185–186° dec (lit.[17] mp 181.5–182.5°).

Dihydrothebainone (**1a**) may be converted to codeinone (**5a**) without purification of intermediate products. Beginning with 6.08 g (20.4 mmol) of **1a**, 5.14 g (85.5%) of crude **5a** was recovered: mp 161–170°. Recrystallization of a portion returned 71% of pure codeinone, mp 184–185°.

Codeine (2) was prepared from codeinone (**5a**) as described.[6]

Dihydrocodeinone Enol Acetate (21). Dihydrocodeinone (1.5 g, 5.02 mmol) was converted to **21** as directed.[18] The yield was 1.17 g (69%), mp 150–152°, from benzene–hexane (1:5) (lit.[18] mp 153–153.5°).

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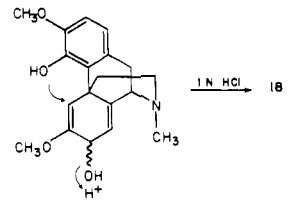

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Conversion of Thebaine to Codeine

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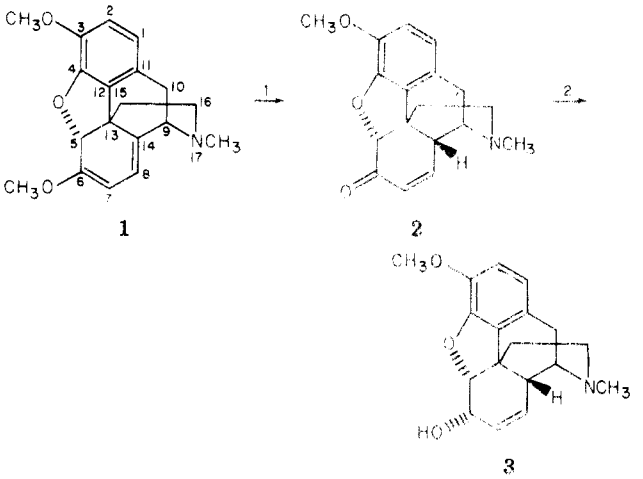
An improved conversion of thebaine to codeine has been developed. Oxymercuration of thebaine with mercuric acetate in refluxing methanol, followed by hydrolysis of the intermediate 7-acetomercurineopinone dimethyl ketal with 3 N acetic acid, or, alternatively, reduction of the organomercury compound with sodium borohydride and mild acid hydrolysis of the resulting neopinone dimethyl ketal, gives neopinone in 95–100% yields. Either acid- or alkali-catalyzed isomerization to codeinone leads to the equilibrium mixture consisting of codeinone–neopinone, 3:1. Complete conversion to codeinone in 85–90% yield results from treatment of neopinone with anhydrous hydrogen chloride or hydrogen bromide in ether–methylene chloride, followed by elimination of hydrogen halide from the intermediate 8-halodihydrocodeinone. The known borohydride reduction of codeinone then gives codeine in 85% overall yield from thebaine.

Codeine is among the most effective and widely used analgesic and antitussive agents. For this reason, most of the morphine isolated along with codeine from *Papaver somniferum* is converted to codeine for medicinal use. Although thebaine is the least abundant among the hydrophenanthrene alkaloids in *P. somniferum*, its conversion to codeine is also of medicinal importance. At present, the most efficient conversion of thebaine to codeine is claimed to proceed in 74% yield.[1] The potential importance of a highly effective thebaine to codeine conversion becomes even more significant when applied to *P. bracteatum*[2] in which thebaine is the major alkaloid and which is actively being considered as a domestic raw material for codeine.[3] These considerations have led us to reexamine this conversion, and we now report a facile new method for obtaining codeine from thebaine in 85% yield.

Conversion of thebaine to codeine involves two fundamental steps: (1) transformation of the dienol ether of thebaine (**1**) to the α,β-unsaturated ketone codeinone (**2**)

and (2) reduction of the α,β-unsaturated ketone to the allylic alcohol codeine (3). Step 2 has been achieved[4] and



1 2 3

proceeds stereospecifically in almost quantitative yield with sodium borohydride in methanol. The difficulty and losses in the overall conversion therefore lie in step 1.

