Facile Synthesis of 8-Benzoylthio-2,6-methano-3-benzazocines and 3-Benzoylthiomorphinans Having Small-Ring Substituents[1)]

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Synthesis of 3-cyclopropylmethyl-, 3-cyclobutylmethyl-, and 3-methyl-8-benzoylthio-2,6-methano-3-benzazocines (1j—l) was performed by regio-selective chlorosulfonation of non-narcotic 8-deoxy derivatives (1a—c) followed by reduction and benzoylation. 3-Benzoylthiomorphinans (2h—j) were also obtained by the same method. Compounds having small-ring substituents (1k, 1l, 2i, 2j) were found to be weak but pure μ- and δ-opioid antagonists. The analgetic activity of 1k was almost equal to that of pentazocine.

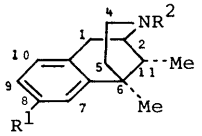
Keywords 2,6-methano-3-benzazocine; morphinan; chlorosulfonation; regio-selective synthesis; analgesic; opioid antagonist; sulfur compound; nitration

We have reported the syntheses and pharmacological activities of 8-acylthio-2,6-methano-3-benzazocines (2′-acylthio-6,7-benzomorphans) and acylthiomorphinans.[1,2)] 8-Benzoylthio-3,6,11-trimethyl-2,6-methano-3-benzazocine (*S*-metazocine, **1j**) was as active as pentazocine (**1e**) in terms of analgetic activity, but **1j** was about 1/40 as strong as **1e** in terms of opioid receptor affinity. For the synthesis of the above compounds, narcotics such as metazocine (**1d**), phenazocine and 3-hydroxy-*N*-methylmorphinan (**2d**) were used as starting materials, and severe thermal conditions were required in the Newman–Kwart rearrangement[3)] as a key step of the syntheses. In order to study the pharmacological activities of these sulfur-containing analgesics, we required a new synthetic procedure which involves mild conditions. In this paper we wish to report a facile synthesis of 8-benzoylthio-2,6-methano-3-benzazocines (**1j—l**) and 3-benzoylthiomorphinans (**2h—j**) from non-narcotic starting materials (**1a—c**, **2a—c**). The pharmacological activities of the products were also examined.

Chemistry

We planned two synthetic routes for the introduction of a sulfur atom into the aromatic ring of **1a** or **2a** by electrophilic substitution, as shown in Chart 1. May and Fry reported the synthesis of **1d** by nitration of **1a** followed by reduction, diazotization and hydrolysis.[4)] The nitration gave only the 8-nitro derivative (**3a**). We have performed nitration of **1a** in order to get the 8-nitro compound by the method reported by May and Fry. However, the nitrated product was proved to be a mixture of 8-nitro (**3a**) and 9-nitro (**3b**) compounds in the ratio of 8:3 as determined from the relative intensities in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, which showed two three-proton singlets at δ 1.47 and 1.44 which are attributable to the C(6)-methyl group of **3a** and **3b**, respectively, and two one-proton doublets at δ 7.27 and 7.48 which are attributed to C(10)-H of **3a** and C(7)-H of **3b**, respectively. Mohacsi *et al.* reported that Friedel–Crafts acylation of morphinan similarly afforded a mixture of 2- and 3-acetylmorphinans in the ratio of 2:1.[5)]

We next examined chlorosulfonation as a key step for the introduction of a sulfur atom into the aromatic ring of **1a** and **2a**.[6)] The reaction of **1a** with chlorosulfonic acid afforded the chlorosulfonyl derivative (**1f**), which was moisture-sensitive. The chlorosulfonyl compound (**1f**) was led to the stable sulfonamide (**1i**) in 26% yield (from **1a**) by treatment with morpholine. The sulfonamide (**1i**) was proved to be a single isomer by the ^{1}H-NMR spectrum, although the position of the morpholinosulfonyl group of **1i** was uncertain. Therefore we led **1f** to *S*-metazocine (**1j**), whose structure has been fully established,[2)] by reduction[7)] of the sulfonyl chloride (**1f**) with $LiAlH_4$ in tetrahydrofuran (THF), followed by benzoylation in 59% yield (from **1a**). Reduction of the sulfonyl chloride (**1f**) with Zn–H_2SO_4 also



