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Thermolysis of *O*-Allyl *S*-Alkyl Dithiocarbonates of Codeine and Isocodeine

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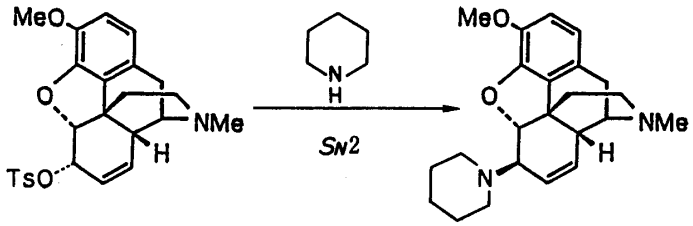
The reactions of *O*-allyl *S*-alkyl dithiocarbonates of codeine and isocodeine were examined under thermal and catalytic conditions. Heating of a xylene solution of xanthates (**3**, **4**, and **5**) gave the corresponding *S*-allyl *S*-alkyl dithiocarbonates (**6**, **7**, and **8**) *via* [3,3] sigmatropic rearrangment in high yields, overcoming the difficulty of attack on the hindered α-face. On the other hand, in the case of isocodeine, the formation of xanthates followed by the rearrangement took place without heating to afford the dithiocarbonates (**9**, **10**, and **11**). Furthermore, compound **10** rearranged with extrusion of COS to give the sulfide (**14**). The reactions of **3**, **6**, and **9** with phosphine–palladium (0) complex and a Lewis acid as catalysts were also examined. When **3** or **6** was treated with $(Ph_3P)_4Pd$, elimination reaction proceeded to give 6-demethoxythebaine (**17**). The reactions of **6** and **9** with $TiCl_4$ yielded the corresponding cyclic dithiocarbonates **18** and **19**.

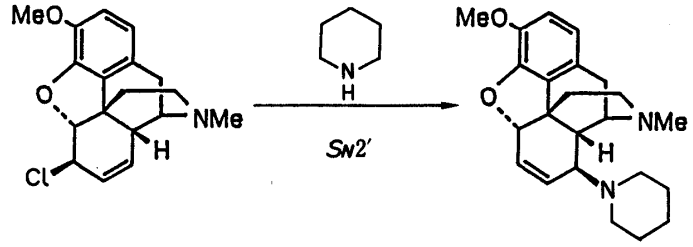
Keywords——codeine; isocodeine; dithiocarbonate; thermal rearrangement; catalytic rearrangement; *SN2′* mechanism; *SNi′* mechanism

Progress in the elucidation of the constitution of morphine (or codeine) was frequently interrupted by the occurrence of complex rearrangements and substitutions. A few typical examples are outlined in Chart 1. Substitutions of codeine derivatives such as codeine tosylate and α-chlorocodide with various kinds of nucleophile were described by various authors[1-4]: the reaction of codeine tosylate with piperidine gave a piperidocodide in which piperidine is attached at C-6, whereas the similar reaction of α-chlorocodide proceeded with rearrangement to afford an allylic isomer which has the piperidide at C-8.[3] A correlation of the dependence of the types of substitution reactions with the stereochemistry of the various codeine isomers has been found.[4] In those cases where back-side approach of anions is unhindered, a normal *SN2* displacement is to be expected as shown in Eq. 1. On the other hand, when the configuration (as in isocodeine, pseudocodeine, and α-chlorocodide) is not compatible with back-side anion approach, displacement is accompanied with rearrangement in both solvolytic and *SN2′* type reactions as shown in Eq. 2. Furthermore, a special type of internal displacement reaction (*SNi′*) may operate in those cases where back-side approach is hindered and there is a suitably located double bond. Typical examples are the conversion of pseudocodeine to α-chlorocodide by thiony chloride as shown in Eq. 3.

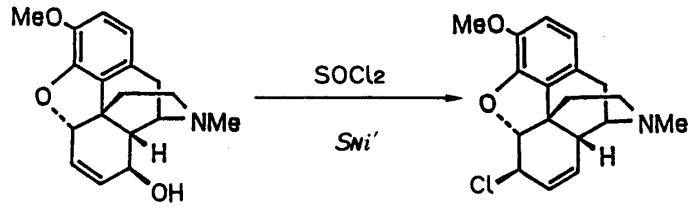
Reactions of *O*-allyl *S*-alkyl dithiocarbonates (xanthates)[5] to allyl alkyl sulfides under thermal or catalytic reaction conditions have recently been reported. Thermolysis[6] of xanthates leads to the sulfide and COS through two sequential [3, 3] sigmatropic rearrangements. In the case of the palladium-catalyzed reaction,[7] the catalytically released sulfur nucleophile attacks the *exo*-face of the co-ordinated π-allyl intermediate. Thus, both of the reactions proceed with overall retention of geometry. Applying these procedures would allow codeine and isocodeine to be stereoselectively transformed to sulfur-containing derivatives in which the sulfur residues have the α and β orientations, respectively (Chart 2). In this paper, we report the reactions of *O*-allyl *S*-alkyl dithiocarbonates of codeine and



(1)



(2)



(3)