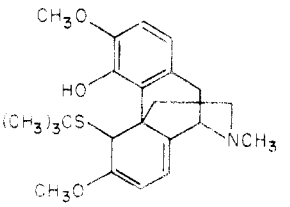
The literature teaches five methods for the conversion of thebaine to codeinone. Three of these methods involve the intermediate 14-bromocodeinone which is reportedly prepared in 85% yield from thebaine.[5,6] 14-Bromocodeinone can be reduced to codeinone by treatment with zinc dust and acetic acid (30%),[7] iron dust and dilute sulfuric acid,[6] or by catalytic reduction to neopinone and isomerization to codeinone with activated charcoal (46%).[5] A fourth method, which is the poorest and proceeds in 5% yield, involves direct acid hydrolysis to thebaine with dilute sulfuric acid.[8] The best reported method[1] involves the addition of 2 mol of anhydrous hydrogen bromide or chloride to thebaine to form 6,8-dibromotetrahydrothebaine, followed by alkaline hydrolysis and dehydrohalogenation to codeinone.

Discussion

In our search for a method of cleaving the enol ether, we have investigated three approaches: (a) enol ether exchange to form a more easily cleaved ether, (b) selective nucleophilic cleavage of the 6-OCH_3, and (c) the addition of an electrophile (i.e., oxymercuration) to the diene with subsequent reduction and hydrolysis. Enol ether exchange was attempted with mercuric acetate[9] and bis(benzonitrile)-palladium chloride[10] as catalysts. Both times benzyl alcohol was used as the exchanging alcohol but either no reaction or decomposition occurred.

The second approach (nucleophilic cleavage) was undertaken with some apprehension, since thebaine has three ether groups, the 3-OCH_3, the 6-OCH_3, and the 5-*O*-allylic ethers. Attack at any or all three positions is possible. However, the report[11] that sodium benzyl mercaptide in dimethylformamide had selectively cleaved a methyl enol ether in the presence of a methyl and benzyl aryl ether supported the possibility that selective cleavage of the *O*-6-methyl enol ether in thebaine might occur. The example cited may be a special case, though, since the enol ether involved has an α-cyano and β-phenyl substituent.

When thebaine was treated with sodium benzyl mercaptide, several products in addition to starting material were observed by TLC, and all had incorporated a benzyl group as observed by NMR. Evidently attack had occurred at C-5. In an attempt to sterically impede attack at this position, the reaction was repeated using a more hindered nucleophile, sodium *tert*-butyl mercaptide. Two products in equal amounts were observed, as well as starting material. One was identified as oripavine, resulting from attack at the 3-*O*-methyl aryl ether. The other product was established as 6,7,8,14-tetradehydro-3,6-dimethoxy-4-hydroxy-5-*tert*-butylthio-17-methylmorphinan (4), resulting from cleavage of the 5-*O*-allylic ether.



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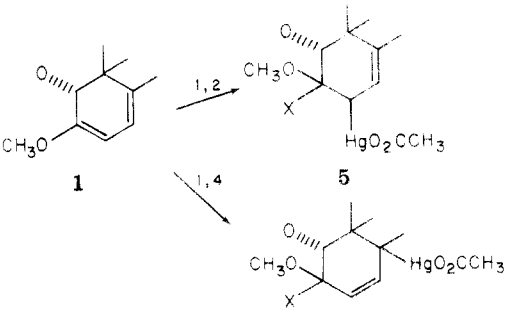
This total absence of enol ether cleavage was surprising. Nucleophilic attack at the allylic ether had been significantly decreased by using *tert*-butyl mercaptide, and it is conceivable that an efficient conversion of thebaine to oripavine could be effected using an even more hindered mercaptide, but this was not pursued. Nucleophilic cleavage of the 3-*O*-methyl ether was suggestive of a potential improved method for the conversion of codeine to morphine.[12] This reaction was explored, and although codeine was in part consumed, no morphine was obtained.

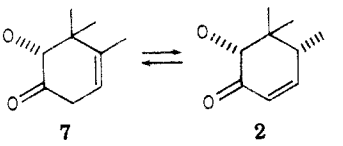
The third approach to cleavage of the enol ether was to add an electrophile to the diene of thebaine, either 1,4 or 1,2. This approach has been used before, employing water,[8] bromine,[5,6] hydrogen bromide, and hydrogen chloride.[1] These methods, however, involve the use of relatively strong acid; most of the side products are alkali soluble and contain one or more of the known rearranged derivatives,[5,13] thebenine, morphothebaine, and the metathebainone precursor.[14] Mercuric acetate, on the other hand, was the electrophile of our choice, since it is known to readily add to olefins[15] and is a very mild acid.

