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A Practical Synthesis of Codeine from Dihydrothebainone

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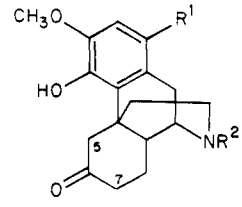
The conversion of dihydrothebainone to codeine or thebaine has been achieved in high yield. Bromination and dehydrobromination constructs the 4,5-oxide bridge to give 1-bromo- and 1,7-dibromodihydrocodeinone which yield dihydrocodeinone practically quantitatively after catalytic debromination. Ketalization and acid-catalyzed elimination of methanol give excellent yields of Δ^6-dihydrothebaine to which is added methyl hypobromite using *N*-bromoacetamide in methanol. The action of potassium *tert*-butoxide in Me_2SO on the resulting 7-bromodihydrocodeinone dimethyl ketal gives codeinone dimethyl ketal selectivity at 60° while at 120° thebaine is the exclusive product. Hydrolysis to codeinone and borohydride reduction give codeine in 70% overall yield. The bromo intermediates in the formation of the 4,5-oxide bridge have been examined. 1,5β,7α-Tribromodihydrothebainone has been identified as the main product in the tribromination of dihydrothebainone.

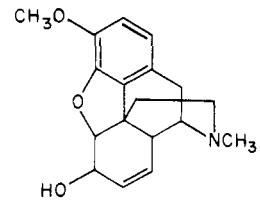
The search for a practical synthesis of dihydrothebainone (**1a**) has persisted since the initial report[1] that **1** could be converted, although in quite low yield, into codeine (**2**). Most approaches have attempted to exploit the Grewe-type[2] morphinan synthesis which readily gives the complex carbon skeleton of morphine from a much simpler benzyloctahydroisoquinoline such as **3**.[3] In the case where R^1 = H (**3a**), cyclization proceeded to give overwhelmingly the wrong isomer,[3a] that is, closure para to the OH group. This mode was successfully blocked with a 1-methyl substituent, **3b**, which gave an excellent yield of the ortho isomer **1b**.[3b] In order to project these modifications to a successful synthesis of the natural product, a removable nondeactivating blocking group is necessary at R^1 in structure **3**; as yet this has not been achieved.[3c]

Should a reasonable synthesis of dihydrothebainone (**1a**) be accomplished, there still remains the problem presented by the very low conversions reported for **1a** to codeine (**2**). Also, a number of thebaine transformations result in dihydrothebainone as a by-product, and these would profit from a feasible conversion to codeine. In this report, we now present a highly efficient process for synthesizing codeine from dihydrothebainone.

There are two general considerations in such a process, namely, the closure of the 4,5-oxide ring and introduction of the 7,8 double bond. The first has been achieved in several ways,[4] the most thoroughly studied path being via bromination–dehydrobromination reactions.[5] Good yields of 1-bromodihydrocodeinone (**4b**) have been obtained.[5f,g] However, introduction of the α,β-unsaturation was extremely poor. For example, the procedure using 2,4-dinitrophenylhydrazine on 1,7-dibromodihydrocodeinone (**4c**) gave overall conversions of 7% from **1a** to **5b**.[1] Removal of bromine at C-1 required drastic conditions (lithium aluminum hydride in refluxing tetrahydrofuran) and led to a 71% yield for the final reduction to codeine,[1,6] 5% overall. Alternatively, the C-1 bromine could be selectively and quantitatively removed at the dihydro stage,



1a, R^1 = H; R^2 = CH_3
b, R^1 = CH_3; R^2 = CHO
c, R^1 = Br; R^2 = CH_3



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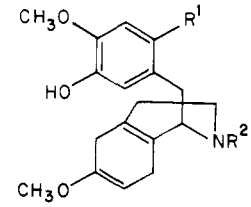
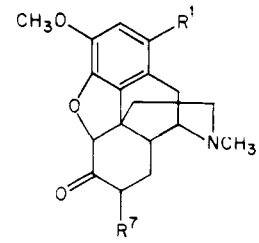
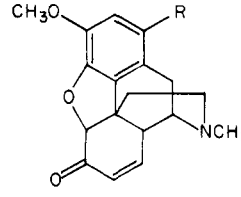


