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Synthesis and Analgetic Activity of Sulfur-Containing Morphinans and Related Compounds[1)]

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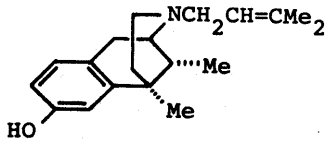
3-Acylthiomorphinans, 3-carbamoylthio-3-deoxydihydromorphine and 3-benzoylthio-9-aza-17-carbamorphinan were synthesized by Newman–Kwart rearrangement of the corresponding *O*-thiocarbamates. The analgetic activities were lower than that of pentazocine, and the opioid receptor binding affinities were very weak. These acylthiomorphinans showed low antinociceptive activity compared with corresponding sulfur-containing benzomorphans. 3-Carbamoylthiodeoxydihydromorphine had no significant analgetic activity.

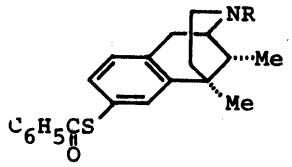
Keywords sulfur-containing morphinan; 3-carbamoylthio-3-deoxydihydromorphine; analgesic; Newman–Kwart rearrangement; opioid receptor; antinociceptive activity

Synthetic researches aimed at the synthesis of non-narcotic strong analgesics have been continued for a long period. Both benzomorphans(2,6-methano-3-benzazocines) and morphinans, which were generated by the simplification of morphine structure, have been investigated from the viewpoint of the structure–activity relationships. These studies showed that the substituents on the nitrogen atom participate in the agonist-antagonist properties of opiates to a considerable extent and that the aromatic ring moiety plays an important role in binding to opioid receptors.[2)] The chemical modification of the phenolic hydroxyl group of opiates has not been examined as thoroughly as that of nitrogen substituents, because the analgetic potency was greatly decreased by the replacement of the phenolic hydroxyl group by other groups such as acyl,[3)] alkyl,[4)] amino,[5)] hydrogen (deoxy) and halogen[6)] groups. In order to substantiate the role of the phenolic hydroxyl group, Reden *et al.* synthesized 3-deoxymorphines and evaluated their pharmacological activities.[7)] They concluded that "the phenolic hydroxyl group generally has a greater effect on binding to the opiate receptor than on antinociception."[7)] We hypothesized that the receptor binding of opiates by use of this phenolic moiety caused narcotism, and that replacement of the hydroxyl group would reduce the addictive character of opiate analgesics. The synthesis of analgesics having a marcapto group instead of the hydroxyl group as a bioisostere was therefore attempted.

We have already reported the synthesis and pharmacology of 8-(acylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines (**1**).[1c)] Interestingly, the analgetic activity of



pentazocine



1a: R = Me
1b: R = $CH_2CH=CMe_2$

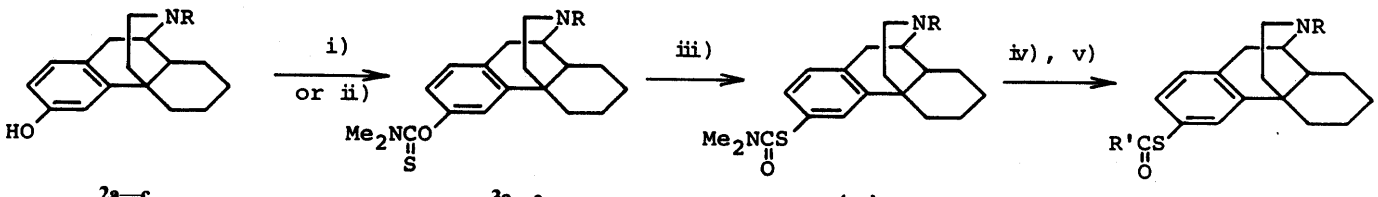
Fig. 1

1a is equipotent to that of pentazocine and the receptor affinity is about 1/38 of that of pentazocine.

