroxy-1-methylbutyl]-6-methoxy-17-methyl-6,14-ethenomorphinan (S-etorphine, 11) was synthesized via the Newman-Kwart rearrangement. S-Etorphine (11) showed analgesic activity 3 times stronger than morphine, though it had very low receptor affinity.

KEYWORDS ——— analgesic activity; Newman-Kwart rearrangement; sulfur-containing etorphine; thebaine; opioid receptor interaction

A phenolic hydroxyl group in narcotic analgesics has been considered to be an important moiety binding to the opioid receptor site.[1] We previously reported the syntheses and pharmacological activities of sulfur-containing benzomorphans (e.g. S-metazocine) which have a benzoylthio group at the 2'-position in place of phenolic OH.[2] These compounds showed strong analgesic activities and less addiction liabilities. So we have been interested in the effects of oxygen-sulfur interconversion on the activities of analgesics with various skeletons. In this paper, we report the synthesis and biological activities of sulfur-containing etorphine derivatives.

Etorphine (8) is known as the strongest semi-synthetic analgesic ever discovered; several thousands times as potent as morphine.[3] To investigate the thermal stabilities of the highly functionalized compounds under the conditions of the Newman-Kwart rearrangement[4] we tried several synthetic approaches from thebaine (1) as shown in Chart 1.

At first, demethylation of 1 was attempted with BBr_3 in CH_2Cl_2 or with EtSNa in DMF; in each case, extensive decomposition occurred on account of the lability of the diene moiety in the C-ring.[5] Therefore, Diels-Alder addition of the diene moiety with methyl vinyl ketone was carried out and then the adduct (4) was demethylated with the same reagents used above. However, the reaction with EtSNa caused decomposition, and in the case of the reaction with BBr_3, the desired phenol (5) was obtained in a very low yield. Reluctantly, 8 was synthesized from 4 by the modification of Bentley's method[3] as shown in Chart 1.