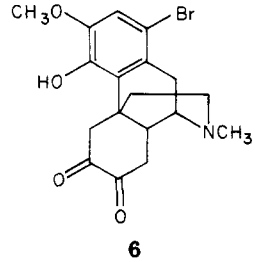
3a, R^1 = H; R^2 = CH_3
b, R^1 = CH_3; R^2 = CHO



4a, R^1, R^7 = H
b, R^1 = Br; R^7 = H
c, R^1, R^7 = Br



5a, R = H
b, R = Br



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effecting an efficient synthesis of dihydrocodeinone (**4a**).[5a] Thus both the C-1–H and C-1–Br series are equally available, and considering the reported difficulty with the labile 7-bromo compound, we decided to explore the conversion of **4a** to codeine. In fact, this transformation

had already been carried out during the first synthesis of thebaine,[7] since one of the reaction intermediates in this sequence was converted to codeinone. It was our intention to investigate this route as a practical synthesis and, in addition, to apply the newer technology for ketone–enone transformations to dihydrocodeinone.

First, the bromination–dehydrobromination ring closure procedure was modified to yield dihydrocodeinone (**4a**) in nearly quantitative yields. To achieve this, it was necessary to consider all reaction products and intermediates of each step in the sequence. The most important modification was to change the conditions for oxide ring closure from the crude bromodihydrothebainone intermediate which had been reported by treatment of the intermediate dibromodihydrothebainone with 7 N sodium hydroxide.[5a,f,g] We found that with both the di- and tribromo intermediates the oxide ring can be closed quantitatively using a two-phase system of chloroform and dilute sodium hydroxide at low temperature. Under these conditions the very reactive 1,7-dibromodihydrocodeinone (**4c**) remained unchanged in the organic phase. This observation is crucial since the brominations did not yield pure materials. Thus it has been reported[5a,b] and we confirmed that when 200 mol % of bromine is added to dihydrothebainone (**1a**) in acetic acid a mixture of 1-bromodihydrothebainone (**1c**), 1-bromodihydrocodeinone (**4b**), and 1,7-dibromodihydrocodeine (**4c**) [or 1-bromosinomoneinone (**6**)] was obtained after alkaline isolation.[8] Treatment of the crude product now with 7 N sodium hydroxide gave very pure **4b** in 73% yield, since all phenolic materials remained in the aqueous base.

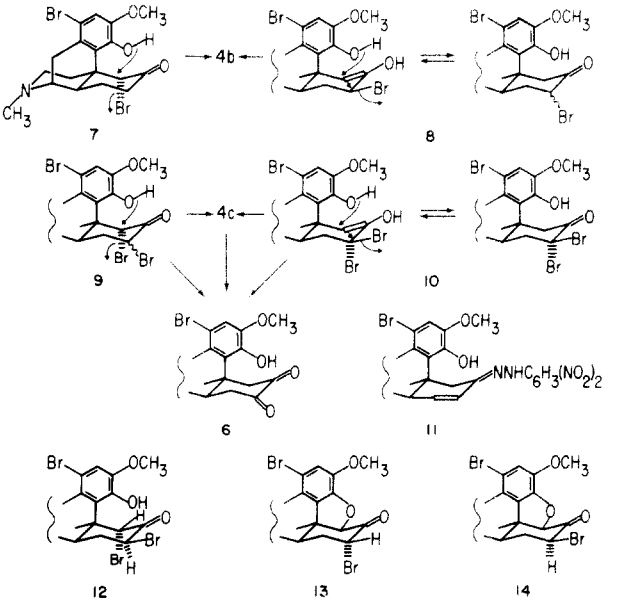
The 25% loss of material was easily avoidable once we learned that **4c** would smoothly yield **4a** by reductive bis-dehalogenation. The hydrogenolysis conditions were similar to those reported.[5a] Interestingly, if sufficient acid was not present, the oxide ring began to be cleaved to give **1a**. If 0.5 N acetic acid was used, 22% of **4a** was converted to **1a** after 2 h at 50 lb of H_2, and triethylamine in ethanol was very reactive in this regard, yielding 41% of **1a** after 2 h. The optimum overall reaction conditions were quickly established. Dihydrothebainone was brominated with 250 mol % of Br_2 to eliminate monobromo products; the reaction mixture treated with $CHCl_3$–1 N NaOH to close the oxide ring and prevent destruction of **4c**; and the crude mixture of brominated dihydrocodeinones was hydrogenated in 2 N HOAc–1.3 N NaOAc with 10% Pd/C to yield **4a** in 100% crude yield.