In this paper, we describe the synthesis and pharmacology of some 3-benzoylthiomorphinans and related compounds as part of a further investigation of the pharmacological properties of sulfur-containing analgesics.

Chemistry Newman–Kwart rearrangement[8)] was used for the replacement of aromatic hydroxyl group of morphinans with a mercapto group. The *O*-thiocarbamates (**3**) were obtained by the reaction of morphinans (**2**) with *N*,*N*-dimethylthiocarbamoyl chloride in the presence of sodium hydride in dimethylformamide (DMF) or with the thiocarbamoyl chloride and sodium ethoxide in ethanol in good yields. These *O*-thiocarbamates (**3**) rearranged thermally to the corresponding *S*-thiocarbamates (**4**) under the conditions described in Table II.

The progress of the pyrolysis was followed by thin-layer chromatography (TLC) and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. The two methyl groups on the nitrogen atom in the *O*-thiocarbamates (**3**) appeared

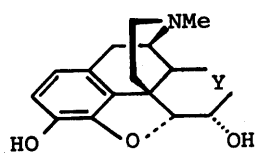


2a—c **3a—c** **4a, b** **5a, b, d**

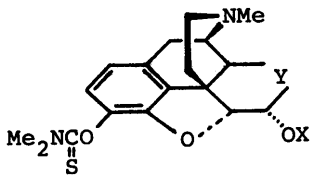
	R	R′
a:	Me	C_6H_5
b:	$CH_2CH_2C_6H_5$	C_6H_5
c:	$CH_2CH=CMe_2$	—
d:	Me	Me

i) Me_2NCSCl, NaH, DMF
ii) Me_2NCSCl, sodium alkoxide, alcohol
iii) 300—320 °C
iv) $LiAlH_4$, THF
v) R′COCl, THF

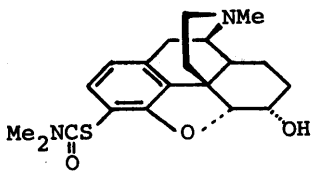
Chart 1



6a morphine
Y=CH=CH
6b dihydromorphine
Y=CH_2CH_2



	X	Y
7a	H	CH=CH
7b	Me_2NC=S	CH=CH
7c	H	CH_2CH_2
7d	Me_2NC=S	CH_2CH_2



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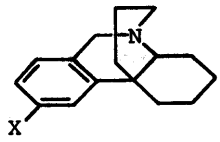

	X
9	HO
10	Me_2NC(=S)O
11	Me_2NC(=O)S
12	C_6H_5C(=O)S

Fig. 2

at δ 3.2—3.5 as a pair of singlet signals in the ^{1}H-NMR spectra. On the other hand, the methyl groups in the *S*-thiocarbamates (**4**) were observed at about δ 3.0 as a single singlet signal.

Hydrolysis of the *S*-thiocarbamates (**4**) by alkali hydroxides in aqueous alcohols gave amorphous mixtures containing disulfides, probably by the rapid oxidation of the thiols during work-up. The isolation of *S*-acylthio derivatives (**5**) was attempted by adding acid chlorides to the hydrolysis solution, but the yields were very poor, so another method was tried. Reduction of the *S*-thiocarbamates (**4**) by lithium aluminum hydride in tetrahydrofuran (THF) followed by treatment with acid chlorides gave the *S*-acylated products (**5**) in moderate yields. Thermolysis of the *N*-allylmorphinan derivative (**3c**) did not give the *S*-thiocarbamate at all, but only decomposition occurred.

