The Synthesis of Thebaine and Northebaine from Codeinone Dimethyl Ketal[1]

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Abstract: A synthesis of thebaine and northebaine has been developed from codeinone dimethyl ketal and norcodeinone dimethyl ketal. Attempts to prepare the ketal by the action of trimethyl orthoformate on codeinone led only to 8-methoxy-Δ^6-dihydrothebaine. However, addition of methyl hypobromite to Δ^6-dihydrothebaine gave 7-bromodihydrocodeinone dimethyl ketal, and dehydrobromination of the latter gave codeinone dimethyl ketal. Acid-catalyzed elimination of methanol resulted in thebaine, but this reaction was erratic and codeinone was an accompanying by-product. Good yields of thebaine from codeinone dimethyl ketal were achieved by using phosphorus oxychloride. Northebaine was obtained in the same way from norcodeinone dimethyl ketal, the latter being prepared by the action of cyanogen bromide on codeinone dimethyl ketal followed by lithium aluminum hydride hydrogenolysis of the N-cyano derivative to the nor compound. A method for separating ketonic, α,β-unsaturated ketonic, and nonketonic alkaloidal material based on formation of the bisulfite addition compounds is described.

Thebaine is prodigious among the morphine alkaloids for the number and variety of its transformation products, providing an extremely versatile starting material for a wide range of derivatives.[3] However, prior to our brief description[4] of a synthesis of thebaine from other alkaloids in the morphine group, these preparations had been wholly dependent on thebaine isolated from natural sources; the limitations imposed by this fact, *e.g.*, in the preparation of isotopically labeled molecules, are obvious. Since then, a thebaine synthesis also has been reported[5] from reticuline in <0.02% yield as judged by radioactivity. This latter synthesis, of course, has no influence on the availability of thebaine or its homologs. We now report the details for our earlier communication[4] plus improvements and additional procedures which have led to a practical synthesis of thebaine and northebaine.

Although thebaine may be considered as the methyl enol ether of codeinone or neopinone, no direct synthesis of such an enol ether was feasible. Instead, our objective became the preparation of codeinone dimethyl ketal to which the methods for converting ketals to enol ethers could then be applied as an entree into the thebaine series.

Very early in the experimental work it became obvious that the development of an efficient and selective method for separating ketonic, α,β-unsaturated ketonic, and nonketonic alkaloidal material would be an extremely important, if not limiting, factor. An appealing method for accomplishing this appeared to be *via* the bisulfite addition products since these might be easily formed, would confer sharp changes in solubility behavior, and should be easily decomposed to regenerate the carbonyl component.

There is an inference in the literature[6] that morphine ketones, *viz.*, dihydrocodeinone, form bisulfite addition compounds. This is based on the observations that dihydrocodeinone is (1) extracted from organic solvents by diluted aqueous bisulfite, and (2) precipitated by saturated aqueous bisulfite. However, neither behavior is sufficient to prove the formation of a bisulfite addition product. Since aqueous bisulfite solutions have pH ~5, dihydrocodeinone (pK = 7.95) as well as other morphine alkaloids (pK = ~8) would be extracted from an organic phase into the aqueous phase owing to protonation on nitrogen. For example, both dihydrocodeinone and Δ^6-dihydrothebaine are removed quantitatively from benzene by this procedure and recovered unchanged by alkalization. Also, precipitation with saturated bisulfite is not sufficient, since it could be the bisulfite salt which is precipitating. Again, both dihydrocodeinone and Δ^6-dihydrothebaine form precipitates with saturated bisulfite from which they can be recovered unchanged.

Definitive evidence that carbonyl–bisulfite addition compounds were actually formed was obtained in the following two ways. First, the effect of bisulfite ion on optical rotation was noted. Since a new asymmetric center is formed and the close environment of another is changed, significant differences in rotation should result from formation of carbonyl addition products. This was found to be the case. The optical rotations of thebaine, codeine, and Δ^6-dihydrothebaine were independent of the anion at pH 5, whereas codeinone and dihydrocodeinone showed strong changes in the presence of bisulfite.

Second, the effect of bisulfite ion on partition coefficient was examined. For alkaloids which could not form carbonyl addition products (Δ^6-dihydrothebaine

(1) This investigation was supported in part by Grant NB 00570 from the National Institutes of Health and in part by the U. S. Atomic Energy Commission.