The mechanism of oxide ring closure has been the subject of considerable speculation[5a,b,9] and later was investigated in detail.[5g] The controversy centered around the nature of phenoxide displacement of bromide in the di- and tribrominated dihydrothebainones. Bromine at C-5 (as in **7** and **9**) will, of steric necessity, be axial and perfectly disposed for SN2 displacement. Bromine at C-7 (as in **8** and **10**), on the other hand, will require an SN2′ reaction via the ketone enol. While other mechanisms, i.e., via cyclopropanes, are possible for C-7 displacement, the SN2′ reaction derives support from its known role in a similar case.[10]

After bromination at C-1, bromination at C-5 was favored[5a,b] since the reaction proceeded cleanly and easily after dibromination giving **4b** in good yields. The tribromo intermediate was assigned to be the 1,5,7 isomer since it gave 1-bromosinomoneinone (**6**) on alkali treatment. Although **4c** could not be prepared, later work[5g] showed chemically that the dibromo intermediate was 1,7-dibromodihydrothebainone (**8**) by conversion to the 2,4-DNP of 1-bromothebainone **11** and via oxidation with Me_2SO to **6**. The equatorial bromine was assigned to **8** since the compound showed an absorbance in the ir at 1725 cm^{-1} while **1a** gave its carbonyl absorption at 1703 cm^{-1}. No tribromo derivative was isolated and **4c** was claimed as the direct product of the reaction, cyclization having occurred in situ.

We thought that NMR would allow us to distinguish not only C-5 or C-7 bromine but also C-7 axial or C-7 equatorial bromine. The results with **8** were disappointing, since the hydrobromide gave no distinguishing absorption in the region δ 4–7. The ir spectrum showed a maximum at 1725 cm^{-1} with shoulders at higher wavenumbers. However, a sample of **1c**·HBr also had an absorbance at 1725 cm^{-1} while **1a**·HBr gave a value of 1718 cm^{-1}. This clouds the former basis for assignment of equatorial bromine at C-7. While **1a**·HBr showed normal carbonyl absorption, **1c** showed a higher wavenumber absorption, indicating **1a** was an unreliable model for compounds brominated at C-1. The reaction of **8** with excess diisopropylamine or triethylamine did not give oxide ring closure to **4b** instantaneously. The reaction was followed in the NMR by the increase in the C-5β-hydrogen of **4b**. Since the tribromo intermediate reacted instantly with triethylamine to give **4c**, this was indirect evidence of C-7 bromine in **8** and C-5 bromine in the tribromodihydrothebainone (**9** rather than **10**).

In our hands the crude tribromination product showed no 5β-hydrogens consistent with ring-closed material. Instead, there was a singlet at δ 6.52 and a doublet of doublets centered at δ 5.70 (J = 7, 14 Hz). Warming in ethanol gave ring closure as evidenced by appearance of the 5β proton of **4c**·HBr at δ 5.52. Since these were the recrystallization conditions originally used,[5g] the discrepancy is explained. The NMR absorptions are consistent with those expected for 1,5β,7α-tribromodihydrothebainone (**12**). The extreme downfield shift of the 5α-hydrogen is explained by a similar situation in **1a**. Exchange with D_2O revealed that the C-5 protons are a quartet with centers at δ 4.22 and 2.19 (J = 14 Hz). The extraordinary shift of the 5α proton is due to its location in the deshielding zone of the aromatic rings and the shift from 4.22 to 6.52 is clearly the result of the 5β-bromine of **12**.

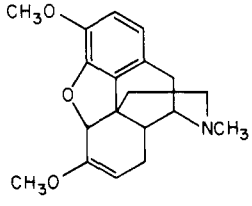


The equatorial assignment of C-7–bromine is based on the NMR spectra of 1,7β- and 1,7α-dibromodihydrocodeinones **13** and **14** produced from **12** upon base treatment of the free amines from the bromination of **4b**. The

isomers are in rapid (6 h at 37°) self-catalyzed equilibrium and can be obtained fairly isomerically pure by silica chromatography. Bromide **13** (70% at equilibrium) shows a 5β-H (s) at δ 5.30 and a 7α-H (t) at δ 4.27 (J = 3.5 Hz), while **14** (30% at equilibrium) gave a 5β-H (s) at δ 4.87 and a 7β-H (dd) at δ 4.70 (J = 5, 13 Hz). The coupling of the C-7 hydrogen of **12** agrees well with **14** and by comparison to **13** the C-7 hydrogens of **12** and **14** are β (axial) and the C-7 hydrogen of **13** is α (equatorial).