The addition of mercuric acetate could occur in two modes, either 1,2 to give **5** or 1,4 to give **6**. We first investigated the use of water–tetrahydrofuran as a solvent



1 5 6, X = OH, OCH_3

at reflux. Reaction occurred slowly to give a mixture of neopinone (**7**) and codeinone (**2**) in the ratio 3:1. These data do not differentiate between the two possible modes of addition in the oxymercuration since isomerization of the unsaturated ketones is possible and/or cleavage of the C–Hg bond may have occurred with rearrangement.



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To resolve the question of mode of addition, methanol was used as the solvent, thereby stabilizing the intermediate mercury compound **5** and/or **6** (X = OCH_3) as the dimethyl ketal instead of the previous hemiketal inter-

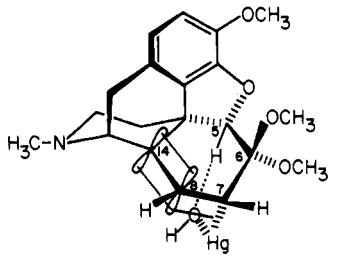


Figure 1. Stereochemistry of the major isomer of 7-hydroxymercurineopinone dimethyl ketal.

mediate (X = OH). With the change of solvent we also hoped to increase the rate of reaction due to enhanced solubility. When thebaine was treated with mercuric acetate in refluxing methanol, reaction was complete after 30 min. The organomercuri product could be isolated and characterized as the bromide of **5** or **6** by addition of bromide ion to displace the acetate. NMR analysis showed the presence of two compounds. Since a total of only one vinyl proton was present, **6** is eliminated as a possible intermediate since it contains two vinyl protons.

The two compounds, observed in the ratio 2:1, are isomers of **5**, epimeric at C-7, and were analyzed as the 7-hydroxymercuri derivatives. From the chemical shifts of the 7-hydroxymercurineopinone dimethyl ketal (Table I), a reasonable stereochemical assignment can be made. In the major isomer, the C-5 proton absorbs at δ 4.90 which is a 0.17- and 0.23-ppm shift downfield from the minor isomer and from neopinone dimethyl ketal, respectively. This can be explained by hydrogen bonding of the Hg–O–H with the C-5 proton in a six-membered ring if the Hg–O–H is β or cis to the C-5 proton as shown in Figure 1. When the 7-hydroxymercuri is α, the effect should be very small, as was seen with only a 0.06-ppm downfield shift for the C-5 proton of the minor isomer.

The chemical shift of the C-8 proton in the major isomer is δ 5.60, which is a 0.33- and 0.22-ppm downfield shift from the minor isomer and neopinone dimethyl ketal, respectively. When the 7-mercuri is β, the C-7–Hg bond is nearly coplanar with the π-electron cloud of C-8 and C-14, thus allowing π-bond interaction with the extensively polarized C-7–Hg σ bond or "σ–π conjugation". Such shifts are not uncommon.[16,17] This is not the case, when the mercury is α. The C-7–Hg bond is almost orthogonal to the π system, therefore having little effect on the C-8 proton.

An attempt was made to prepare a mixed methyl benzyl ketal by performing the reaction in benzyl alcohol; however, addition did not occur as readily.

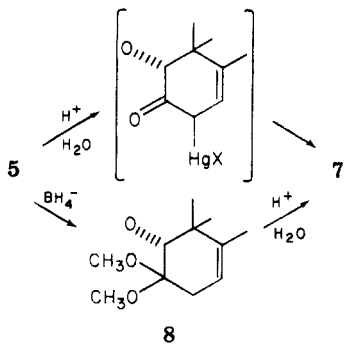
Hydrolysis of the ketal and the reduction of the C–Hg bond of **5** could be performed in either one or two steps. Reduction of **5** with sodium borohydride gave an excellent yield of neopinone dimethyl ketal[18] (**8**) which could be hydrolyzed to neopinone (**7**) with aqueous formic or acetic acid. The entire operation could be performed in one step by treatment of **5** with aqueous formic or acetic acid at room temperature with an overall yield of 95–100% from thebaine. This facile hydrolysis of the carbon–mercury bond indicates that the first step is probably ketal to ketone hydrolysis since α-keto organomercuri compounds are known to cleave readily whereas others are more stable to acid.