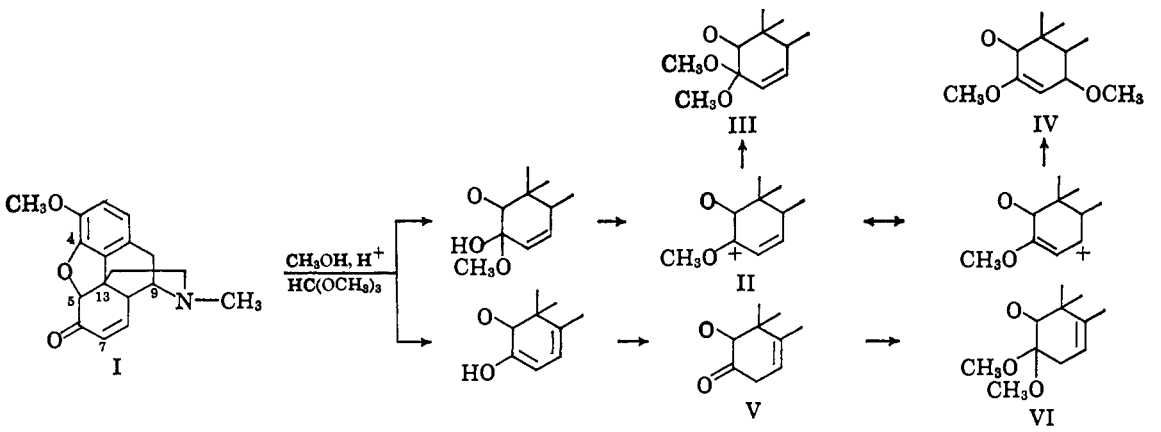
(2) U. S. Public Health Service Postdoctoral Fellow.

(3) L. F. Small and R. E. Lutz, "Chemistry of the Opium Alkaloids," Suppl. 103, Public Health Reports, U. S. Government Printing Office, Washington, D. C., 1932; K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, England, 1954; G. Stork, *Alkaloids*, **6**, 228 (1960).

(4) H. Rapoport, H. N. Reist, and C. H. Lovell, *J. Am. Chem. Soc.*, **78**, 5128 (1956).

(5) D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 203 (1963); D. H. R. Barton, D. S. Bhakuri, R. James, and G. W. Kirby, *J. Chem. Soc., Org.*, 128 (1967). Other oxidations of reticuline have not resulted in any salutaridine [*e.g.*, W. Wan-Chiu Chan and P. Maitland, *ibid.*, 753 (1966); A. H. Jackson and J. A. Martin, *Chem. Commun.*, 420 (1965); *J. Chem. Soc., Org.*, 2061 (1966); G. Blaschke, personal communication].

(6) M. M. Baizer, K. S. Ellner, and A. Loter, *J. Am. Pharm. Assoc., Sci. Ed.*, 40, 580 (1951); U. S. Patent 2,577,947 (1951).



and codeine), the apparent partition coefficient (P') between benzene and water at pH 7 was quite independent of the anion. However, for dihydrocodeinone and codeinone, which can form addition products, P' increased in favor of water by factors of 15 and 25, respectively. This behavior is expected since formation of the bisulfite addition product would greatly increase the water solubility.

These observations provide definitive proof of carbonyl–bisulfite addition product formation with morphine ketones; they also form the basis for development of a facile and selective method for separating ketonic, α,β-unsaturated ketonic, and nonketonic alkaloids. By operating with bisulfite at pH 7 where only partial protonation occurs and by using several back washes, all nonketonic material can be left in the organic phase while the total ketonic fraction is removed into the aqueous phase. Changing the pH of the aqueous phase to 10 reverses the bisulfite addition and the liberated saturated ketonic material (*e.g.*, dihydrocodeinone) is now easily extracted. However, codeinone remains in the aqueous phase under these conditions because 1,4 addition of bisulfite had occurred and this is not reversed at pH 10. It can be reversed at pH 13, where elimination of the β-sulfonic acid is induced,[7] and good recovery of codeinone obtained.