Morphine (**6a**) gave a mixture of the 3-*O*-thiocarbamate (**7a**) and the 3,6-*O*,*O*-bis(thiocarbamate) (**7b**) under the same conditions as used for morphinans (**2**). The monothiocarbamate (**7a**) of morphine was obtained quantitatively by applying the Schotten–Baumann procedure to **6a** with the thiocarbamoyl chloride in aqueous alkaline solution. The 3,6-*O*,*O*-bis(thiocarbamate) (**7b**) was obtained under the conditions of two fold excess of the thiocarbamoyl chloride and base, as in the case of the preparation of morphinan thiocarbamates (**3**). The monothiocarbamate (**7c**) and bis(thiocarbamate) (**7d**) of dihydromorphine were also synthesized similarly. Rearrangement of 3-*O*-thiocarbamates (**7a, c**) and 3,6-*O*,*O*-bis(thiocarbamates) (**7b, d**) was unsuccessful, resulting in decomposition as in the case of **3c**. By the use of high-boiling-point reaction media (Dowtherm A,[9] triphenyl phosphate and diphenylsulfone), thermal rearrangement of those thermo-vulnerable *O*-thiocarbamates (**3c**, **7**) was investigated. The thermolysis of **7d** in Dowtherm A gave 3-*S*-

Table I. *O*-Thiocarbamates of Morphinans and Morphines (**3**, **7**, **10**)

Compd.	Method[a]	Yield (%)	Analysis Calcd (Found) C	H	N	Formula	mp (°C)	Recryst. solvents[b]
(±)-**3a**	A	72.6	69.73	8.19	8.13	$C_{20}H_{28}N_2OS$	120—121	L
			(69.85	8.41	8.14)			
(−)-**3a**	A	75.3	69.73	8.19	8.13	$C_{20}H_{28}N_2OS$	101—102	L
			(69.69	8.43	8.14)			
(+)-**3a**	A	73.9	69.73	8.19	8.13	$C_{20}H_{28}N_2OS$	102—103	L
			(69.75	8.40	8.12)			
3b	B	82.9	74.59	7.88	6.47	$C_{27}H_{34}N_2OS$	150—152	L
			(74.38	7.88	6.38)			
3c	B	83.6	72.30	8.59	7.06	$C_{24}H_{34}N_2OS$	142—144	L
			(72.09	8.78	7.06)			
7a	C	95.6	64.47	6.49	7.55	$C_{20}H_{24}N_2O_3S$	207—208	M
			(64.20	6.55	7.40)			
7b	A	73.0	60.08	6.36	9.18	$C_{23}H_{29}N_3O_3S_2$	212—214	N
			(60.02	6.32	9.28)			
7c	C	96.2	64.12	7.00	7.51	$C_{20}H_{26}N_2O_3S$	177—178	M
			(64.02	7.21	7.40)			
7d	A	72.2	59.82	6.77	9.14	$C_{23}H_{31}N_3O_3S_2$	196—198	N
			(59.59	6.89	9.02)			
10	B	85.0	69.03	7.93	8.51	$C_{19}H_{26}N_2OS$	133—134	L
			(69.02	7.95	8.40)			

a) Methods A, B and C correspond to procedures A, B and C, respectively, as described in the experimental section. *b*) L=ether–hexane; M=no recrystallization (see ref. 13); N=AcOEt–ether.

Table II. *S*-Thiocarbamates of Morphinans and Dihydromorphine (**4**, **8**, **11**)

Compd.	Conditions Temp (°C)	Time (min)	Yield (%)	Analysis Calcd (Found) C	H	N	Formula	mp (°C)	Recryst. solvents[a]
(±)-**4a**	315	5.0	90.8	62.57	7.00	6.11	$C_{20}H_{28}N_2OS \cdot C_4H_4O_4$[b]	196—197 (dec.)	A
				(62.45	7.17	6.09)			
(−)-**4a**	320	4.5	95.4	60.79	6.96	6.47	$C_{20}H_{28}N_2OS \cdot C_2H_2O_4$[c]	172—174	A
				(60.53	7.07	6.37)			
(+)-**4a**	320	4.5	96.5	60.79	6.96	6.47	$C_{20}H_{28}N_2OS \cdot C_2H_2O_4$[c]	173—174	A
				(60.67	7.02	6.40)			
4b	315	6.0	92.5	66.37	6.91	5.36	$C_{27}H_{34}N_2OS \cdot C_2H_2O_4$[c]	188—191 (dec.)	A
				(66.30	7.09	5.41)			
8	DA[d]	15.0	4.7	58.75	6.16	5.73	$C_{20}H_{26}N_2O_3S \cdot C_4H_4O_4$[b]	146—148 (dec.)	B
				(58.53	6.40	5.68)			
11	DA[d]	90.0	60.3	59.96	6.71	6.69	$C_{19}H_{26}N_2OS \cdot C_2H_2O_4$[c]	109—111	A
				(59.81	6.83	6.65)			