Chart 1

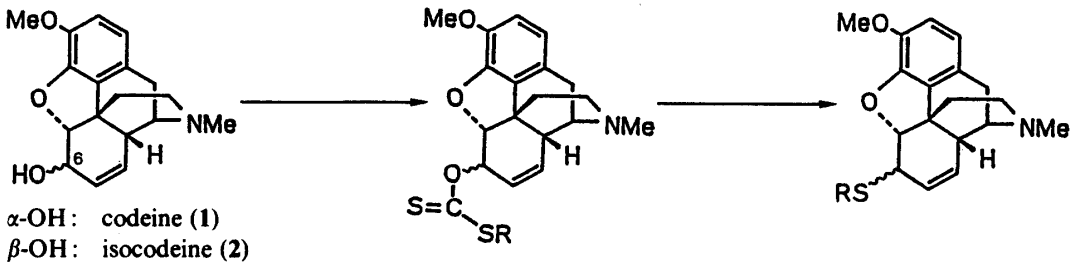


Chart 2

isocodeine under the above reaction conditions, and discuss the stereochemistry at C-6 of codeine and isocodeine which controls the reactivities of the dithiocarbonates. The sulfur-containing codeine (or morphine) derivatives[8] may serve as opioid receptor probes for elucidation of the mechanism of action of opiates and the conformational change of opioid receptors affecting the selectivities of ligand-receptor interaction regulated by a sulfhydryl group mechanism.[9]

Thermal Rearrangement of Codeine and Isocodeine Xanthates

Codeine xanthates were easy to prepare[10]; the sodium salt of codeine (**1**) was treated with carbon disulfide in dimethyl formamide and the resulting xanthate was alkylated with benzyl chloride, methyl tosylate, and chloromethyl methyl ether to give the corresponding xanthates (**3**, **4**, and **5**) in 70—80% yields (Chart 3). A xylene solution of **3** was heated at 150 °C in a sealed tube for 5 h to give the dithiocarbonate (**6**)[5] in quantitative yield. Variation of the *S*-alkyl group of xanthates did not affect the essential feature of this thermal rearrangement.

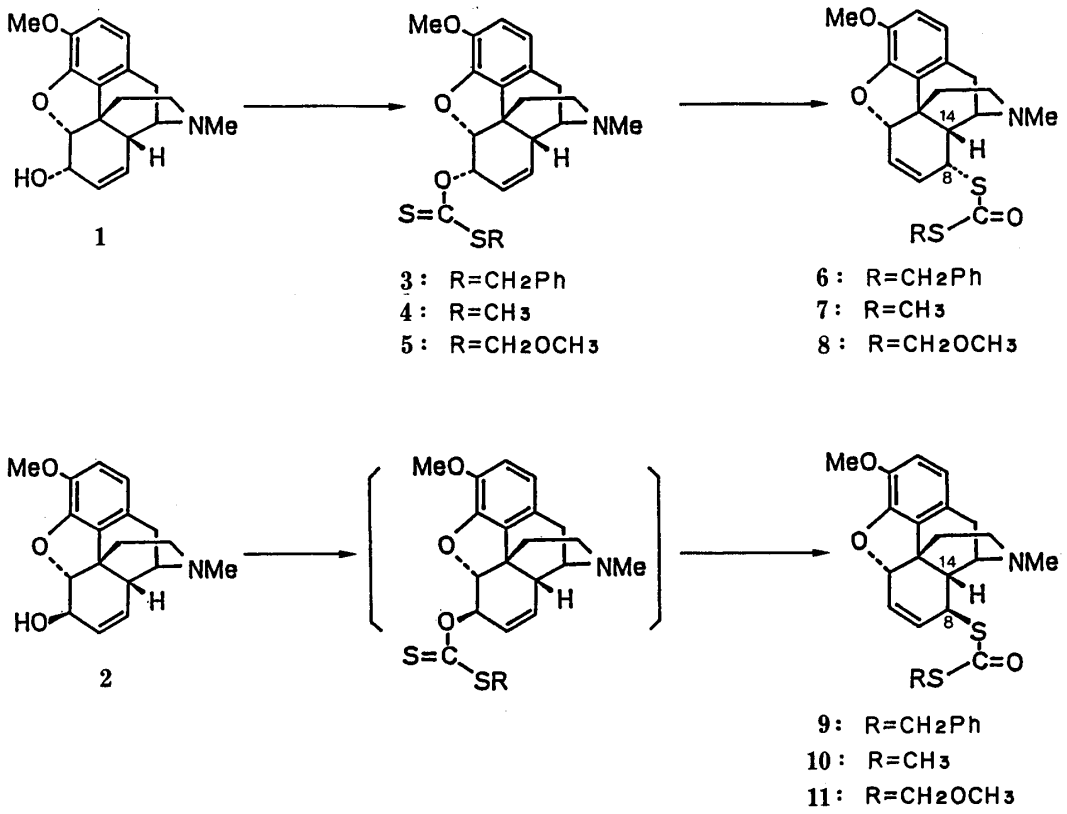
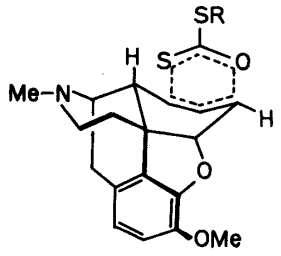


Chart 3

Indeed, heating of **4** and **5** proceeded completely under the above conditions to afford **7** and **8**, respectively. Evidence for the rearrangement was provided by the observation that the infrared (IR) spectrum[11] of the products after heating showed characteristic absorption bands at 1625 and 880 cm^{-1} due to the dithiocarbonate moiety instead of those at 1200 and 1058 cm^{-1} due to the xanthate moiety. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum[11] of the rearrangement product exhibited the signals of two olefinic protons (H-6 and H-7) at δ 5.83—5.86. This spectral pattern for the olefinic protons is similar to that of the *SN*2′ product such as 8β-bis(2-chloroethyl)aminomorphine reported by Portoghese *et al.*[12] The stereochemical assignment at C-8 was based on the generally recognized [3, 3] sigmatropic reaction mode and the magnitude of the coupling constant, J=6.9 Hz between H-8 and H-14.