Compound (8) was treated with NaH at 0°C and then N,N-dimethylthiocarbamoyl

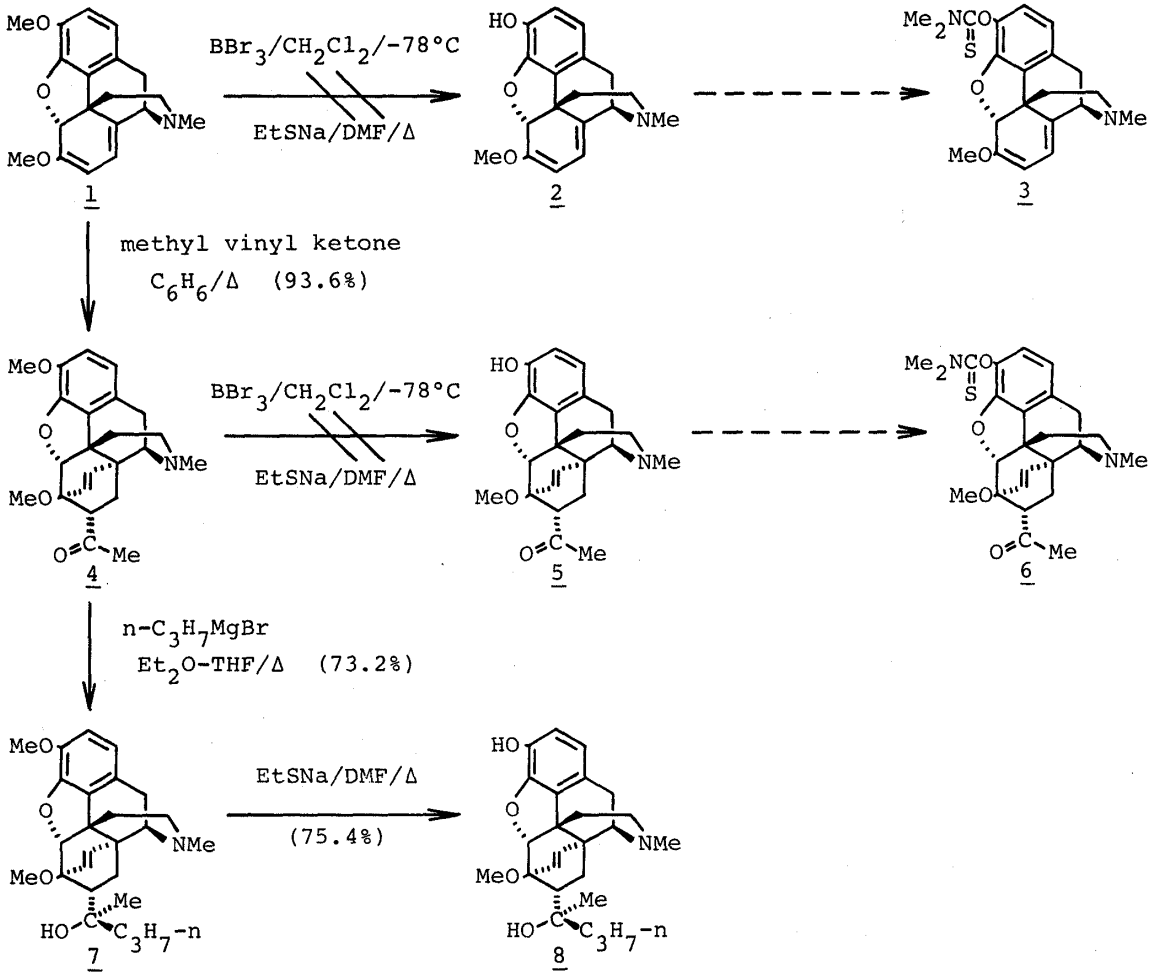

Chart 1

chloride at room temperature in DMF to afford the O-dimethylthiocarbamate (9) in 80.5% yield. In this reaction, the tertiary hydroxyl group at the 20-position did not react with the thiocarbamoyl chloride because of steric hindrance. The thermal rearrangement of 9 was then investigated. In our previous report, the rearrangement of the benzomorphan series took place over 300°C and the yields were affected by the thermal lability of their N-substituents.[2] Fortunately, 9 was thermally stable for several minutes in spite of the existence of many functional groups. The conditions of high temperature and short time were better than those of low temperature and long time. O-Thiocarbamate (9) did not rearrange to 10 but gradually decomposed below 290°C, and the thermal decomposition of 9 overcame the rearrangement above 320°C. Therefore, we conducted the thermal rearrangement at 300°C for 4 min as the optimum reaction conditions, and obtained the dimethylcarbamoylthio derivative (10) in 60.3% yield. Compound 10 was reduced with $LiAlH_4$ and benzoylated successively to give the objective 3-benzoylthioetorphine (S-etorphine, 11) in 78.2% yield. The structures of 9, 10 and 11 were confirmed by ^{1}H-NMR, IR and mass spectra and elemental analysis.[6]

The biological activities of S-etorphine (11) thus prepared are shown in Tables I and II. ED_{50} values were determined by Haffner's method. The anal-

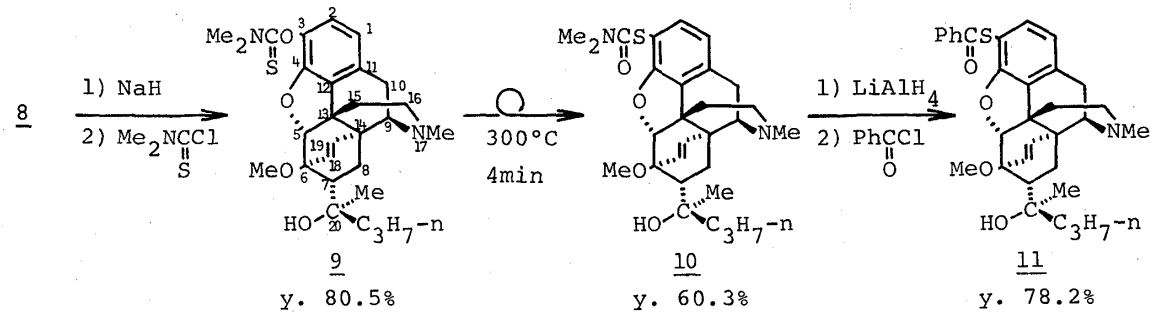

Chart 2

Table I. Analgesic Activity: Haffner Method, in Mice

			ED_{50} (mg/kg)
S-Etorphine (11)	fumarate	(s.c.)	2.1 (1.33 – 3.32)
		(p.o.)	2.7 (1.61 – 4.54)
Etorphine (8)	fumarate	(s.c.)	0.011 (0.0056 – 0.0217)
		(p.o.)	0.109 (0.0553 – 0.2147)
Morphine	HCl salt	(s.c.)	5.9 (5.6 – 6.3)