The presence of some 1,7,7-tribromo intermediate **10** cannot be ruled out. Integration of the C-5 and C-7 protons of **12** vs. either the C-2–H (δ 7.03) or N–CH_3 (δ 3.75) showed that 35% of the material is not accounted for by NMR. The NMR between δ 5.70 and 3.75 has numerous small absorptions which were not identified. In any event, the major product is 1,5β,7α-tribromodihydrothebainone (**12**).

There are two problems inherent in the introduction of a 7,8 double bond into **4a**. First, the 7 position must be functionalized in the presence of other very reactive positions (C-1, NCH_3) and, second, both the 7-functionalized ketone and the α,β-unsaturated ketone product are labile systems. In the thebaine synthesis[7] both of these difficulties were eliminated in a single reaction. While bromination of **4a** results first in bromination at C-1, reaction of dihydrocodeinone methyl enol ether (**15**) with methyl hypobromite gave selective reaction at C-7 and produced 7-bromodihydrocodeinone dimethyl ketal (**16**) in moderate yields. Since the ketal now lowers the reactivity of the system, conventional dehydrobromination conditions were employed and good yields of codeinone dimethyl ketal (**17**) were obtained.



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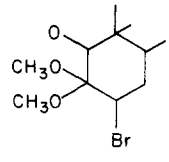

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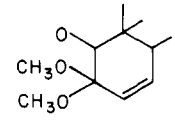

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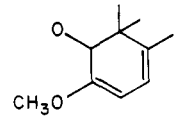

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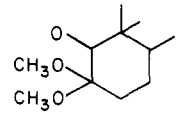

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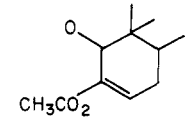

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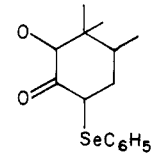

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The feasibility of this route depended on an efficient synthesis of **15**. In the past it was most conveniently prepared by diimide reduction of thebaine (**18**),[11] a route not available to us. Alternatively, a 65% crude yield of **15** was obtained from **4a** by the action of potassium *tert*-butoxide and methyl sulfate.[12] Enol ether **15** along with dihydrocodeinone dimethyl ketal was reported[7] by direct ketalization and similar results were obtained in the 14-hydroxydihydrocodeinone series.[13] We explored direct ketalization and found only quantitative conversion to the ketal **19**. Since the elimination of methanol in the conversion of **17** to **18** occurred so readily ($POCl_3$–pyridine–toluene) we expected easy conversion of **19** to **15**. The same conditions[7,11] which gave thebaine (**18**) also eliminated CH_3OH from **19** but resulted in a heterogeneous reaction. However, heating a solution of **19** and *p*-toluenesulfonic acid in $CHCl_3$ gave nearly quantitative yields of **15**, and crystallization gave an 82% yield for the two steps from **4a**.

The addition of CH_3OBr to **15** proceeded best when the HBr salt was employed, conveniently prepared by the two-phase reaction of **15** in $CHCl_3$ with stoichiometric amounts of concentrated (48%) HBr. Methyl hypobromite then gave crude bromoketal **16** in nearly quantitative yield.

The literature procedure at this point called for prolonged heating of the bromide with potassium *tert*-amylate in *tert*-amyl alcohol. While yields were high we sought less drastic conditions, which were realized using potassium *tert*-butoxide in Me_2SO. This combination gave an 87% yield of pure **17**. The necessary conditions were strictly defined. At 60° only HBr elimination occurred even at prolonged times, and the only material present (TLC, GC, NMR) was **17**. At higher temperatures (90°) substantial conversion of **17** to thebaine (**18**) occurred, and at 120° this conversion was complete in 1 h. Yields of chromatographically pure **18** were 95%, and 72% was obtained after recrystallization. The alkoxide-catalyzed elimination of **17** to **18** has been conducted in alcohol and hydrocarbons,[11] but yields were uniformly poorer. Using alkoxide in Me_2SO we found easily differentiable conditions whereby 7-bromodihydrocodeinone dimethyl ketal (**16**) may be converted to either codeinone dimethyl ketal (**17**) or thebaine (**18**) in high yield. Stirring the ketal **17** in 3 N acetic acid for several hours at 25°, followed by a careful alkaline isolation, yielded nearly pure codeinone, which after a simple recrystallization gave 82% of pure **5a**.