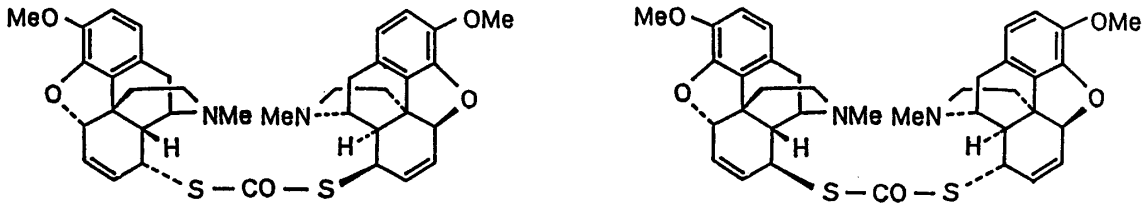
In order to further study this rearrangement, the analogous reactions of isocodeine (**2**) in which the hydroxy group is in the 6β-position were examined (Chart 3). Surprisingly, when **2** was converted to xanthates, the rearrangement proceeded rapidly at room temperature to give the corresponding dithiocarbonates (**9**, **10**, and **11**) in moderate yields. These compounds showed characteristic absorption bands of the dithiocarbonate group at 1640 and 880 cm^{-1} in the IR spectrum.[13] The stereochemistry of C-8 was determined by the observation that in the ^{1}H-NMR spectrum the coupling constant between the C-8 and C-14 protons is 10.8 Hz.[13] This large J value indicates a diaxial arrangement between the C-8 and C-14 protons, and therefore, the dithiocarbonate group possesses the β-configuration.[12]

The [3, 3] sigmatropic rearrangement of isocodeine xanthates proceeds more easily than that of codeine xanthates. This facile rearrangement isocodeine xanthates is attributed to the proximity of the xanthate group to the C_7–C_8 double bond. [14] One of the factors is the unhindered β-face in the morphine skeleton, as is generally recognized in nucleophilic substitutions of morphine alkaloids.[3,4] Thus, orientation of the xanthate group in isocodeine derivatives is favorable to form a six-membered ring transition state such as A, depicted in



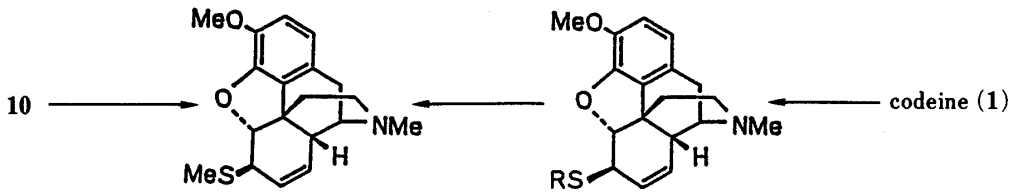
A

Fig. 1



12 13

Fig. 2



14 15: R=Ac
16: R=H

Chart 4

Fig. 1.[10] On the other hand, the equatorial xanthate group in codeine derivatives is relatively remote from the double bond, making it difficult to form the cyclic intermediate.

In the thermolysis of the benzyl (**6** and **9**) and methoxymethyl (**8** and **11**) dithiocarbonate analogues in diphenyl ether, the α and β isomers were both degraded to give a complex mixture along with the unchanged dithiocarbonates. When these reactions were examined in a polar solvent such as acetonitrile, both α and β isomers of the methoxymethyl analogues (**8** and **11**) underwent transesterification to **12** and **13** in 29% and 35% yields, respectively (Fig. 2). When the methyl analogues (**7** and **10**) were heated in diphenyl ether at 240 °C for 8 h, only the β-isomer (**10**) rearranged to give the corresponding sulfide (**14**) in 60% yield (Chart 4).

It has also been confirmed that the methyl sulfide group is located in the β-position since the coupling constant between H-5 and H-6 is 0.5 Hz in the ^{1}H-NMR spectra. Furthermore, **14** was identical with a sample prepared from codeine (**1**) by an alternative procedure: nucleophilic substitution of **1** with thioacetic acid (AcSH/dimethylformamide dineopentylacetal/toluene) afforded the thioacetate (**15**) in 87% yield. Hydrolysis (0.2 N-KOH/EtOH) of **15** followed by alkylation (methyl tosylate/NaH/DMF) of the resulting thiol (**16**) yielded the sulfide (**14**, 47% yield from **1**) (Chart 4). Rapoport's method[15] for the inversion of codeine to isocodeine is applicable to this case by exchanging acetic acid with thioacetic acid. Generally, the rearrangement with extrusion of carbon oxysulfide requires a higher temperature compared with the initial rearrangement of xanthates to dithiocarbonates. Therefore, at the required temperature, dithiocarbonates of codeine (**1**) and isocodeine (**2**) are degraded to give a complex mixture. We have found that the β-methyl dithiocarbonate (**10**) can only undergo the rearrangement under thermal conditions due to the less hindered α-face of the molecule coupled with the presence of a small substituent.