To convert neopinone (**7**) to codeinone (**2**) we first investigated the equilibrium between these two isomers. Equilibration was easily established with aqueous formic acid or sodium bicarbonate. The equilibrium mixture at various temperatures was always a mixture of codeinone and neopinone in the ratio 3:1. Attempts at equilibration

Table I. Proton NMR Assignments

Compound	N-CH_3	3-OCH_3	6-OCH_3	1,2	5	7[b]	8[b]
Thebaine (**1**)	2.43	3.83	3.57	6.57	5.24	5.52 (J = 6)	4.97 (J = 6)
Neopinone (**7**)	2.47	3.88		6.65	4.95		5.45 (J = 6, 2)
Neopinone dimethyl ketal (**8**)	2.43	3.90	2.95, 3.48	6.60	4.67		5.38 (J = 3)
Codeinone (**2**)	2.47	3.87		6.63	4.67	6.07	6.69 (J_{14} = 3, J_8 = 11)
Codeinone dimethyl ketal	2.33	3.72	3.00, 3.34	6.41	4.58	5.41	5.41
7-Hydroxymercurineopine dimethyl ketal							
Major isomer	2.43	3.90	2.92, 3.50	6.60	4.90		5.60 (J = 6.5)
Minor isomer	2.43	3.90	2.92, 3.53	6.60	4.73		5.27 (J = 6.5)
7-Bromomercurineopinone dimethyl ketal (**5**, Br replaces CH_3CO_2)							
Major isomer	2.42	3.88	2.88, 3.50	6.62	4.78		5.65 (J = 6.5)
Minor isomer	2.42	3.88	2.88, 3.50	6.62	4.78		5.35 (J = 6.5)
8-Chlorodihydrocodeinone hydrochloride (**9**, X = Cl)							
Isomer A	3.07	3.83		6.87			
Isomer B	3.07	3.90		6.87			
8-Bromodihydrocodeinone hydrobromide (**9**, X = Br)							
Isomer A	3.07	3.90		6.87			
Isomer B	3.07	3.85		6.87			
Oripavine	2.48		3.60	6.63	5.18	5.60 (J = 6)	5.07 (J = 6)
6,7,8,14-Tetradehydro-3,6-dimethoxy-4-hydroxy-5-*tert*-butylthio-17-methylmorphinan (**4**)[a]	2.47	3.80	3.57	6.60	5.25	5.77 (J = 6.5)	4.80 (J = 6.5)

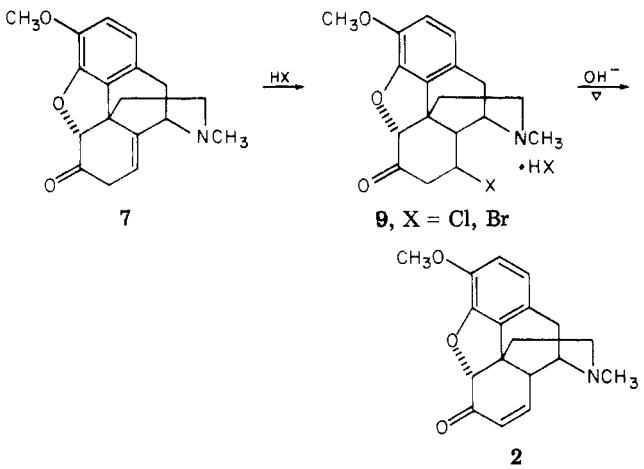
[a] Compound **4** also shows absorption at δ 1.48 [s, 9 H, 4-$(CH_3)_3CS$–]. [b] J values in hertz.



or isomerization under anhydrous condition with aluminum isopropoxide or toluenesulfonic acid failed.

Another approach for converting neopinone to codeinone was formation of a dienamine from neopinone which upon hydrolysis and kinetic protonation might give a mixture more favorable to codeinone. Codeinone pyrrolidininenamine (**10**) was prepared from neopinone in 70% yield using the procedure previously applied to codeinone.[19] When **10** was hydrolyzed using 3 N acetic acid, a 3:1 mixture of neopinone and codeinone was obtained. Protonation via the codeinone–neopinone enolate was also investigated; however, this also led to a 2:1 mixture of neopinone and codeinone. Thus, kinetic protonation favors neopinone formation.