The overall yield of **1a** to **5a**, based upon purified materials, was 42%. Without exception, the reactions give extremely pure products which in most cases are single substances. The entire sequence is thus applicable to work with crude intermediates from the previous steps, and 6.08 g of dihydrothebainone (**1a**) was converted into 5.14 g (85.5%) of codeinone (**5a**), chromatographically and spectrally pure; recrystallization returned 71% of pure **5a** (61% from **1a**). For the final step, **5a** was reduced to codeine with sodium borohydride in methanol as described.[6] The overall transformation of **1a** to pure codeine (**2**) was 68%, a considerable improvement over the 5% previously reported.

The successful route from dihydrocodeinone (**4a**) to codeine (**2**) required the enol ether **15** for selective activation of the 7 position of **4a**. A possible path to **16** without the intermediacy of **15** was via ketalization of **4c**. The resultant bromoketal **20** would potentially be convertible to **16** via selective dehalogenation of the C-1 aromatic bromine. Unfortunately, **4c** failed to ketalize under conditions which readily yielded **19** from **4a**.

The syn elimination of sulfoxides and selenoxides has proved quite valuable for the introduction of α,β-unsaturation into ketones.[14] We examined the application of this route to the complex dihydrocodeinone system and chose the selenoxide approach since the elimination occurs under much milder conditions than the sulfoxides. Attempts to prepare the required selenides for oxidation and elimination were unsuccessful. The enolate of **4a**, generated in THF–HMPA at −78° with lithium diisopropylamide, did not react with selenenyl bromide even after warming to 0° although apparently the selenenyl bromide was consumed.

The reaction of **4a** with phenylselenenyl chloride proved to be troublesome as did the reaction of phenylselenenyl bromide with dihydrocodeinone enol acetate (**21**) or enol

ether **15**. A 1:1 complex of amine and reagent was immediately formed, and attempts using the HBr salts of **4a** or **21** were no better. With **15**·HBr, a new compound resulted which could also be formed by the action of 200 mol % of phenylselenenyl bromide on **15**. NMR showed loss of the C-7 vinyl proton and the product was presumed to be selenide **22**. Attempted isolation of the free amine caused decomposition, and oxidation of the crude (100 mol % of *m*-chloroperbenzoic acid) resulted in a mixture which was primarily **4a** and contained no **5a** or **17**.

In this case, then, the more classical route via the ketal is the superior path for converting ketone to enone. Although more steps are required (ketalization, elimination to enol ether, methyl hypobromite addition to bromoketal, elimination to unsaturated ketal, hydrolysis), the products of the individual reactions are very pure, are isolated in high yield, and may be used directly in the next step. The same is true for the oxide ring-closure sequence; when combined, an excellent process in now available for converting dihydrothebainone (**1a**) to codeine (**2**) or thebaine (**18**) in high overall yield.

Experimental Section[15]

Conversion of Dihydrothebainone (1a) to Dihydrocodeinone (4a). *Dihydrothebainone* **1a** *(6.62 g, 22 mmol)*[16] dissolved in 120 ml of acetic acid was treated dropwise (2 h) with Br_2 (7.20 g, 45 mmol) in 75 ml of acetic acid at 25°. The pale yellow solution was stirred (22 h) and then evaporated to a viscous foam which readily dissolved in 300 ml of $CHCl_3$. The cooled (5°) solution was poured into 1 N NaOH (100 ml, 0°), the aqueous phase was washed with 50 ml of $CHCl_3$, and the combined $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to give 8.8 g of a foam, shown by TLC to consist mostly of **1-bromodihydrocodeinone (4b)** (see below).