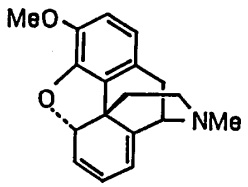


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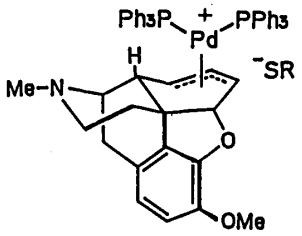
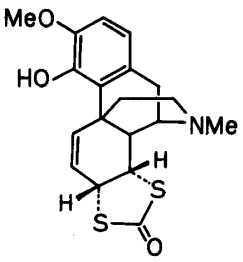
Fig. 3



B

Fig. 4



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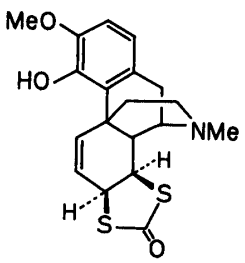

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Fig. 5

Catalytic Rearrangements of Codeine and Isocodeine Xanthates

We have examined the reactions of benzyl xanthates of codeine and isocodeine by using phosphine–palladium(0) complex and a Lewis acid as catalysts. When codeine xanthate (**3**) was treated with tetrakis(triphenylphosphine)palladium(0) in chloroform at room temperature, elimination reaction occurred to give 6-demethoxythebaine (**17**) in 17% yield (Fig. 3). The similar reaction of **6** with $(Ph_3P)_4Pd$ smoothly proceeded to afford **17** in 78% yield. In the case of **9** possessing a β-dithiocarbonate group, however, neither allylation nor elimination have been observed. The above results can be most reasonably explained by considering the stereochemistry of morphine skeleton and the mode of oxidative addition of allylic substrate to palladium(0) complexes[16-19]: in the case of the reaction of **3** or **6**, oxidative addition proceeds with inversion of configuration to from the π-allyl intermediate such as B (Fig. 4). However, this intermediate resists attack by the catalytically released nucleophile (RS^-) due to steric hindrance of the α-face, so that decomposition of the π-allyl complex takes place to give the conjugated diene.[20,21] On the other hand, no π-allyl intermediate is generated from the dithiocarbonate (**9**) for the same reason.

We have also examined the catalytic rearrangement of xanthates and dithiocarbonates with titanium(IV) chloride. Even alkyl xanthates which lack an anchimeric group such as dialkylamino and double bonds in the neighborhood of the xanthate group can be rearranged to the corresponding dithiocarbonates by using a Lewis acid as a catalyst.[22] Treatment of the dithiocarbonated (**6**) with $TiCl_4$ (2.0 eq) in dichloroethane for 10 h under reflux gave the cyclic dithiocarbonate (**18**) in a moderate yield. Similarly, isocodeine dithiocarbonate (**9**), when heated with $TiCl_4$ for 1 h, afforded the cyclic dithiocarbonate (**19**) as the sole product in 84% yield (Fig. 5). The difference of steric hindrance of the α and β faces influences this cyclization reaction: **9** is easy to cyclize in comparison with **6**. Neither cyclic compounds nor the rearrangement products were obtained from the xanthate (**3**). The structures of **18** and **19** were determined on the basis of the spectroscopic data. In the ^{1}H-NMR spectra, the *cis*-fused ring system in **18** and **19** was confirmed by the observation that the coupling constants between H-7 and H-8 were 5.1 and 5.4 Hz, respectively.

We have been able to prepare various sulfur-containing codeine derivatives, which are biologically very interesting, by examination of the thermolysis of codeine and isocodeine xanthates. It is most noteworthy that xanthates (**3**, **4**, and **5**) could rearrange to give the corresponding dithiocarbonates (**6**, **7**, and **8**) through an *SNi'* mechanism, overcoming the difficulty of attack on the more hindered α-face.

Experimental

All melting points were measured with a Yanagimoto micro melting point apparatus and uncorrected. Optical rotations were measured on a JASCO DIP-360 digital polarimeter using a 5-cm path length cell. IR spectra were determined in the indicated solvent on a JASCO IR A-100 infrared spectrophotometer. The ^{1}H-NMR spectra were taken with a JEOL PS-100 (100 MHz) or JEOL JNM-GX 270 (270 MHz) spectrometer with tetramethylsilane as an

internal standard; chemical shifts are expressed in δ values. Mass spectra (MS) were determined on a JEOL-D300 equipped with a JMA 3100/3500 accessory at an ionization voltage of 30 eV; data are reported as *m/z* (relative intensity) values. Elemental analyses were performed on Yanagimoto MT2 CHN recorder. Analytical and preparative thin-layer chromatographies (TLC) were performed by using E. Merck silica gel 60 PF-254, and column chromatography was done by using 70—230 mesh Silica gel 60 (E. Merck). The extracts were dried over anhydrous $MgSO_4$.