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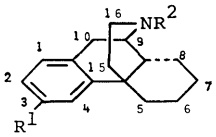
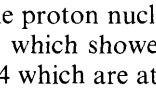
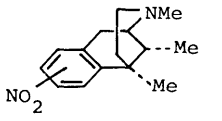


2

	R^1	R^2
1a	H	Me
1b	H	▷CO
1c	H	◇CO
1d	HO	Me
1e	HO	$CH_2CH{=}CMe_2$
1f	$ClSO_2$	Me
1g	$ClSO_2$	▷CO
1h	$ClSO_2$	◇CO
1i		Me
1j	PhCOS	Me
1k	PhCOS	▷CH_2
1l	PhCOS	◇CH_2

	R^1	R^2
2a	H	Me
2b	H	▷CO
2c	H	◇CO
2d	HO	Me
2e	$ClSO_2$	Me
2f	$ClSO_2$	▷CO
2g	$ClSO_2$	◇CO
2h	PhCOS	Me
2i	PhCOS	▷CH_2
2j	PhCOS	◇CH_2



3a 8-nitro

3b 9-nitro

Fig. 1

introduction of sulfur group

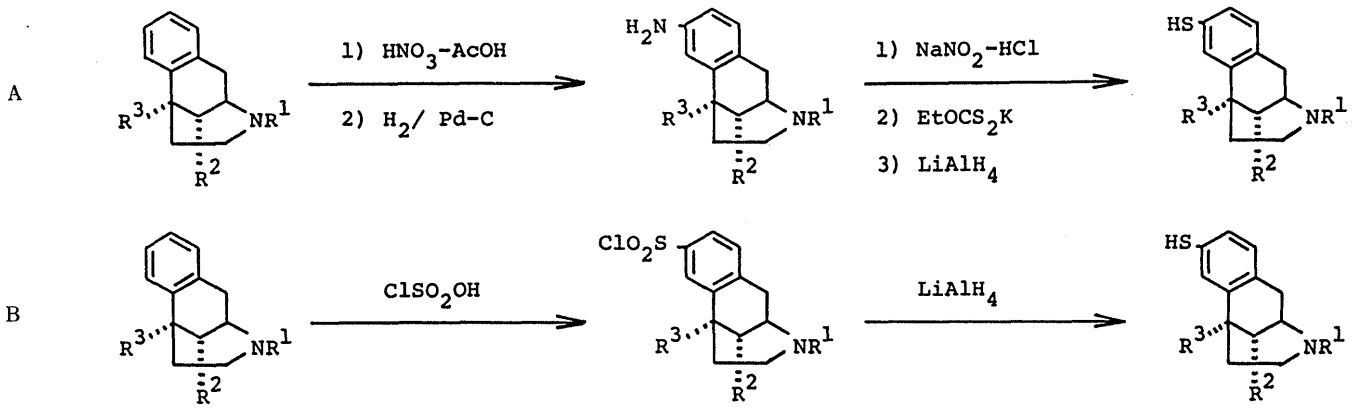


Chart 1

TABLE I. Pharmacology of Sulfur-Containing Compounds

Compound	Analgetic activity[a] ED_{50} (95% CL) mg/kg	Opioid receptor binding[b] IC_{50} (μM) Rat brain			Human placenta
		No DTNB	+DTNB	DTNB index	
1k	1.7 (1.02— 2.86)	4.8	1.8	0.4	0.84
1l	2.6 (1.60— 4.15)	7.2	3.6	0.5	2.4
2i	4.8 (2.12— 9.95)	5.9	3.0	0.5	0.97
2j	6.3 (3.30—11.7)	7.4	5.3	0.7	2.5
Pentazocine	1.6 (1.02— 2.51)	0.32	0.99	3.1	0.04
Morphine	0.47 (0.31— 0.71)	0.058	1.07	18.4	1.50
Naloxone		0.003	0.003	1.0	0.02
DADLE		0.048	1.92	40.4	10000<

a) The 0.6% AcOH-induced writhing inhibition method (male mouse), s.c. *b*) Inhibition of opioid receptor binding of ^{3}H-diprenorphine (1 nM). CL, clearance.