With this isolation procedure at hand, we turned to the preparation of codeinone dimethyl ketal (III), and our first approach was direct ketalization. Reaction of codeinone (I) with trimethyl orthoformate, methanol, and acid can conceivably give three products. Addition of methanol forms the hemiketal, protonation of which leads to the stabilized carbonium ion II. Methanol attack on II at C-6 would give codeinone dimethyl ketal (III); attack at C-8 results in 8-methoxy-Δ^6-dihydrothebaine (IV). On the other hand, initial acid-catalyzed enolization and isomerization to neopinone (V) could be followed by ketalization to neopinone dimethyl ketal (VI). All three possible products, codeinone dimethyl ketal (III), neopinone dimethyl ketal (VI), and 8-methoxy-Δ^6-dihydrothebaine (IV), contain two additional methoxyl groups and are isomeric.

Carrying out the direct ketalization of codeinone (I) and removing a small amount of ketonic material left a single crystalline compound having the required molecular formula (III, IV, or VI). Its structure was established as 8-methoxy-Δ^6-dihydrothebaine (IV) by the following reactions.

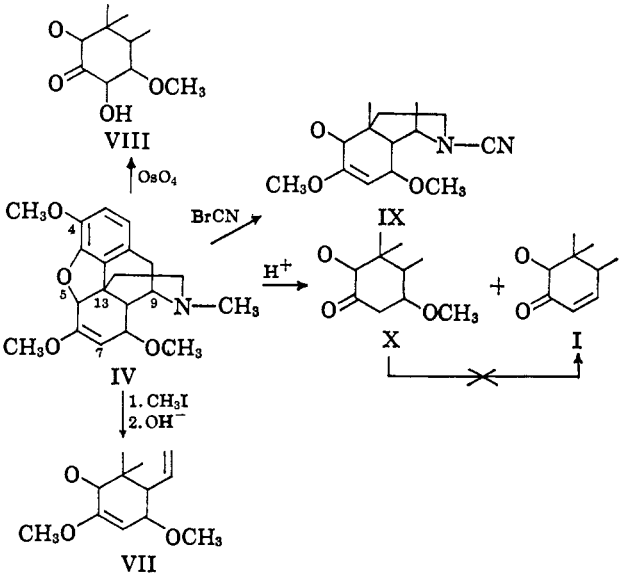
(7) F. Tiemann, *Ber.*, **31**, 3297 (1898); E. Knoevenagel. *ibid.*, **37**, 4038 (1904).

1. Degradation led to the methine VII which has a typical α-methine styrene chromophore at λ_{max} 272 mμ (ϵ 10,500). Had the double bond been Δ^8, a β-methine would have been obtained with phenylbutadiene absorption at λ_{max} 315–320 mμ (ϵ ~10,000). Confirmation of the absence of a Δ^8 unsaturation followed from demethylation with cyanogen bromide to the N-cyanonor compound IX; had the double bond been Δ^8, cleavage of the allylic N–C-9 bond would have occurred rather than demethylation. Since the α-methine VII does not isomerize to a β-methine on treatment with alkali, the double bond is not Δ^7. This eliminates structures III (Δ^7) and VI (Δ^8).

2. Hydroxylation of the double bond with osmium tetroxide gave 7-hydroxy-8-methoxydihydrocodeinone (VIII).

3. Acid hydrolysis gave a mixture of codeinone (I) and 8-methoxydihydrocodeinone (X), and the latter was not converted to the former by further acid treatment. This requires two independent paths for hydrolysis; presumably (a) proton attack at the C-8 methoxyl to give carbonium ion II followed by reaction with water leads to codeinone (I), and (b) proton attack at C-7 followed by nucleophilic addition of water leads to the hemiketal and then 8-methoxydihydrocodeinone (X).

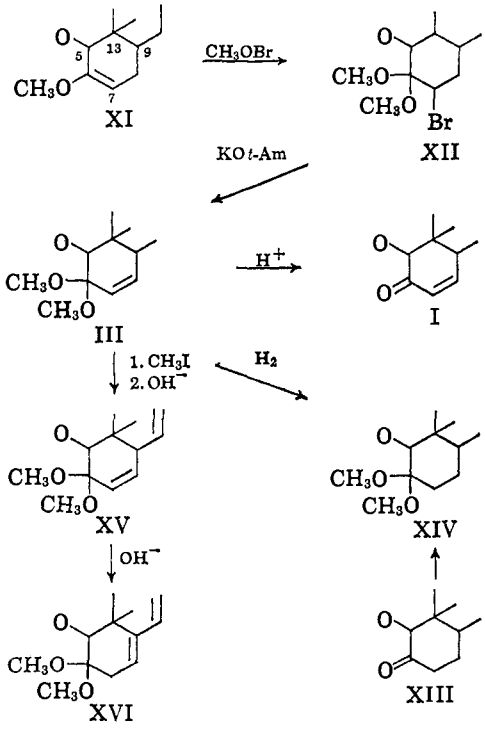
These reactions clearly establish 8-methoxy-Δ^6-dihydrothebaine (IV) as the exclusive nonketonic product of the reaction of codeinone (I) with trimethyl orthoformate, methanol, and acid.