General Procedure for Preparation of Codeine Xanthates (3—5) and Isocodeine Dithiocarbonates (9—11)——The preparation of **3** is described as an illustrative case. A solution of **1** (100 mg, 0.33 mmol) in dry dimethylformamide (3 ml) was treated with 16 mg (0.66 mmol) of sodium hydride. The mixture was stirred at room temperature for 30 min under Ar, then 0.03 ml (0.5 mmol) of carbon disulfide was added under ice cooling. The mixture was further stirred for 2 h and then 42 mg (0.38 mmol) of benzyl chloride was added. After stirred for 8 h, the resulting mixture was poured into ice-water, rendered alkaline with saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The extracts were washed with water and brine, dried, and evaporated *in vacuo*. Column chromatography of the brown residue on silica gel with $CHCl_3$–MeOH (30 : 1) gave **3** (121 mg, 79%), which was recrystallized from EtOH to afford colorless prisms, mp 158 °C. IR ($CHCl_3$): 1200, 1058 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81—2.30 (4H, m), 2.43—2.55 (1H, m, H-10α), 2.45 (3H, s, NMe), 2.78—2.82 (1H, m, H-14), 3.06 (1H, d, J=18.7 Hz, H-10β), 3.38 (1H, dd, J= 3.5, 5.9 Hz, H-9), 3.81 (3H, s, OMe), 4.25, 4.56 (2H, ABq, J=13.5 Hz, SC$\underline{H}_2$Ph), 5.22 (1H, dd, J=1.0, 5.9 Hz, H-5), 5.42—5.71 (2H, m, H-7 and 8), 5.97—6.11 (1H, m, H-6), 6.54, 6.68 (2H, ABq, J=8.4 Hz, H-1 and 2), 7.21—7.37 (5H, m). MS *m/z*: 465 (M^+, 3), 282 (100), 91 (3). $[\alpha]_D^{26}$ −158.40° (*c*=0.5, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{27}NO_3S_2$: C, 67.07; H, 5.84; N, 3.01. Found: C, 67.29; H, 6.02; N, 2.92.

Codeine Methyl Xanthate (**4**): Orange prisms, mp 115—118 °C. IR ($CHCl_3$): 1200, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83—2.67 (5H, m), 2.45 (3H, s, NMe), 2.58 (3H, s, SMe), 2.73—2.84 (1H, m, H-14), 3.05 (1H, d, J=18.6 Hz, H-10β), 3.38 (1H, dd, J=3.4, 5.8 Hz, H-9), 3.86 (3H, s, OMe), 5.23 (1H, dd, J=0.8, 6.9 Hz, H-5), 5.39—5.52 (1H, m, H-8), 5.66—5.79 (1H, m, H-7), 5.94—6.09 (1H, m, H-6), 6.53, 6.67 (2H, ABq, J=8.1 Hz, H-1 and 2). MS *m/z*: 389 (M^+, 7) 282 (100), 60 (33). $[\alpha]_D^{27}$ −181.1° (*c*=0.56, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{23}NO_3S_2$: C, 61.67; H, 5.95; N, 3.59. Found: C, 61.86; H, 6.23; N, 3.46.

Codeine Methoxymethyl Xanthate (**5**): Colorless prisms, mp 110—112 °C. IR ($CHCl_3$): 1205, 1058 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.63 (5H, m), 2.42 (3H, s, NMe), 2.75—2.83 (1H, m, H-14), 3.06 (1H, d, J=18.7 Hz, H-10β), 3.37 (1H, dd, J=3.2, 6.0 Hz, H-9), 2.41 (3H, s, OMe), 3.86 (3H, s, OMe), 5.23 (1H, dd, J=0.9, 6.7 Hz, H-5), 5.21, 5.42 (2H, ABq, J=11.3 Hz, OC$\underline{H}_2$S), 5.42—5.58 (1H, m, H-8), 5.65—5.81 (1H, m, H-7), 5.92—6.10 (1H, m, H-6), 6.54, 6.68 (2H, ABq, J=8.1 Hz, H-1 and 2). MS *m/z*: 419 (M^+, 3), 374 (5), 359 (2), 282 (100). $[\alpha]_D^{24}$ −191.9° (*c*=1.34, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{25}NO_4S_2$: C, 60.12; H, 6.01; N, 3.34. Found: C, 59.90; H, 6.03; N, 3.35.

Isocodeine Benzyl Dithiocarbonate (**9**): Colorless prisms, mp 138—141 °C. IR ($CHCl_3$): 1640, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.79—1.92 (2H, m), 2.22—2.56 (2H, m), 2.38 (1H, dd, J=2.8, 10.8 Hz, H-14), 2.41 (3H, s, NMe), 2.57 (1H, dd, J=6.0, 18.8 Hz, H-10α), 3.02 (1H, d, J=18.8 Hz, H-10β), 3.35 (1H, dd, J=2.8, 6.0 Hz, H-9), 3.76—3.88 (1H, m, H-8), 3.85 (3H, s, OMe), 4.16, 4.24 (2H, ABq, J=13.7 Hz, SC$\underline{H}_2$Ph), 4.96 (1H, s, H-5), 5.75—5.77 (2H, m, H-6 and 7), 6.69, 6.72 (2H, ABq, J=8.4 Hz, H-1 and 2), 7.20—7.32 (5H, m, C$_6\underline{H}_5$). MS *m/z*: 465 (M^+, 22), 314 (8), 282 (100), 91 (27). $[\alpha]_D^{26}$ +30.9° (*c*=0.86, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{27}NO_3S_2$: C, 67.07; H, 5.84; N, 3.01. Found: C, 67.22; H, 5.97; N, 2.98.