The foam was dissolved in 120 ml of 2 N acetic acid containing 13.2 g of anhydrous sodium acetate and 1.6 g of 10% Pd/C was added. The mixture was hydrogenated at 55 lb of H_2 pressure for 12 h; the catalyst was removed, resuspended, and shaken with 50 ml of 2 N acetic acid. The combined, cooled aqueous solution was then adjusted to pH 10 with 6 N NaOH and extracted with $CHCl_3$ (100, 20 ml). Drying (Na_2SO_4) and evaporation gave 6.65 g (100%) of crude **4a**, mp 189–192°, and recrystallization from ethyl acetate returned 5.45 g (82%) of dihydrocodeinone (**4a**), mp 195–196° (lit.[5a] mp 193–194°).

Bromination of Dihydrothebainone (1a). Characterization of Intermediates. 1-Bromodihydrocodeinone (4b). In the same manner as above, dihydrothebainone (**1a**, 4.32 g, 15 mmol) was treated with Br_2 (4.8 g, 30 mmol). The crude bromination residue was dissolved in 75 ml of CH_3OH and added to 75 ml of 6 N NaOH at 0° and then heated on the steam bath for 15 min. The cooled suspension was extracted with benzene (3 × 75 ml), and the organic phase was washed with 20 ml of H_2O and saturated NaCl, dried (Na_2SO_4), and evaporated to yield 4.2 g (73%) of **4c**, mp 200–203°. Recrystallization from ethyl acetate raises the melting point to 205–206° (lit.[1] mp 204.5–206.5°).

Dibromo- and Tribromodihydrothebainones (8 and 12). The brominations of **1a** with 200 or 300 mol % of Br_2 were carried out as described in the preparation of **4a**. The crude residue after removal of the acetic acid was dissolved in a minimum of $CHCl_3$ and added to a 30-fold excess of ether, and the mixture was cooled (0°, 12 h) and filtered. The recovery of solid was generally 90% of the theoretical for the hydrobromides of **8** and **12**. The crude dibrominated material had mp 210–217° dec (lit.[5a] mp 215–225° dec). It could be converted to 1-bromodihydrocodeinone (**4b**) as described above or by treatment with excess diisopropylamine or triethylamine in $CHCl_3$. The latter reactions required 8 h for completion at 25°: NMR δ 7.06 (s, 1 H), 3.75 (s, 3 H); ir 1725 cm^{-1} for **8** with shoulders at 1728, 1732 cm^{-1}.

The ir of 1-bromodihydrothebainone (**1c**)·HBr, prepared by addition of 100 mol % of Br_2, showed absorption at 1725 cm^{-1} and melted at 162–165° (lit.[5a] mp 167°).

The crude tribrominated material **12** had mp 200° dec and was only sparingly soluble in $CHCl_3$. Reaction with base as described in the preparation of **4a** yielded a mixture of **13** and **14** as did triethylamine in $CHCl_3$, these ring closures occurring instantaneously: NMR δ 7.03 (s, 1 H), 6.52 (s, 0.65 H), 5.70 (dd, 0.65 H, J = 7, 14 Hz), 3.75 (s, 3 H).

Deuterium Exchange of Dihydrothebainone. Dihydrothebainone (**1a**, 100 mg, 0.34 mmol) and K_2CO_3 (276 mg, 2.0 mmol) were added to 2.5 ml of D_2O and 2.5 ml of dioxane and refluxed for 8 h. The cooled solution was added to 10 ml of $CHCl_3$ and poured into saturated NaCl, and the organic phase was dried (Na_2SO_4) and evaporated to yield 102 mg of a light brown glass. NMR showed only dihydrothebainone [N-CH_3 (δ 3.80), O-CH_3 (2.46), and aromatic protons (6.50)] with loss of absorption at δ 4.2 (d, J = 14 Hz) and 2.19 (d, J = 14 Hz).

Dihydrocodeinone Dimethyl Ketal (19). Dihydrocodeinone (**4a**, 1.00 g, 3.3 mmol), trimethyl orthoformate (1.54 g, 14.4 mmol), and 16.5 ml of CH_3OH were heated to effect solution, 310 μl of H_2SO_4 was added dropwise, and the solution was refluxed for 5 h. The cooled solution was added to 25 ml of cold 0.5 M Na_2CO_3 and 25 ml of $CHCl_3$. The separated organic phase was washed with saturated NaCl, dried (Na_2SO_4), and evaporated to yield ketal **19** (1.14 g, 100%) as an oil which solidified and was pure (TLC, GC, NMR). The material was recrystallized from hexane–benzene (10:1), mp 112–120° (lit.[7] mp 122–123°). The unrecrystallized material was used in all reactions.

