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# A Rapid, High-Yield Conversion of Codeine to Morphine

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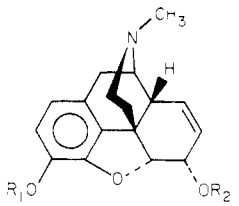
Brief treatment of codeine (1) in chloroform with boron tribromide has consistently given morphine (2) in 90–91% yield after a simple isolation procedure. The yield and simplicity of operation in this method are vastly superior to those previously reported for this transformation.

Essentially all the codeine (1) produced today is prepared by the O-methylation of morphine (2), the major alkaloid of the opium poppy, *Papaver somniferum*. Because of the possible shortage of licit opium[1] and the diversion of morphine (2) to the illicit production of heroin (3), thebaine (4) which is elaborated (to the exclusion of morphine) by *Papaver bracteatum* is under serious consideration[2,3] as a source of the widely used codeine (1). Thus, a practical procedure for the conversion of 1 (for which a commercially feasible total synthesis may eventually be developed)[1] to the oft-prescribed 2 would be highly desirable.

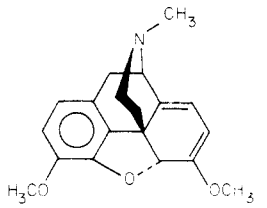
Pyridine hydrochloride at elevated temperature has been used by Rapoport[4] for O-demethylation of a $^{14}C$-labeled 1, by Gates[5] in his total synthesis of (−)-2, and by Goto[6] in the preparation of (+)-2. Practical difficulties were encountered in isolation and purification and yields were low (15–34%). More recently, Takeda et al. have utilized lithium diphenylphosphide to convert B/C *trans*-codeine (5)[7] and B/C *trans*-isocodeine (6)[8] to the corresponding morphines (7 and 8) in 61% yield (in the case of 8), but this procedure appears to lack practicability for large-scale preparation. In this paper, a solution to the long-standing problem of simple, efficient conversion of 1 to 2 is reported.

The method consists of addition of a chloroform solution of 1 to excess boron tribromide in chloroform with brief stirring, followed by quenching the reaction mixture with ice–ammonium hydroxide and simply filtering the 2 hydrate which results. The slightly off-white 2 hydrate which was obtained reproducibly[9] in this manner (87–88% yield) was chromatographically homogeneous on TLC and identical with an authentic sample. Work-up of the filtrate, as described below, afforded additional material (2–3%, total yield 90–91%).

Although boron tribromide has been used to cleave methyl ethers of phenols[10] previously, this high-yielding O-demethylation of 1 seems remarkable in view of the labile nature[4,11] of the oxide bridge and allylic alcohol functions, present in 1 and 2, toward strongly acidic reaction conditions.



1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = R_2 = H$
3, $R_1 = R_2 = Ac$



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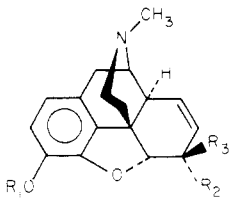

5, $R_1 = CH_3$; $R_2 = OH$; $R_3 = H$
6, $R_1 = CH_3$; $R_2 = H$; $R_3 = OH$
7, $R_1 = R_3 = H$; $R_2 = OH$
8, $R_1 = R_2 = H$; $R_3 = OH$

## Experimental Section

The NMR ($Me_2SO$-$d_6$), ir (KBr), and mass spectra (70 eV) were determined using a Varian HR-220, Perkin-Elmer 257, or Hitachi Perkin-Elmer RMU6E spectrometer, respectively. Melting points were determined in open capillary tubes and are corrected. The composition of the reaction mixtures from various runs was monitored by TLC on silica gel 60 GF plates (Analtech, Inc., Newark, Del.) which were developed with either $CHCl_3$–MeOH (85:15) or $CHCl_3$–MeOH–$NH_4OH$ (80:18:2).

**O-Demethylation of Codeine (1) to Morphine (2).** A solution of 2.99 g (10 mmol) of anhydrous 1 in 25 ml of $CHCl_3$[12] was added during 2 min to a well-stirred solution of 15 g (59.9 mmol) of $BBr_3$ in 175 ml of $CHCl_3$[12] maintained in the range 23–26 °C. A 10-ml portion of $CHCl_3$, which was used to rinse the addition funnel, was added to the reaction mixture and stirring was continued for 15 min at 23–26 °C. The reaction mixture which consisted of a suspension of white solid (in $CHCl_3$) was then poured into a well-stirred mixture of 80 g of ice and 20 ml of concentrated (28–30% $NH_3$) $NH_4OH$. The two-phase system was kept at −5 to 0 °C for 0.5 h (continuous stirring) and filtered. The resulting crystalline material was washed thoroughly with small portions of cold $CHCl_3$ and $H_2O$ and dried to give 2.67 g (88.1%) of slightly off-white $2 \cdot H_2O$, mp 252.5–254 °C dec (lit.[3] mp 254–256 °C), which was homogeneous on TLC and identical (NMR, ir, MS, and TLC) with an authentic sample. The aqueous phase from the filtrate above was saturated with NaCl and extracted with 4 × 50 ml of $CHCl_3$–EtOH (3:1). The combined extracts were evaporated and the residue (151 mg) was dissolved in 2 ml