Isocodeine Methyl Dithiocarbonate (**10**): Viscous oil. IR ($CHCl_3$): 1640, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.79—2.54 (4H, m), 2.38 (1H, dd, J=2.8, 11.0 Hz, H-14), 2.40 (3H, s, SMe), 2.42 (3H, s, OMe), 2.57 (1H, dd, J=5.9, 18.7 Hz, H-10α), 3.06 (1H, d, J=18.7 Hz, H-10β), 3.39 (1H, dd, J=2.8, 5.9 Hz, H-9), 3.75—3.83 (1H, m, H-8), 3.82 (3H, s, OMe), 4.81 (1H, s, H-5), 5.73—5.77 (2H, m, H-6 and 7), 6.69, 6.72 (2H, ABq, J=8.4 Hz, H-1 and 2). MS *m/z*: 389 (M^+, 19), 282 (100), 60 (21).

Isocodeine Methoxymethyl Dithiocarbonate (**11**): Colorless prisms, mp 250—253 °C. IR (CHC_3): 1640, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.79—2.56 (4H, m), 2.39 (1H, dd, J=2.9, 11.0 Hz, H-14), 2.41 (3H, s, NMe), 2.55 (1H, dd, J=5.9, 18.7 Hz, H-10α), 3.04 (1H, d, J=18.7 Hz, H-10β), 3.33 (3H, s, OMe), 3.36 (1H, dd, J=2.9, 5.9 Hz, H-9), 3.76—3.92 (1H, m, H-8), 3.85 (3H, s, OMe), 4.96 (1H, s, H-5), 5.11 (2H, s, SC$\underline{H}_2$O), 5.75—5.78 (2H, m, H-6 and 7), 6.64, 6.74 (2H, ABq, J=8.3 Hz, H-1 and 2). MS *m/z*: 419 (M^+, 3), 359 (10), 282 (100), 64 (22). $[\alpha]_D^{25}$ +79.2° (*c*=0.5, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{25}NO_4S_2$: C, 60.12; H, 6.01; N, 3.34. Found: C, 60.21; H, 6.03; N, 3.28.

General Procedure for Thermolysis of Codeine Xanthates (3—5)——The reaction of **3** is described as an illustrative case. A xylene solution (5 ml) of **3** (50 mg, 0.11 mmol) was heated at 150 °C for 5 h in a sealed tube and then the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel with $CHCl_3$–MeOH (30 : 1) to give **6** (47 mg, 94%), which was recrystallized from EtOH to afford colorless prisms; mp 151—153 °C. IR ($CHCl_3$): 1625, 880 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.64 (4H, m), 2.39 (3H, s, NMe), 2.77—2.89 (2H, m), 2.99 (1H, dd, J=2.4, 6.9 Hz, H-14), 3.29 (1H, dd, J=2.4, 5.9 Hz, H-9), 4.17 (2H, s, SC$\underline{H}_2$Ph), 4.57 (1H, m, H-8), 4.90 (1H, s, H-5), 5.83—5.86 (2H, m, H-6 and 7), 6.60, 6.76 (2H, ABq, J=8.4 Hz, H-1 and 2), 7.26 (5H, s, C$_6\underline{H}_5$). MS *m/z*: 465 (M^+, 2), 314 (2), 282 (100), 91 (17), 60 (11). $[\alpha]_D^{28}$ −210.4° (*c*=0.9, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{27}NO_3S_2$: C, 67.07; H, 5.84; N, 3.01. Found: C, 66.98; H, 5.60; N, 3.12.

Codeine Methyl Dithiocarbonate (**7**): Viscous oil. IR ($CHCl_3$): 1640, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.68

(4H, m), 2.41 (3H, s, SMe), 2.42 (3H, s, NMe), 2.77—2.96 (2H, m), 2.95 (1H, dd, J=2.5, 6.3 Hz, H-14), 3.35 (1H, dd, J=2.5, 5.9 Hz), H-9), 3.83 (3H, s, OMe), 4.48—4.62 (1H, m, H-8), 4.85 (1H, d, J=0.7 Hz, H-5), 5.79—5.87 (2H, m, H-6 and 7), 6.65, 6.78 (2H, ABq, J=8.4 Hz, H-1 and 2). MS m/z: 389 (M^+, 7), 314 (3), 282 (100), 60 (7).

Codeine Methoxymethyl Dithiocarbonate (**8**): Viscous oil. IR ($CHCl_3$): 1625, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63—2.71 (4H, m), 2.39 (3H, s, NMe), 2.78—2.99 (2H, m), 2.98 (1H, dd, J=2.5, 6.2 Hz, H-14), 3.30 (3H, s, OMe), 3.37 (1H, dd, J=2.5, 6.0 Hz, H-9), 3.82 (3H, s, OMe), 4.51—4.65 (1H, m, H-8), 4.95 (1H, d, J=0.7 Hz, H-5), 5.10 (2H, s, SCH_2O), 5.82—5.91 (2H, m, H-6 and 7), 6.64, 6.77 (2H, ABq, J=8.4 Hz, H-1 and 2). MS m/z: 419 (M^+, 2), 359 (4), 282 (100), 60 (42).

Thermolysis of the Dithiocarbonates (8 and 11) in Acetonitrile——A solution of **8** (50 mg, 0.11 mmol) in acetonitrile (5 ml) was heated at 100 °C for 6 h in a sealed tube. The solvent was evaporated off *in vacuo* and then the brown residue was subjected to column chromatography on silica gel with $CHCl_3$–MeOH (15 : 1) to give **12** (23 mg, 29%) as a pale yellow solid, mp 245—247 °C. IR ($CHCl_3$): 1625, 860 cm^{-1}. ^{1}H-NMR δ: 1.81—2.68 (10H, m), 2.39 (6H, s, NMe), 2.72—2.85 (4H, m), 3.02 (2H, dd, J=2.5, 6.2 Hz, H-14), 3.25 (2H, dd, J=2.5, 6.0 Hz, H-9), 3.86 (6H, s, OMe), 4.50—4.58 (2H, m, H-8), 4.91 (2H, d, J=0.7 Hz, H-5), 5.82—5.86 (4H, m, H-6 and 7), 6.57, 6.75 (4H, ABq, J=8.4 Hz, H-1 and 2). MS m/z: 656 (M^+, 1), 359 (0.6), 327 (2), 315 (9), 282 (100), 60 (14).