Table II. Opioid Receptor Binding: ^{3}H-Naloxone(5nM), Rat Brain Homogenate P_2 Fr.

	IC_{50} (nM)
S-Etorphine (11)	327.7
Etorphine (8)	0.3757
Morphine	8.0
Pentazocine	42

gesic activity of 11 was about three times as potent as morphine in s.c. administration and even twice as potent in p.o. administration. Today, the opioid receptor is believed to be classified into some subtypes; e.g. μ, δ, σ and κ.[7] The opioid receptor interactions were measured by the inhibition of ^{3}H-naloxone as a μ-ligand in rat brain homogenate. This new sulfur-substituted compound (11) showed very low receptor affinity compared with that of morphine or pentazocine. From these results, we suggest that 11 shows its analgesic activity by binding to the subtype receptors other than μ. Further investigation of the synthesis of related compounds is now in progress.

ACKNOWLEDGEMENT Partial support of this work was provided by a Grant-in-Aid for Scientific Research (No. 58771595) administered by the Ministry of Education, Science and Culture of Japan.

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6) 9: Colorless prisms, mp 239-240°C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, 20-Me), 2.34 (3H, s, NMe), 3.24, 3.35 [each 3H, each s, $Me_2NC(=S)$], 3.68 (3H, s, 6-OMe), 4.50 (1H, br s, 5-H), 4.88 (1H, s, 20-OH), 5.42 (1H, d, J=9Hz, 18-H), 5.96 (1H, d, J=9Hz, 19-H), 6.57 (1H, d, J=8.5Hz, 1-H), 6.66 (1H, d, J=8.5Hz, 2-H). IR (KBr): 1530cm^{-1} [>NC(=S)]. MS (m/e): 498 (M^+). Anal. Calcd for $C_{28}H_{38}O_4N_2S$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.18; H, 7.71; N, 5.59.
10: Fumarate, pale yellow needles, mp 204-206°C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s, 20-Me), 2.36 (3H, s, NMe), 2.99 [6H, s, $Me_2NC(=O)$], 3.70 (3H, s, 6-OMe), 4.54 (1H, br s, 5-H), 4.95 (1H, s, 20-OH), 5.44 (1H, d, J=9Hz, 18-H), 6.02 (1H, d, J=9Hz, 19-H), 6.58 (1H, d, J=7.5Hz, 1-H), 7.00 (1H, d, J=7.5Hz, 2-H). IR (KBr): 1720cm^{-1} [>NC(=O)]. MS (m/e): 498 (M^+). Anal. Calcd for $C_{28}H_{38}O_4N_2S \cdot C_4H_4O_4$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.35; H, 7.07; N, 4.42.
11: Fumarate·hemihydrate, colorless needles, mp 179-182°C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s, 20-Me), 2.38 (3H, s, NMe), 3.60 (3H, s, 6-OMe), 4.55(1H, br s, 5-H), 4.88 (1H, s, 20-OH), 5.55 (1H, d, J=9Hz, 18-H), 6.07 (1H, d, J=9Hz, 19-H), 6.64 (1H, d, J=7.5Hz, 1-H), 7.01 (1H, d, J=7.5Hz, 2-H). IR (KBr): 1680cm^{-1} (C=O). MS (m/e): 531 (M^+). Anal. Calcd for $C_{32}H_{37}O_3NS \cdot C_4H_4O_4 \cdot 1/2H_2O$: C, 65.83; H, 6.45; N, 2.13. Found: C, 65.94; H, 6.49; N, 2.13.

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(Received January 30, 1984)