proceeded well. The physico-chemical data for **1j** were identical with those of an authentic sample.[2] The above procedure was applied to *N*-methylmorphinan (**2a**), giving 3-benzoylthio-*N*-methylmorphinan (**2h**).[8] Consequently, it was elucidated that the chlorosulfonation of **1a** or **2a** occurred regio-selectively at the 8-position of **1a** or at the 3-position of **2a**.

Similar treatment was adopted for *N*-cyclopropylcarbonyl- and *N*-cyclobutylcarbonyl-2,6-methano-3-benzazocines (**1b, c**) and morphinans (**2b, c**). As the small-ring carbamides resisted chlorosulfonation, the compounds (**1b, 1c, 2b, 2c**) were successfully converted into *N*-cyclopropylmethyl- or *N*-cyclobutylmethyl-2,6-methano-3-benzazocines (**1k, l**) or morphinans (**2i, j**), respectively, by this procedure.

As described above, the chlorosulfonation proceeded regioselectively at the 8-position of 2,6-methano-3-benzazocines or the 3-position of morphinan under mild conditions. Thus, it is established that this method is advantageous for the large-scale synthesis of *S*-metazocine (**1j**) and its analogues having small-ring nitrogen substituents.

Pharmacology

Pharmacological activities of sulfur-containing compounds are summarized in Table I. Analgetic activity was measured by the acetic acid-induced writhing inhibition method.[2] Opioid receptor binding affinity was determined in terms of IC_{50} values against ^{3}H-diprenorphine in rat brain homogenate P_2 fraction (μ- and δ-receptor) or in human placenta preparation (κ-receptor).[9] The μ- and δ-agonist-antagonist character was evaluated by the DTNB index.[10] Compound **1k** was almost equipotent with pentazocine in terms of analgetic activity. All compounds (**1k, 1l, 2i, 2j**) were found to have μ- and δ-opioid antagonist activity. For comparison, the Na index value of the *N*-methyl derivative (**1j**) was 6, indicating that **1j** is a partial agonist.[11] Both 2,6-methano-3-benzazocine (**1k**) and morphinan (**2i**) showed similar features in opioid receptor binding, but **1k** was somewhat more active than **2i** in terms of antinociceptive activity. The same relationship was also observed between **1l** and **2j**.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-1 or A-100 spectrometer. ^{1}H-NMR spectra were obtained for solutions in $CDCl_3$ on a Hitachi R-20B instrument with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS-DX300 spectrometer with a direct-insertion probe at 70 eV.

Nitration of 1a To an ice-cooled mixture of fuming HNO_3 (d=1.50, 16 ml) and AcOH (10 ml), 4 g of **1a** in 6 ml of AcOH was slowly added with stirring and the mixture was stirred overnight at room temperature. The solution was evaporated under reduced pressure, dilute NH_4OH solution was added and the mixture was extracted with ether. The extracts were dried over K_2CO_3, and the solvent was evaporated off to give 3.6 g of an oil. A solution of the oil in 16 ml of acetone was added to an acetone solution (80 ml) of picric acid (4.0 g), and the 8-nitro derivative (**3a**) was precipitated as the picrate; crude yield, 4.8 g (53%). The picrate was recrystallized from acetone to give yellow prisms, mp 247—250 °C (dec.) [lit.[4] mp 248—250 °C (dec.)]. Hydrochloride, colorless needles, mp 253—257 °C (dec.) from acetone [lit.[4] 253—254 °C (dec.)]. ^{1}H-NMR (free base in $CDCl_3$) δ: 0.86 (3H, d, J=7 Hz, C-11 Me), 1.47 (3H, s, C-6 Me), 2.42 (3H, s, NMe), 7.27 (1H, d, J=8 Hz, C-10 H), 7.95 (1H, dd, J=8, 2 Hz, C-9