Our second approach to the preparation of codeinone dimethyl ketal (III) was *via* the addition of methyl hypobromite to Δ^6-dihydrothebaine (XI) and elimination of hydrogen bromide from the addition product. The starting material, Δ^6-dihydrothebaine, is readily available as one of a number of compounds resulting on hydrogenation of thebaine,[8] by alkali-catalyzed enol ether formation from dihydrocodeinone,[9] and from the direct ketalization of dihydrocodeinone (see following).

Addition of methyl hypobromite was effected in excellent yield by treating a cold suspension of Δ^6-dihydrothebaine (XI) with N-bromoacetamide in methanol, with exclusion of light. Boiling in *t*-amyl alcohol with potassium *t*-amylate gave clean dehydrobromination, and the olefinic product was formulated as codeinone dimethyl ketal (III). This structure was established by the following reactions.

1. Acid hydrolysis gave codeinone (I).
2. Catalytic hydrogenation gave dihydrocodeinone dimethyl ketal (XIV), identical with an authentic sample prepared by direct ketalization of dihydrocodeinone (XIII). This latter reaction also gave some enol ether, Δ^6-dihydrothebaine (XI), which was separated by chromatography.
3. The methiodide was degraded to the methine XV with typical α-methine absorption at λ_{max} 274 mμ (ϵ 8500). This α-methine was isomerized by alcoholic alkali to the $\Delta^{8(14),9}$-methine XVI with typical β-methine absorption [λ_{max} 318 mμ (ϵ 9000)], proving that the original double bond was Δ^7.



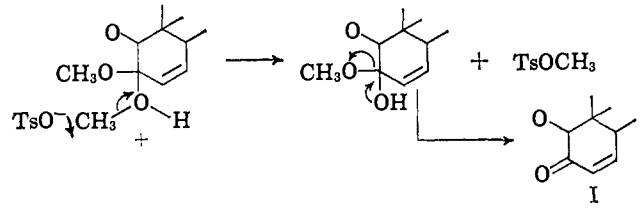
With codeinone dimethyl ketal (III) readily at hand, the problem was now to eliminate methanol to get into the thebaine series. Acid-catalyzed elimination was first explored and led to an early initial success when the ketal III, treated with a dried solution of *p*-toluenesulfonic acid in chloroform, gave a 40% yield of thebaine (XVII). However, yields were not reproducible and became much poorer as the scale increased.

These difficulties led to a detailed study of the reaction, particularly the effect of the molar ratio of *p*-toluenesulfonic acid and water. Thin layer chromatography showed that the chief impurity was codeinone (I), and, since an obvious explanation for the formation of codeinone was the presence of water, the reaction was next carried out with the scrupulous exclusion of water. To our amazement, no thebaine was present and a good yield of pure codeinone had been formed.

The acid-catalyzed elimination was studied further by conducting a series of reactions to which measured amounts of water were deliberately added. The maximum yield of thebaine (40%) occurred at 3 mole % water; either more or less water led to increasing amounts of codeinone and decreased thebaine.

The fact that codeinone (I) is formed both in the complete absence of water and in the presence of significant quantities of water indicates that two mechanisms are probably acting in its formation. Only under conditions when both routes (hydrous and anhydrous) to codeinone are minimal, at ~3 mole % water, is a significant yield of thebaine formed. Also, that codeinone was not originating from thebaine was shown by the absence of codeinone and the stability of thebaine when exposed to the reaction conditions.

Formation of codeinone (I) from codeinone dimethyl ketal (III) under hydrous acid conditions appears straightforward and may be formulated as simple hydrolysis through the usual carbonium ion mechanism. However, under anhydrous acid conditions, the path is obscure; we suggest the nucleophilic attack of *p*-toluenesulfonate anion (present as a result of reaction of the acid with the tertiary amine) on the protonated ketal, as follows.