The final approach was to convert neopinone to β-halodihydrocodeinone (**9**), which upon alkaline treatment under nonequilibrating conditions would produce co-



deinone. This can be accomplished by treatment of neopinone with anhydrous hydrogen chloride or bromide to form the intermediate β-halo ketone, followed by treatment with aqueous sodium hydroxide and elimination to codeinone. In the case of hydrogen chloride, rapid equilibration is most likely set up followed by 1,4 addition of hydrogen chloride to the α,β-unsaturated carbonyl of codeinone, thus driving the equilibrium to codeinone. With hydrogen bromide this may also be the reaction mechanism; however, there is the possibility of anti-Markownikoff addition to the $\Delta^{8,14}$ double bond. The use of strong acids at this stage is permissible since the C-4,5-α-epoxy bridge is no longer allylic.

Inspection of the NMR data (Table I) for the 8-halodihydrocodeinone hydrohalides clearly shows the presence of two methoxy groups and thus two isomers. In both cases (Cl and Br) the two isomers occur in similar amounts and must be the result of epimeric halogen at C-8.

Reduction of codeinone to codeine with sodium borohydride in methanol proceeded well (90–95% yield) as reported.[4] The overall yield of codeine from thebaine without purification of any of the intermediates was 85%.

Experimental Section[20]

Reaction of Thebaine with Sodium *tert*-Butyl Mercaptide. Formation of Oripavine and 6,7,8,14-Tetradehydro-3,6-dimethoxy-4-hydroxy-5-*tert*-butylthio-17-methylmorphinan (4). Sodium hydride (384 mg, 8.0 mmol, as a 51% oil dispersion) was washed with hexane (3 × 20 ml) and then dispersed in 5 ml of DMF. To this dispersion was added a solution of *tert*-butyl mercaptan (0.25 ml, 2.2 mmol) in 2 ml of DMF over a period of 1 min, followed by a solution of thebaine (622 mg, 2.0 mmol) in 3 ml of toluene and 4 ml of DMF, and the mixture heated at 80° for 24 h under N_2. The reaction was quenched by adding 0.3 N HCl to extract the alkaloids and washing several times with ether to remove the *tert*-butyl mercaptan and DMF. Adjustment of the pH to 8.5, extraction with chloroform, and evaporation of the chloroform resulted in 647 mg of an oil. A portion of this material (434 mg) was chromatographed by preparative TLC ($CHCl_3$–MeOH, 85:15) and two bands were collected: thebaine (147 mg, R_f 4.2) and product (94 mg, R_f 2.1). The product was chromatographed again to give 62 mg which by NMR consisted of equal amounts of two components. This material was dissolved in chloroform and washed with 0.2 N NaOH. The aqueous extract was adjusted to pH 8.5 and extracted with chloroform to give 12 mg of oripavine as identified by NMR (Table I). The original chloroform layer gave 28 mg of **4**: NMR, see Table I; uv λ_{max} (C_2H_5OH) 290 nm; high-resolution MS *m/e* 401.2030 ($C_{23}H_{31}O_3NS$, 401.2036).

Reaction of Thebaine (1) with $Hg(OAc)_2$ in Aqueous THF. A solution of thebaine (311 mg, 1.0 mmol) in 10 ml of THF was added via syringe to a stirred suspension of mercuric acetate (319 mg, 1.0 mmol, crystallized from C_2H_5OH) in 5 ml of water and heated to reflux under N_2. After 3 h, another equal portion of mercuric acetate in 5 ml of H_2O and 10 ml of THF was added. After 7 h, saturated aqueous NaCl was added, the mixture was extracted with chloroform (3 × 50 ml), and the chloroform was evaporated to yield 118 mg of an oil. The NMR of this material is that of a mixture of neopinone and codeinone in the ratio of 1:3 by integration of the 5β protons. Reduction of this material with $NaBH_4$ gave a mixture of neopine and codeine (1:3).

7-Bromomercurineopinone Dimethyl Ketal (5, X = OCH_3; Br Replaces CH_3CO_2). A solution of thebaine (311 mg, 1.0 mmol) in 10 ml of methanol was added to a suspension of mercuric acetate (478 mg, 1.5 mmol, crystallized from ethanol) in 10 ml of methanol at reflux under N_2 with stirring for 30 min. The hot mixture was filtered, the precipitate was washed with a small amount of methanol, and the filtrate was evaporated to a residue of 921 mg. This residue was taken up in $CHCl_3$, washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and filtered, and the solvent was evaporated to give 325 mg which by NMR (Table I) was a mixture of epimers at C-7. This compound is 7-hydroxymercurineopinone dimethyl ketal resulting from the aqueous alkaline wash. It was taken up in 4 ml of methanol, filtered through a millipore filter, and treated with a saturated aqueous solution of KBr to give a grey precipitate which was removed by filtration. The filtrate was concentrated to remove the methanol and the resulting aqueous mixture was extracted with chloroform. The chloroform extracts were washed with water, dried over Na_2SO_4, filtered, and evaporated to give 278 mg of residue which was recrystallized from methanol to give the major isomer: mp 140–145° dec; NMR, see Table I; $[\alpha]_D$ −599.7° ($CHCl_3$). Anal. ($C_{20}H_{24}NO_4HgBr$) C, H, N.