a) A=acetone; B=acetone–MeOH. *b*) Fumarate. *c*) Oxalate. *d*) Refluxed in Dowtherm A.

TABLE III. Acetylthio- and Benzoylthiomorphinans (5, 12)

Compd.	Yield (%)	Analysis Calcd (Found) C	H	N	Formula	mp (°C)
(±)-5a	80.8	68.13	6.33	2.84	$C_{24}H_{27}NOS \cdot C_4H_4O_4$[a]	173—174
		(68.01	6.37	2.77)		(dec.)
(−)-5a	82.1	68.13	6.33	2.84	$C_{24}H_{27}NOS \cdot C_4H_4O_4$[a]	131—133
		(68.02	6.39	2.80)		(dec.)
(+)-5a	81.7	68.13	6.33	2.84	$C_{24}H_{27}NOS \cdot C_4H_4O_4$[a]	130—132
		(67.92	6.44	2.75)		(dec.)
5b	83.4	72.01	6.39	2.41	$C_{31}H_{33}NOS \cdot C_4H_4O_4$[a]	198—200
		(71.85	6.61	2.45)		
5d	56.8	64.01	6.77	3.26	$C_{19}H_{25}NOS \cdot C_4H_4O_4$[a]	113—115
		(63.80	6.93	3.15)		(dec.)
12	81.6	67.61	6.09	2.93	$C_{23}H_{25}NOS \cdot C_4H_4O_4$[a]	201—203
		(67.38	6.20	2.89)		

a) Fumarate, recrystallized from acetone–MeOH.

TABLE IV. Pharmacological Activity of Sulfur-Containing Morphinans

Compd.	Analgetic activity[a] ED_{50} (95% CL) mg/kg	Receptor binding[b] IC_{50} (nM)
1a	1.03 (0.65 — 1.66)	1540
(−)-2c levorphanol	0.10 (0.087— 0.122)	4.2
4a	15.5 (11.3 —18.1)	—
4b	23.9 (16.4 —44.2)	20%: 1000
(±)-5a	6.3 (2.5 —14.5)	20%: 1000
(−)-5a	5.80 (3.95 — 8.51)	1806
(+)-5a	Inactive	—
5b	20.6 (17.2 —29.3)	10%: 1000
5d	40%: 100	—
6a morphine	0.52 (0.33 — 0.83)	8.0
8	4.20 (2.01 — 8.52)	882
11	16.2 (13.3 —19.2)	2007
12	15.7 (12.9 —18.1)	1980
Pentazocine	1.25 (0.79 — 1.97)	42

a) The 0.6% AcOH writhing inhibition test (mouse), s.c. b) Inhibition of opioid receptor binding of ^{3}H-naloxone (5 nM) in rat brain homogenate P_2 fraction.