Δ^6-Dihydrothebaine (15). To a dried solution of *p*-toluenesulfonic acid (590 mg, 343 mmol) in 30 ml of $CHCl_3$ was added ketal **19** (985 mg, 2.86 mmol) in 30 ml of $CHCl_3$. The solution was heated in a 120° bath and a distillate (30 ml) was collected over 20 min. The cooled (5°) solution was added to 0.5 M Na_2CO_3 (30 ml, 5°), the aqueous phase was washed with 10 ml of $CHCl_3$, and the organic phase was washed with saturated NaCl, dried (Na_2SO_4), and evaporated to give 918 mg of enol ether **15**, pure by TLC, GC, and NMR. Recrystallization from ethyl acetate gave 760 mg (85%), mp 158–160° (lit.[7] mp 160–161°).

7-Bromodihydrocodeinone Dimethyl Ketal (16). Enol ether **15** (855 mg, 2.83 mmol) was dissolved in 100 ml of $CHCl_3$ and at −5° was treated with HBr–H_2O (8.98 M, 315 μl, 2.8 mmol) and shaken for 2 min, saturated NaBr (75 ml, 0°) was added and the mixture shaken, and the layers were separated. The aqueous phase was washed with 15 ml of $CHCl_3$, the organic phase was dried (Na_2SO_4) and evaporated, and the foamy residue was dissolved in 35 ml of CH_3OH, cooled (0°), and treated dropwise with a cooled (0°) solution of NBA (391 mg, 2.83 mmol) in 25 ml of CH_3OH over 30 min. The colorless solution was evaporated and dissolved by shaking with 100 ml of $CHCl_3$ and 20 ml of 2 N NaOH, the aqueous phase was washed with 20 ml of $CHCl_3$, and the combined chloroform extracts were washed with H_2O and saturated NaCl, dried (Na_2SO_4), and evaporated to yield a solid which was recrystallized from hexane–benzene (10:1) and gave 1.0 g (83%) of pure (GC, TLC, NMR) bromoketal **16**, mp 112–114° (lit.[7] mp 116–117°).

Codeinone Dimethyl Ketal (17). The bromoketal **16** (425 mg, 1 mmol) and potassium *tert*-butoxide (224 mg, 2 mmol) were dissolved in 10 ml of Me_2SO and heated at 60° for 7 h. The cooled solution was mixed with 80 ml of benzene and washed with 75 ml of H_2O, and the aqueous phase was washed with 20 ml of benzene. The combined organic phase was washed with H_2O and saturated NaCl and dried (Na_2SO_4) to give pure (NMR, TLC) **17** (339 mg, 98%), mp 131–133°. Recrystallization from hexane–benzene (10:1) gave 299 mg (87%), mp 134–135° (lit.[7] mp 138–139°).

Thebaine (18). Bromoketal **16** (213 mg, 0.5 mmol) and potassium *tert*-butoxide (140 mg, 1.25 mmol) were dissolved in 5 ml of Me_2SO and heated at 120° for 1 h. The darkened, cooled solution was mixed with benzene and washed with H_2O and the aqueous phase extracted with benzene. The combined organic phase was washed with H_2O and saturated NaCl, dried (Na_2SO_4), and evaporated to yield 149 mg (96%) of pure thebaine (TLC, GC, NMR), mp 185–189°. Recrystallization (CH_3OH–H_2O) gave 112 mg (72%), mp 193–194° (lit.[7] mp 192–194°).

Codeinone (5a). The ketal **17** (274 mg, 0.80 mmol) was dissolved in 3 N HOAc and stirred 4 h at 25°. The cooled (0–5°) solution was mixed with $CHCl_3$, neutralized with cold 6 N NaOH, and extracted with $CHCl_3$ (2 × 10 ml), and the combined $CHCl_3$ was washed with saturated NaCl, dried (Na_2SO_4), and evaporated to give 230 mg (97%) of **5a**. Recrystallization (benzene–cyclohexane, 1:10) returned 195 mg (83%) of pure **codeinone**, mp

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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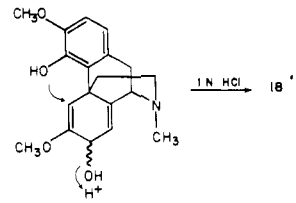

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Conversion of Thebaine to Codeine

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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**)