The similar reaction of **11** (80 mg, 0.19 mmol) in acetonitrile (6 ml) gave **13** (43 mg, 35%) as a tan solid, mp 252—253 °C. IR ($CHCl_3$): 1640, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.79—2.56 (8H, m), 2.37 (2H, dd, J=2.7, 11.0 Hz, H-14), 2.39 (6H, s, NMe), 2.49 (2H, dd, J=6.2, 18.7 Hz, H-10α), 3.00 (2H, d, J=18.7 Hz, H-10β), 3.31 (2H, dd, J=2.7, 6.2 Hz, H-9), 3.70—3.82 (2H, m, H-8), 3.85 (6H, s, OMe), 4.95 (2H, s, H-5), 5.75 (4H, s, H-6 and 7), 6.68, 6.74 (4H, ABq, J=8.1 Hz, H-1 and 2). MS m/z: 656 (M^+, 9), 375 (2), 315 (2), 315 (13), 282 (100), 76 (19), 58 (12).

Isocodeine 6-Thioacetate (15)——A mixture of dimethylformamide dineopentylacetal (0.55 ml, 1.95 mmol) and thioacetic acid (0.14 ml, 1.98 mmol) in toluene (6 ml) was added to a solution of **1** (200 mg, 0.66 mmol) in toluene (25 ml) at 80 °C under Ar with stirring. The mixture was heated at 80 °C. with stirring for 3 h, then *o*-xylene was added and evaporated at 80 °C. *o*-Xylene was added and evaporated twice more to give a brown residue. Column chromatography on silica gel with $CHCl_3$–MeOH (15 : 1) gave **15** (205 mg, 87%), which was recrystallized from EtOH to afford pale yellow prisms, mp 156.3—157 °C. IR ($CHCl_3$): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18—3.14 (6H, m), 2.34 (3H, s, SCOMe), 2.44 (3H, s, NMe), 3.05 (1H, d, J=18.3 Hz, H-10β), 3.33 (1H, dd, J=3.1, 6.2 Hz, H-9), 3.86 (3H, s, OMe), 4.23 (1H, dd, J=0.5, 6.2 Hz, H-6), 4.79 (1H, d, J=0.5 Hz, H-5), 5.52 (1H, dd, J=2.0, 9.8 Hz, H-8), 5.73—5.92 (1H, m, H-7), 6.53, 6.68 (2H, ABq, J=8.1 Hz, H-1 and 2). MS m/z: 357 (M^+, 19), 282 (100), 40 (40). $[\alpha]_D^{28}$ −407.7° (c=0.56, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.48; N, 3.92. Found: C, 67.31; H, 6.61; N, 3.78.

Isothiocodeine (16)——A 0.2 N KOH-EtOH solution (5 ml) was added to a stirred solution of **15** (201 mg, 0.56 mmol) in EtOH (5 ml), and the mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with 20 ml of water and extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (10 : 1) to afford **16** (167 mg, 95%) as colorless prisms, mp 124—125 °C. The thiol (**16**) is degraded slowly on standing to give many spots on TLC analysis. ^{1}H-NMR ($CDCl_3$) δ: 1.75—3.13 (7H, m), 2.45 (3H, s, NMe), 3.02 (1H, d, J=18.1 Hz, H-10β), 3.24 (1H, dd, J=3.1, 6.2 Hz, H-9), 3.53—3.66 (1H, m, H-6), 3.83 (3H, s, OMe), 4.91 (1H, d, J=0.5 Hz, H-5), 5.41 (1H, dd, J=2.0, 10.0 Hz, H-8), 5.84—5.95 (1H, m, H-7), 6.52, 6.69 (2H, ABq, J=8.3 Hz, H-1 and 2). MS m/z: 315 (M^+, 21), 282 (100), 178 (10). $[\alpha]_D^{27}$ −351.1° (c=1.03, $CHCl_3$).

Isocodeine 6-Methylsulfide (14)——A solution of methyl tosylate (40 mg, 0.22 mmol) in dry dimethylformamide (2 ml) was added to a stirred suspension of **16** (58 mg, 0.18 mmol) and sodium hydride (6.5 mg, 0.27 mmol) in dry dimethylformamide (4 ml), and then the mixture was stirred at room temperature under Ar for 1 h. The resulting mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water and brine, dried and evaporated *in vacuo*. The yellow residue was subjected to preparative TLC on silica gel with $CHCl_3$–MeOH (40 : 1) to give **14** (34 mg, 57%) as a viscous oil, whose spectral data was identical with those of a sample prepared from **10** by thermolysis. ^{1}H-NMR ($CDCl_3$) δ: 1.80—3.17 (6H, m), 2.18 (3H, s, SMe), 2.51 (3H, s, NMe), 3.08 (1H, d, J=18.7 Hz, H-10β), 3.39—3.45 (1H, m, H-6), 3.41 (1H, dd, J=3.1, 6.2 Hz, H-9), 3.85 (3H, s, OMe), 4.95 (1H, d, J=0.5 Hz, H-5), 5.48 (1H, dd, J= 1.5, 10.0 Hz, H-8), 5.77—5.94 (1H, m, H-7), 6.56, 6.69 (2H, ABq, J=8.4 Hz, H-1 and 2). MS m/z: 329 (M^+, 10), 282 (100). $[\alpha]_D^{27}$ −204.3° (c=0.64, $CHCl_3$).