TABLE V. Spectral Data

Compd.	IR (KBr) (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ	MS (m/z) (M^+)	$[\alpha]_D^{25}$ (c, solvent)[a]
(±)-3a	1215	2.40 (3H, s, NMe)	344	
(−)-3a	(C=S)	3.32, 3.44 (each 3H, each s, $Me_2NC=S$)		−68.3°
(+)-3a		6.86 (1H, dd, J=7.5, 2.5 Hz, 2-H), 6.93 (1H, d, J=2.5 Hz, 4-H), 7.11 (1H, d, J=7.5 Hz, 1-H)		(1.0, E) +68.4° (1.0, E)
3b	1220 (C=S)	2.78 (4H, br s, NCH_2CH_2Ph), 3.31, 3.44 (each 3H, each s, $Me_2NC=S$), 7.26 (5H, br s, $C_6H_5CH_2CH_2$)	434	
3c	1210 (C=S)	1.70 (6H, s, $C=CMe_2$), 3.30, 3.45 (each 3H, each s, $Me_2NC=S$), 5.28 (1H, t, J=7.5 Hz, $NCH_2CH=C$)	398	
(±)-4a	1660	2.38 (3H, s, NMe)	344	
(−)-4a	(C=O)	3.04 (6H, s, $Me_2NC=O$)		−12.4°
(+)-4a		7.16 (1H, dd, J=7.5, 1.5 Hz, 2-H), 7.23 (1H, d, J=7.5 Hz, 1-H), 7.38 (1H, d, J=1.5 Hz, 4-H)		(0.5, W)[b] (0.5, W)[b]
4b	1650 (C=O)	2.79 (4H, br s, NCH_2CH_2Ph), 3.05 (6H, s, $Me_2NC=O$), 7.26 (5H, br s, $C_6H_5CH_2CH_2$)	434	
5a	1675 (C=O)	2.40 (3H, s, NMe) 7.15—7.70 (6H, m, ArH) 7.90—8.20 (2H, m, ArH)	377	−21.8° (0.5, W)[c] +22.0° (0.5, W)[c]
5b	1675 (C=O)	2.78 (4H, br s, NCH_2CH_2Ph), 7.15—7.70 (6H, m, ArH), 7.25 (5H, br s, $C_6H_5CH_2CH_2$), 7.90—8.20 (2H, m, ArH)	467	
5d	1700 (C=O)	2.35 (3H, s, MeC=O), 2.40 (3H, s, NMe), 7.15—7.35 (2H, m, 1,2-H), 7.40 (1H, br s, 4-H)	315	
7a	1220 (C=S)	2.45 (3H, s, NMe), 3.34, 3.46 (each 3H, each s, $Me_2NC=S$), 6.68 (1H, d, J=8 Hz, 1-H), 6.70 (1H, d, J=8 Hz, 2-H)	372	−331° (0.2, E)
7b	1190 1215 (C=S)	2.46 (3H, s, NMe), 3.21, 3.40 (each 3H, each s, 6-$Me_2NC=S$), 3.31, 3.42 (each 3H, each s, 3-$Me_2NC=S$), 6.65 (1H, d, J=8.5 Hz, 1-H), 6.76 (1H, d, J=8.5 Hz, 2-H)	459	−295° (0.2, E)
7c	1210 (C=S)	2.35 (3H, s, NMe), 3.26, 3.38 (each 3H, each s, $Me_2NC=S$), 4.53 (1H, d, J=5.5 Hz, 5-H), 6.60 (1H, d, J=8.5 Hz, 1-H), 6.62 (1H, d, J=8.5 Hz, 2-H)	374	−274° (0.2, E)
7d	1190 1215 (C=S)	2.38 (3H, s, NMe), 3.20, 3.38 (each 3H, each s, 6-$Me_2NC=S$), 3.30, 3.41 (each 3H, each s, 3-$Me_2NC=S$), 4.65 (1H, d, J=5.5 Hz, 5-H), 6.69 (1H, d, J=8.5 Hz, 1-H), 6.77 (1H, d, J=8.5 Hz, 2-H)	461	−252° (0.2, E)
8	1650 (C=O)	2.35 (3H, s, NMe), 2.98 (6H, s, $Me_2NC=O$), 4.51 (1H, d, J=5 Hz, 5-H), 6.62 (1H, d, J=7.5 Hz, 1-H), 7.08 (1H, d, J=7.5 Hz, 2-H)	374	−179° (0.2, W)[c]
10	1225 (C=S)	3.35, 3.47 (each 3H, each s, $Me_2NC=S$), 3.75 (1H, d, J=18.5 Hz, 10α-H), 4.37 (1H, d, J=18.5 Hz, 10β-H), 6.90 (1H, dd, J=7.5, 2.5 Hz, 2-H), 6.99 (1H, d, J=2.5 Hz, 4-H), 7.08 (1H, d, J=7.5 Hz, 1-H)	330	
11	1650 (C=O)	3.04 (6H, s, $Me_2NC=O$), 3.66 (1H, d, J=18 Hz, 10α-H), 4.32 (1H, d, J=18 Hz, 10β-H), 7.08 (1H, dd, J=7, 2 Hz, 2-H), 7.26 (1H, d, J=7 Hz, 1-H), 7.40 (1H, d, J=2 Hz, 4-H)	330	
12	1680 (C=O)	3.68 (1H, d, J=18 Hz, 10α-H), 4.35 (1H, d, J=18 Hz, 10β-H), 7.08 (1H, dd, J=7, 2 Hz, 2-H), 7.20—7.70 (5H, m, ArH), 7.90—8.20 (2H, m, ArH)	363	