of $H_2O$ containing 1 drop of 37% HCl. After addition of 0.5 ml of $CHCl_3$, the pH of the aqueous phase was adjusted to 9.0 (Hydrion paper) with concentrated $NH_4OH$ while stirring. The crystalline material which soon separated was filtered, washed with cold $H_2O$ and $CHCl_3$, and then dried to give 86 mg (total yield 2.76 g, 91%) of **2**·$H_2O$, mp 251–253 °C dec. Additional **2**·$H_2O$ could be obtained by further extraction of the aqueous phase and (presumably) by chromatography of the foam (317 mg) which resulted from evaporation of the $CHCl_3$ phase from the original filtrate. This foam was shown by TLC ($CHCl_3$–MeOH, 85:15) to contain **1**, **2**, and three unidentified by-products.

## References and Notes


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(9) Using the procedure described here, the total isolated yields of **2**·$H_2O$ for three identical runs were 90–91%.
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(11) Significantly longer reaction times than reported here gave increased amounts of two by-products and lower yields of **2**·$H_2O$. Less satisfactory results were obtained with other solvents or with boron trichloride.
(12) Reagent grade $CHCl_3$ (J. T. Baker) containing 0.75% EtOH was used throughout in this work.


# An Improved Method for O-Demethylation of Codeine

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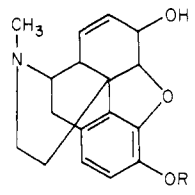
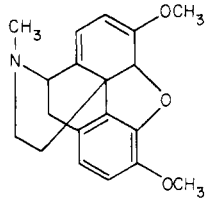
The O-demethylation of codeine was effected by sodium propylmercaptide in dimethylformamide at 125 °C to afford morphine in 80% yield. Similar treatment of thebaine was unrewarding.

Exposure of codeine or morphine to strong acid or alkaline conditions, respectively, at higher temperatures is known to promote substantial decomposition of these alkaloids. Thus, conventional procedures for ether cleavage have been unsuccessful when applied to the conversion of codeine to morphine. Rapoport et al.[1] reported the production of morphine in 22% yield when codeine was treated with pyridine hydrochloride for a brief period at 220 °C. Gates and Tschudi,[2] in their total synthesis of morphine, repeated this method and achieved a 34% yield of morphine by a slight modification of the work-up phase. The use of diphenyl phosphide ion was reported[3] in a patent claim to effect the demethylation of a compound related to codeine.




codeine, R = $CH_3$
morphine, R = H




thebaine

We report an improved and convenient procedure for O-demethylation of codeine that takes place under comparatively mild conditions and would appear to be applicable to most alkaloidal aromatic ethers. The method is based on the studies of Feutrill and Mirrington[4] who found that treatment of aromatic methyl ethers with sodium alkylmercaptides in dimethylformamide at elevated temperatures resulted in cleavage to phenolic products.

Treatment of codeine with an excess of sodium propylmercaptide in dimethylformamide solution at 125 °C for 45 min afforded morphine in 80% yield. Temperature and reaction time could be varied with similar results. Scrupulous exclusion of oxygen during the reaction coupled with the use of sodium bisulfite in aqueous solutions during work-up tended to decrease coloration in the product. When the O-demethylation reaction was applied to thebaine, however, none of the expected oripavine product was recovered. Thin-layer chromatography showed the disappearance of thebaine after 3 h at 110 °C, but an NMR spectrum of the product still showed strong signals for the 3- and 6-methoxy groups. Apparently, an alternate reaction course is available in the thebaine case, competitive with demethylation.

**Morphine.** A solution of 3.00 g (10 mmol) of codeine in 60 ml of dry dimethylformamide was degassed under nitrogen by repeatedly stirring under vacuum, followed by inletting nitrogen. Following the addition of 3.00 g (26.7 mmol) of potassium *tert*-butoxide, the degassing process was repeated and 3.0 ml (32.7 mmol) of *n*-propanethiol was injected by syringe. The mixture was stirred at 125 °C under nitrogen for 45 min (similar results at 110 °C for 3 h), cooled, and quenched with 3.0 ml of acetic acid. The solvent was removed under high vacuum and the residue dissolved in 30 ml of 1 N hydrochloric acid. The acid solution was washed with several portions of ether, treated with 5 ml of 20% sodium bisulfite, and alkalized to pH 9 with ammonium hydroxide. The precipitated solid was collected, washed with water, and dried in vacuo (100 °C) to leave 2.30 g (80%) of morphine as tan crystals. The material was pure by NMR and chromatographic comparison with authentic morphine. An acid solution of the product was treated with Norite ($NaHSO_3$ present) and reprecipitated to yield 1.58 g (55%) of off-white solid, mp 249–250 °C (authentic morphine, mp 246–248 °C).

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