Hydrolysis of 7-Bromomercurineopinone Dimethyl Ketal. 7-Bromomercurineopinone dimethyl ketal (100 mg, 0.16 mmol) was mixed with 3 N formic acid (100 ml) and stirred at 20° for 21 h. The reaction mixture was cooled to 0° and adjusted to pH 10 with 3 N NaOH in the presence of chloroform. Separation of the chloroform layer and further extractions of the aqueous layer with chloroform gave, after washing with water, drying over Na_2SO_4, filtering, and evaporating, a residue of 49 mg (100%) of an oil which by NMR was a mixture of codeinone–neopinone (3:1).

Conversion of Neopinone (7) to Codeinone (2) via 8-Bromo- and 8-Chlorodihydrocodeinone (9). A solution of neopinone [7, 100 mg, 0.336 mmol, containing about 25% codeinone (**2**)] in 0.45 ml of methylene chloride at 0° was treated with anhydrous

Table II

Starting material	Time	Temp, °C	Codeinone–neopinone ratio in product
Codeinone	44 h	60	75:25
Codeinone	13 days	23	74:26
Neopinone–codeinone (80:20)	4 h	90	75:25
Neopinone–codeinone (80:20)	5 days	40	75:25

HBr in ether (0.45 ml, 2.4 g of HBr–10 ml of Et_2O) for 5 min. A precipitate formed immediately upon the addition of the HBr–Et_2O. The reaction was quenched by partitioning between 0.2 N NaOH and chloroform, the aqueous phase was extracted with several protions of chloroform, and the chloroform extracts were combined, washed with water, dried over Na_2SO_4, filtered, and evaporated to give 95 mg of product, 100% codeinone as analyzed by NMR (Table I) and reduction to codeine with sodium borohydride[4] and analysis of the codeine by GC. When dimethoxyethane was used as solvent instead of ether, the product still contained neopinone. Neopinone could be converted to codeinone using 0.45 ml of HCl–Et_2O (1.1 g of HCl–10 ml of ether) at room temperature for 30 min instead of HBr–Et_2O at 0° for 5 min.

The intermediate 8-halodihydrocodeinone hydrohalides could be isolated by evaporating the reaction solvents and crystallization of the resulting solid from methanol; NMR's for the bromo and chloro compounds were similar, each indicating the presence of two isomers in equivalent amounts, epimers at C-8, by two 3-OCH_3 absorptions. The chloro compound gave the correct elemental analysis. Anal. ($C_{18}H_{21}NO_3Cl_2$) C, H, N.

Conversion of Thebaine (1) to Neopinone (7). A solution of thebaine (1.00 g, 3.22 mmol) in 40 ml of methanol was added to a stirred suspension of mercuric acetate (1.54 g, 4.82 mmol, 150 mol %) in 30 ml of methanol at reflux under N_2. After 50 min of reflux, the warm mixture was filtered and the solvent evaporated to give 2.67 g of residue which was taken up in 100 ml of 3 N acetic acid and stirred at room temperature under N_2 for 100 min at which time 70 ml of saturated aqueous KBr was added. The precipitated mercury salts were removed by filtering through filter-aid after stirring for 1 h, 50 ml of chloroform was added to the filtrate, the mixture was cooled to 0°, and the pH of the aqueous phase was adjusted to ~12 with concentrated aqueous NaOH. The chloroform layer was separated, the aqueous layer was washed with several portions of chloroform, the chloroform extracts were combined, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and evaporated, and a residue of 0.995 g, 100% yield, of crystalline neopinone was obtained. Subsequent reaction on a 3.0-g scale gave 97% of neopinone: NMR, see Table I. If care is not taken during the isolation procedure, some isomerization results, giving a codeinone–neopinone mixture.