H), 8.13 (1H, d, J=2 Hz, C-7 H). From the filtrate, 1.9 g (21%) of the picrate of the 9-nitro isomer (**3b**) was obtained after evaporation. The crude crystals were recrystallized from MeOH–acetone to form pale yellow prisms, mp 235—237 °C (dec.). ^{1}H-NMR (free base in $CDCl_3$) δ: 0.86 (3H, d, J=7 Hz, C-11 Me), 1.44 (3H, s, C-6 Me), 2.42 (3H, s, NMe), 7.48 (1H, d, J=9.5 Hz, C-7 H), 7.90—8.22 (2H, m, arom H). *Anal.* Calcd for $C_{15}H_{20}N_2O_2 \cdot C_6H_3N_3O_7$: C, 51.53; H, 4.74; N, 14.31. Found: C, 51.48; H, 4.78; N, 14.30.

(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-3,6,11-trimethyl-8-morpholinosulfonyl-2,6-methano-3-benzazocine (1i) A mixture of 1.0 g of **1a** hydrochloride[4] and 1 ml of chlorosulfonic acid was stirred for 1 h at room temperature. After removal of excess chlorosulfonic acid under reduced pressure, 3 ml of morpholine was added to the residue. The mixture was heated on a water bath to dissolve solid materials. The solution was poured into 10% K_2CO_3 and extracted with ether. The extracts were dried (K_2CO_3) followed by evaporation under reduced pressure to give 0.37 g (26%) of crude crystals. Recrystallization from ether gave colorless prisms, mp 145—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=7 Hz, C-11 Me), 1.42 (3H, s, C-6 Me), 2.40 (3H, s, NMe), 2.76—3.10, 3.60—3.90 (8H, m, morpholine H), 7.15—7.68 (3H, m, arom H). IR (KBr) cm^{-1}: 1345 (SO_2), 1160 (SO_2). MS *m/z*: 364 (M^+). *Anal.* Calcd for $C_{19}H_{28}N_2O_3S$: C, 62.61; H, 7.74; N, 7.69. Found: C, 62.40; H, 7.67; N, 7.68.

(2*RS*,6*SR*,11*SR*)-8-Benzoylthio-1,2,3,4,5,6-hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocine (1j) Method A: Chlorosulfonic acid (2 ml) was added to 2.0 g of **1a** in 20 ml of $CHCl_3$ with ice-cooling. The resulting mixture was stirred for 1 h at that temperature and for 12 h at room temperature, poured into a mixture of 50 g of ice and 10 g of NH_4Cl, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$), and concentrated under reduced pressure. The product was suspended in 25 ml of THF, then $LiAlH_4$ (1.2 g) was added portionwise and the mixture was stirred for 24 h. Benzoyl chloride (10 ml) in 50 ml of ether was added under ice-cooling and the reaction mixture was stirred for 3 h at room temperature. After the addition of 20 ml of saturated NH_4Cl, the mixture was extracted with ether, dried (K_2CO_3) and evaporated. The residue was purified by column chromatography on silica gel (benzene, then AcOEt : Et_3N = 30 : 1) to give 1.65 g (59%) of **1j**. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=7 Hz, C-11 Me), 1.40 (3H, s, C-6 Me), 2.44 (3H, s, NMe), 7.00—7.65 (6H, m, arom H), 7.90—8.15 (2H, m, arom H). IR (KBr) cm^{-1}: 1675 (C=O). The hydrochloride of **1j** was obtained as colorless needles (acetone), mp 220—222 °C.