a) E=EtOH; W=H_2O. b) Oxalate. c) Fumarate.

thiocarbamate (**8**), but in only a small amount.

9-Aza-17-carbamorphinan (**9**) is an interesting compound as a nitrogen positional isomer of morphinan, in which the nitrogen atom in the morphinan nucleus is moved from the 17-position to the 9-position. The analgetic potency of **9** is half that of morphine.[10] Thermal rearrangement of the *O*-thiocarbamate (**10**), derived from **9**, gave the

S-thiocarbamate (**11**) in a smaller yield than expected, although it has a rigid skeleton and no sensitive functional group.

Pharmacology The biological activities of these 3-mercaptomorphinans and related compounds are summerized in Table IV. The analgetic activities were measured by the mouse acetic acid writhing inhibition method.[1c] The activities of all mercapto derivatives were much decreased from that of 3-hydroxy-*N*-methylmorphinan (**2a**), though benzoylthiobenzomorphan (**1a**) is more active than mercaptomorphinans (**5**) or carbamoylthiodeoxydihydromorphine (**8**). The opioid receptor binding affinities were determined by *in vitro* radio-receptor assay; the inhibitory activities against ^{3}H-naloxone (5 nM) binding were measured by the rapid filtration method in rat brain crude synaptosomal membrane preparations (P_2 fraction) without cerebellum.[1c] The IC_{50} values of all mercapto derivatives were very large, namely the receptor binding affinities were very weak. The antinociceptive activity of (±)-**5a** was almost as potent as that of (−)-**5a**, though (+)-**5a** was inactive. The analgetic activity of 3-carbamoylthio-3-deoxydihydromorphine (**8**) was not as strong as that of **1a**, but **8** had the strongest receptor affinity among these mercapto compounds. All benzoylthio derivatives (**5a**, **5b**, **12**) were somewhat more potent than the corresponding *S*-thiocarbamates (**4a**, **4b**, **11**) and an acetylthio derivative (**5d**) as regards antinociceptive activity. 3-Mercapto-9-aza-17-carbamorphinans (**11**, **12**) were weak in both analgetic activity and opioid receptor affinity.

Experimental

All melting points are uncorrected. Infrared absorption (IR) spectra, ^{1}H-NMR spectra, mass spectra (MS) and optical rotations were taken on a JASCO IRA-1 spectrometer, a Hitachi R-20B NMR instrument (with tetramethylsilane as an internal standard), a JEOL JMS-D300 spectrometer and a JASCO DIP-4 digital polarimeter (with a 1 dm cell), respectively. Radial TLC was performed with a Chromatotron model 7924 (Harrison Research), on silica gel (Merck Kieselgel 60PF254 gypsum, Art. 7749). Column chromatography was performed on silica gel (Fuji-Davison silica gel BW-820 MH).