Direct Conversion of Neopinone (7) to Codeine (3). Applying the procedure described above via 8-chlorodihydrocodeinone (9) to pure neopinone, the crude codeinone so obtained was immediately reduced with sodium borohydride in methanol.[4] Crystalline pure codeine, identical with an authentic sample in melting point and GC and NMR spectrum, was obtained in 90% overall yield from neopinone on a 3-g scale.

Neopinone Dimethyl Ketal (8). A solution of thebaine (311 mg, 1.0 mmol) in 10 ml of methanol was added to a mixture of mercuric acetate (637 mg, 2.0 mmol) in 10 ml of methanol at reflux under N_2. After 35 min of reflux, the reaction mixture was cooled to 0°, 10 ml of 3 N NaOH was added, and then the mixture was treated with 10 ml of 3 N NaOH that was 0.5 M in $NaBH_4$. Evaporation of the methanol, extraction of the aqueous phase with chloroform, and evaporation of the $CHCl_3$ gave 382 mg of an oil which was further purified by chromatography on silica ($CHCl_3$–MeOH, 85:15) and Kugelrohr distillation [90° (0.1 mmHg)] to give 214 mg of neopinone dimethyl ketal (8) as a colorless oil: NMR, Table I, similar to lit.[18] values; $[\alpha]_D$ –661.9° ($CHCl_3$). Anal. ($C_{20}H_{25}NO_4$) C, H, N.

Table III. Chromatographic Systems and Constants

Compound	TLC, R_f[a]	GC, R_T, min[b]
Thebaine (1)	0.45	7.2[c]
Neopinone (7)	0.38	*d*
Neopinone dimethyl ketal (8)	0.60	7.4[e]
Codeinone (2)	0.38	*f*
Codeine (3)	0.25	5.8,[c] 10.2[g]
Neopine	0.23	7.0,[c] 12.0[g]
Oripavine	0.20	
6,7,8,14-Tetradehydro-3,6-dimethoxy-4-hydroxy-5-*tert*-butylthio-17-methylmorphinan (4)	0.15	

[a] TLC on Camag Kieselgel, D-5 with 5% $CaSO_4$ and 1% w/w Electronic Phosphor Type P-1 (General Electric Co.) with $CHCl_3$–MeOH (85:15) as eluent; visualized by uv and iodoplatinate reagent. [b] GC on 6-ft column; OV-25 on Chromosorb W; He, 67 ml/min; all glass system. [c] T = 251°. [d] Analyzed by reducing with $NaBH_4$ and analyzing as neopine. [e] T = 210°. [f] Analyzed by reducing with $NaBH_4$ and analyzing as codeine. [g] T = 221°.

Hydrolysis of Neopinone Dimethyl Ketal (8). Neopinone dimethyl ketal (255 mg, 0.75 mmol) was mixed with 20 ml of 3 N formic acid and stirred at 20° under N_2. Aliquots, reduced with $NaBH_4$ and analyzed by GC for the disappearance of 8 and the appearance of codeine and neopine, showed that the reaction was complete after 4 days. The reaction was then quenched by basifying with saturated aqueous K_2CO_3 in the presence of $CHCl_3$. The chloroform layer was separated, the aqueous layer was extracted again with $CHCl_3$, and the combined $CHCl_3$ extracts were washed with water, dried over Na_2SO_4, filtered, and evaporated to give 200 mg of oil which was a mixture of neopinone and codeinone, 3:1.

Equilibration of Neopinone (7) and Codeinone (2) with Aqueous Acid. All equilibrations were performed in 3 N formic acid on a 1–2% solution of unsaturated ketone and under N_2, except for the equilibration at 90° in which 3 N chloroacetic acid was used (Table II).

Equilibration of Neopinone (7) and Codeinone (2) with Aqueous Alkali. Codeinone (150 mg, 0.505 mmol) in 2 ml of chloroform was shaken with 10 ml of saturated aqueous $NaHCO_3$ at room temperature for 22 h. The organic phase was separated and evaporation gave 142 mg of material which by NMR was codeinone–neopinone (74:26). This material was resubjected to the above conditions at 0° for 72 h to give 130 mg of material which by NMR was codeinone–neopinone (75:25) (Table III).