Method B: Chlorosulfonic acid (5 ml) was added portionwise to 5.16 g of **1a** under ice-cooling, and the mixture was heated on a boiling water bath for 0.5 h. Then, a mixture of 20 ml of H_2SO_4 and 60 ml of water was added portionwise. After the addition of 10 g of zinc powder the reaction mixture was heated on a boiling water bath for 6 h. It was then allowed to cool, and 30 ml of benzoyl chloride, 120 ml of aqueous 30% K_2CO_3 and 150 ml of benzene were successively added with stirring. The resulting mixture was stirred at room temperature for 12 h. The benzene layer was separated, and the aqueous layer was extracted twice with 10 ml of benzene. The extracts were dried (K_2CO_3) and evaporated. The residue was purified by column chromatography on silica gel (AcOEt : hexane : Et_3N = 1 : 1 : 0.1) to obtain 3.68 g (43%) of **1j** as a colorless oily product. The spectral data were identical with those of the product obtained by the method noted above.

(2*RS*,6*SR*,11*SR*)-8-Benzoylthio-3-cyclopropylmethyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine (**1k**): Yield 46.3% (from **1b**). ^{1}H-NMR ($CDCl_3$) δ: −0.1—0.7 (5H, m, cyclopropyl H), 0.87 (3H, d, J=7 Hz, C-11 Me), 1.39 (3H, s, C-6 Me), 7.1—7.65 (6H, m, arom H), 7.8—8.2 (2H, m, arom H). IR (CCl_4) cm^{-1}: 2910, 1675 (C=O), 1205, 900. MS *m/z*: 391 (M^+), 350 (base). Fumarate · hemihydrate: mp 127—129 °C (dec.) from acetone. *Anal.* Calcd for $C_{25}H_{29}NOS \cdot C_4H_4O_4 \cdot 1/2H_2O$: C, 67.42; H, 6.63; N, 2.71. Found: C, 67.31; H, 6.90; N, 2.63.

(2*RS*,6*SR*,11*SR*)-8-Benzoylthio-3-cyclobutylmethyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine (**1l**): Yield 44.7% (from **1c**). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=7 Hz, C-11 Me), 1.38 (3H, s, C-6 Me), 7.05—7.75 (6H, m, arom H), 7.9—8.25 (2H, m, arom H). IR (CCl_4) cm^{-1}: 2910, 1675 (C=O), 1205, 900. MS *m/z*: 405 (M^+), 350 (base). Fumarate · hemihydrate: mp 116—119 °C (dec.) from acetone. *Anal.* Calcd for $C_{26}H_{31}NOS \cdot C_4H_4O_4 \cdot 1/2H_2O$: C, 67.90; H, 6.84; N, 2.64. Found: C, 68.14; H, 6.92; N, 2.71.

(9*RS*,13*RS*,14*RS*)-3-Benzoylthio-17-cyclopropylmethylmorphinan (**2i**): Yield 43.5% (from **2b**). ^{1}H-NMR ($CDCl_3$) δ: −0.1—0.7 (5H, m, cyclopropyl H), 7.0—7.7 (6H, m, arom H), 7.85—8.2 (2H, m, arom H). IR (CCl_4) cm^{-1}: 2920, 1680 (C=O), 1205, 900. MS *m/z*: 417 (M^+), 376 (base). Fumarate · hemihydrate: mp 131—134 °C (dec.) from acetone. *Anal.* Calcd for $C_{27}H_{31}NOS \cdot C_4H_4O_4 \cdot 1/2H_2O$: C, 68.61; H, 6.69; H, 2.58. Found: C, 68.62; H, 7.16; N, 2.57.

(9*RS*,13*RS*,14*RS*)-3-Benzoylthio-17-cyclobutylmethylmorphinan (**2j**): Yield 42.4% (from **2c**). ^{1}H-NMR ($CDCl_3$) δ: 7.0—7.65 (6H, m, arom H), 7.85—8.2 (2H, m, arom H). IR (CCl_4) cm^{-1}: 2920, 1680 (C=O), 1205, 900. MS *m/z*: 431 (M^+), 376 (base). Fumarate · hemihydrate: mp 124—127 °C (dec.) from acetone. *Anal.* Calcd for $C_{28}H_{33}NOS \cdot C_4H_4O_4 \cdot 1/2H_2O$: C, 69.03; H, 6.88; N, 2.52. Found C, 69.19; H, 6.99; N, 2.66.

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