Materials 3-Hydroxymorphinans (**2**) were prepared by the method of Schnider and Hellerbach.[11] 3-Hydroxy-9-aza-17-carbamorphinan (**9**) was prepared by the method of Sugimoto and Kugita.[12]

Preparation of *O*-Thiocarbamates Procedure A: A 50% dispersion of NaH in mineral oil (0.96 g, 20 mmol) was added to an ice-cooled dry DMF (25 ml) solution of **2a** (2.57 g, 10 mmol) and the mixture was stirred for 30 min under N_2. *N*, *N*-Dimethylthiocarbamoyl chloride (1.48 g, 12 mmol) was added and the reaction was continued for 3 h at room temperature. The reaction mixture was poured into a mixture of ice (150 g) and 5% KOH solution (50 ml), then extracted with benzene (20 ml × 3). The organic layer was extracted with a 10% HCl solution (20 ml × 5). The acidic extracts were basified by adding concentrated NH_3 solution. The alkaline solution was extracted with benzene (20 ml × 3). The benzene layer was washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dissolved in ether (10 ml), and the solution was cooled in an ice bath. Recrystallization of the product from ether–hexane gave **3a** (2.50 g, 72.6%).

Procedure B: Compound **2b** (3.48 g, 10 mmol) was dissolved in a 0.5 M ethanolic sodium ethoxide solution (30 ml). *N*,*N*-Dimethylthiocarbamoyl chloride (1.48 g, 12 mmol) was added to the solution, and the mixture was stirred for 3 h at room temperature under N_2. The reaction mixture was worked up according to the above procedure to give **3b** (3.60 g, 82.9%).

Procedure C: Morphine monohydrate (3.03 g, 10 mmol) was dissolved in 30 ml of a 5% NaOH solution. *N*,*N*-Dimethylthiocarbamoyl chloride (1.36 g, 11 mmol) was added to the above solution with stirring in an ice bath. After 2 h, the precipitates were collected by filtration, washed with water, and dried *in vacuo* to give **7a** as a crystalline powder (3.56 g, 95.6%).

Thermolysis of *O*-Thiocarbamates Method A: An *O*-thiocarbamate (200 mg) was heated in a metal bath under N_2. The reaction mixture was purified by radial chromatography (hexane : AcOEt : Et_3N = 20 : 20 : 1). *S*-Thiocarbamate oxalates were crystallized from acetone.

Method B: A dispersion of an *O*-thiocarbamate (200 mg) in Dowtherm A[9] (20 ml) was refluxed under N_2. The reaction mixture was diluted with ether (100 ml), and extracted with a 10% HCl solution (10 ml × 6). The acidic extracts were basified by adding K_2CO_3, and extracted with CH_2Cl_2 (5 ml × 4). The organic layer was washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by radial chromatography (hexane : AcOEt : Et_3N = 20 : 20 : 1).

3-Acylthiomorphinans A solution of *S*-thiocarbamate (10 mmol) in THF (10 ml) was added dropwise to a suspension of $LiAlH_4$ (570 mg, 15 mmol) in THF (20 ml) at 0°C. The reaction was continued for 5 h at room temperature. An acid chloride (25 mmol) in THF (10 ml) was added to this mixture. After 12 h the reaction mixture was poured on ice (100 g), basified with 1 M K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography. After benzoate and benzyl alcohol were eluted with hexane : CH_2Cl_2 = 1 : 1, an acylthiomorphinan was eluted (AcOEt : Et_3N = 40 : 1) and crystallized from AcOEt–ether with cooling. Yields were *ca.* 80%.

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