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(20) Solvent evaporations were carried out in vacuo using a Berkeley rotary evaporator. All melting points are uncorrected. Nuclear magnetic resonance spectra were taken in $CDCl_3$, and mass spectra were obtained on CEC 103 and 110B instruments. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Modification of the 5′ Position of Purine Nucleosides. 1. Synthesis and Biological Properties of Alkyl Adenosine-5′-carboxylates

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A series of esters of adenosine-5′-carboxylic acid has been prepared. Most of the compounds were nontoxic, causing prolonged increases in coronary sinus PO_2 when administered to anesthetized dogs; the ethyl ester was most active. Nitrosation and oxidation of the ethyl ester **12** gave respectively inactive inosine ethyl ester **30** and the fairly active N^1-oxide ethyl ester **29**.

The overall pharmacological profile of ethyl adenosine-5′-carboxylate (**12**) has been reported.[2-5] Evaluation of **12** in animals shows a profile of activity which suggests possible antianginal properties in man. Thus, **12** represents a new type of relatively nontoxic potent coronary vasodilator,[5] orally active in the dog. Currently, **12** is undergoing extensive clinical evaluation as a potential antianginal agent.

Studies aimed at delineating the structure–activity relationships of esters of adenosine-5′-carboxylic acid (**8**) are reported in this paper.

Chemistry. The synthetic steps leading to the formation of the esters (**4–7**, Table I) of 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid[6,7,11] are outlined in Scheme I. Similarly, the esters (**11–25**, Table II) of adenosine-5′-carboxylic acid (**8**)[6-11] were prepared by the reaction of appropriate alcohols with an uncharacterized acid chloride **9** (obtained from **8** and $SOCl_2$) or alternatively by other methods summarized in Scheme II.

Since a wide variety of esters were desired for pharmacological screening, an extensive study of esterification methods was made. Four different methods were required for the preparation of the esters listed in Tables I and II.

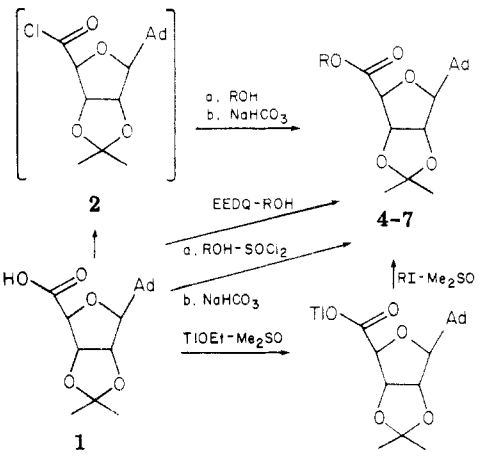
The thallous ethoxide method, which was used first, was found to be inconvenient due to the poor solubility of the intermediate thallous salts obtained from **1** and **8**.

Esterification of **1** and **8** with alcohols in the presence of $SOCl_2$ proceeded normally in most cases. However, in some cases, as in the esterification of **1** with 2-propanol and 1-butanol, the isopropylidene group was cleaved to the extent of 30–40%.

The carboxylic acids (**1** and **8**) on treatment with $SOCl_2$ gave the uncharacterized acid chlorides **2** and **9**. Reaction of **2** and **9** with the appropriate alcohol followed by $NaHCO_3$ was the next method of choice. However, in this case, traces of water in the alcohol caused the formation of varying amounts of the acids (**1** and **8**) as by-products.

The attempted synthesis of the 5′-*N*-alkylamide of **1** using an aliphatic amine and EEDQ in alcohol as a solvent gave a mixture of amide and ester (corresponding to the alcohol used). This observation led to the use of EEDQ as an esterification catalyst, as in the preparation of the *sec*-butyl ester **7**.

Scheme I



Ad = 9-adenyl

It was also observed that boiling ethanol or methanol in the presence of a small amount of benzene converted the β-chloroethyl ester **10** into the ethyl (**13**) or the methyl (**11**) ester in less than 30 min. The methyl ester **11** itself was unaffected even after a 24-h reflux period in ethanol. Use of a β-chloroethyl ester for such a mild ester interchange does not appear to have been reported before.

The 6-NH_2 group of **12** was smoothly deaminated by nitrosation in dilute acetic acid to give ethyl inosine-5′-carboxylate (**30**, Table III) in high yield. Another route for the preparation of **30** was by the esterification of inosine-5′-carboxylic acid.[12,13]

Oxidation of **1** by H_2O_2–AcOH gave adenosine-5′-carboxylic acid N^1-oxide (**28**) in good yield. The latter, on esterification, gave **29** (Table III), the desired N^1-oxide of **13**. Details of the methods are described in the Experimental Section.

Nuclear Overhauser studies[18] of the most active ester, **12**, show that there is 11.4% enhancement of H-8 reso-