Reactions of the Xanthate (3) and the Dithiocarbonate (6) with Tetrakis(triphenylphosphine)palladium——A mixture of a solution of **3** (200 mg, 0.43 mmol) in $CHCl_3$ (10 ml) and 149 mg (0.13 mmol) of $(Ph_3P)_4Pd$ was stirred at room temperature for 10 h, then the solvent was evaporated off *in vacuo*. Column chromatography of the residue on silica gel with $CHCl_3$–MeOH (16 : 1) gave 6-demethoxythebaine (**17**, 18 mg, 15%), which was identical with an authentic sample prepared by Rapoport's method.[23]

Reaction of **6** (200 mg, 0.43 mmol) using 149 mg of $(Ph_3P)_4Pd$ followed by similar work-up and column chromatography afforded **17** (94 mg, 78%).

Reaction of Dithiocarbonates (6 and 9) with Titanium(IV) Chloride——A 1.0 M dichloromethane solution of $TiCl_4$ (0.86 ml) was added of **6** (200 mg, 0.43 mmol) in dichloroethane (25 ml), and then the mixture was refluxed for 10 h under Ar. The resulting mixture was poured into ice-water, rendered alkaline with NH_4OH and extracted with

$CHCl_3$. The extract was washed with brine, dried and evaporated *in vacuo*. Preparative TLC of the brown residue on silica gel with EtOAc–MeOH (30 : 1) afforded **18** (38 mg, 24%) which was recrystallized from EtOH to give colorless needles, mp 138—140 °C. IR ($CHCl_3$): 3530, 1640, 880 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.72 (1H, dt, J=4.6, 12.5 Hz, H-15). 1.96 (1H, ddd, J= 1.9, 3.5, 12.5 Hz, H-15), 2.18 (1H, dt, J=3.5, 12.2 Hz, J-16), 2.41, (3H, s, NMe), 2.58 (1H, ddd, J=1.9, 4.6, 12.2 Hz, H-16), 2.67 (1H, dd, J= 1.6, 3.9 Hz, H-14), 2.75 (1H, dd, J=4.6, 17.8 Hz, H-10α), 3.08 (1H, d, J=17.8 Hz, H-10β), 3.14 (1H, dd, J=3.9, 4.6 Hz, H-9), 3.86 (3H, s, OMe), 4.46 (1H, td, J=1.6, 5.1 Hz, H-8), 4.62 (1H, ddd, J=1.9, 2.1, 5.1 Hz, H-7), 5.54 (1H, ddd, J=1.6, 1.9, 10.3 Hz, H-6), 6.56, 6.69 (2H, ABq, J=8.4 Hz, H-1 and 2), 6.98 (1H, dd, J=2.1, 10.3 Hz, H-5). MS m/z: 375 (M^+, 100) 282 (66), 178 (92), 59 (90). $[\alpha]_D^{26}$ −260.2° (c=1.58, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{21}NO_3S_2$: C, 60.77; H, 5.63; N, 3.73. Found: C, 61.01; H, 5.68; N, 3.54.

Reaction of **9** (106 mg, 0.24 mmol) using a 1.0 M dichloromethane solution (0.48 ml) of $TiCl_4$ followed by similar work-up and preparative TLC afforded **19** (75 mg, 84%), which was recrystallized from EtOH to give colorless needles, mp 243—244 °C. IR ($CHCl_3$): 3520, 1640, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.84 (1H, dt, J=4.6, 12.7 Hz, H-15), 2.00 (1H, ddd, J=1.8, 3.3, 12.7 Hz, H-15), 2.14 (1H, dt, J=3.3, 11.7 Hz, H-16), 2.43 (3H, s, NMe), 2.48 (1H, dd, J=5.8, 18.5 Hz, H-10α), 2.58 (1H, ddd, J=1.8, 4.6, 11.7 Hz, H-16 , 2.66 (1H, dd, J=3.9, 12.3 Hz, H-14), 3.04 (1H, d, J=18.5 Hz, H-10β), 3.43 (1H, dd, J=3.9, 4.4 Hz, H-9), 3.86 (3H, s, OMe), 3.89 (1H, dd, J=5.4, 12.3 Hz, H-8), 4.91 (1H, ddd, J=1.2, 4.2, 5.4 Hz, H-7), 5.75 (1H, dd, J=4.2, 10.2 Hz, H-6), 6.62, 6.73 (2H, ABq, J=8.4 Hz, H-1 and 2), 6.91 (1H, dd, J=1.2, 10.2 Hz, H-5). MS m/z: 375 (M^+, 19), 282 (100), 178 (20), 60 (34). $[\alpha]_D^{26}$ +13.6° (c=1.13, $CHCl_3$); *Anal.* Calcd for $C_{19}H_{21}NO_3S_2$: C, 60.77; H, 5.63; N, 3.73. Found: C, 60.61; H, 5.63; N, 3.76.

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