In both cases, thebaine formation then becomes the competing reaction by carbonium ion formation at C-6 followed by stabilization through loss of the C-14 proton. We cannot explain why this latter reaction reaches its maximum at 3 mole % water.

Since *p*-toluenesulfonic acid catalyzed elimination to thebaine was so unreliable and sensitive, we sought a better method. Alkali-catalyzed elimination of ketals to enol ethers has been successful in several instances,[10] but codeinone dimethyl ketal (III) proved to be stable to potassium *t*-butoxide in *t*-butyl alcohol and sodium amide in several solvents. Another reagent for this purpose is phosphorus oxychloride in pyridine which has been used to convert the diethyl acetal of an α,β-unsaturated aldehyde to a conjugated vinyl ether.[11]

(8) M. Freund, E. Speyer, and E. Guttmann, *Ber.*, **53**, 2250 (1920).
(9) A. H. Homeyer, *J. Org. Chem.*, **21**, 370 (1956).
(10) A. C. Cope, S. F. Schaeren, and E. R. Trumbull, *J. Am. Chem. Soc.*, **76**, 1096 (1954); S. M. McElvain and G. R. McKay, *ibid.*, 77 5601 (1955).
(11) O. Isler, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 259 (1956).

When this reagent was applied to codeinone dimethyl ketal, no codeinone was formed, and an 80% yield of thebaine (XVII) was obtained. No extraordinary precautions for dryness are necessary, and the high yield and reproducibility make it by far the method of choice.

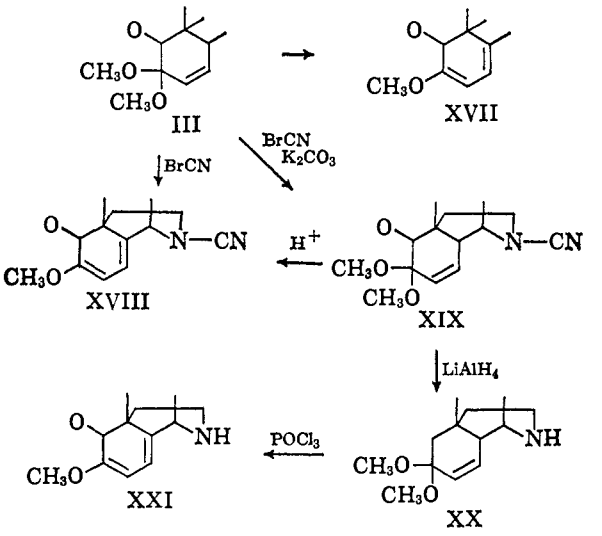
This may be considered a synthesis of thebaine since it proceeds from Δ^6-dihydrothebaine which has been prepared from dihydrocodeinone by acid- or alkali[9]-catalyzed enol ether formation; dihydrocodeinone has been prepared from codeine,[3,12] and codeine has been synthesized.[13]

We now turned to the synthesis of northebaine (XXI), a potentially valuable intermediate for preparing various N-substituted thebaine analogs. When codeinone dimethyl ketal (III) was treated with cyanogen bromide in chloroform, a good yield of N-cyanonorthebaine (XVIII) was formed, and both displacement of the N-methyl group by the cyano group and methanol elimination had occurred. Of these two processes, formation of the N-cyano compound to give the intermediate N-cyanonorcodeinone dimethyl ketal (XIX) must have occurred first, followed by methanol elimination from the latter to the N-cyanonorthebaine (XVIII). Methanol elimination could not have been the first step, since this would have resulted in thebaine (XVII), and it is known that cyanogen bromide converts thebaine to N-cyanonorthebenine, a completely aromatized phenanthrene derivative.[14]

The formation of N-cyanonorthebaine in this reaction can be explained by the presence of a small amount of acid to catalyze methanol elimination. This acid could not exert its catalytic effect in the presence of the tertiary amine, but could do so after the amine was converted to the nonbasic N-cyano derivative. This explanation was put to the test by carrying out the cyanogen bromide reaction in the presence of potassium carbonate. Now N-cyanonorcodeinone ketal (XIX) was the sole product and with acid it was converted to N-cyanonorthebaine (XVIII).

Several attempts were made to convert this easily available N-cyanonorthebaine (XVIII) to northebaine (XXI). Replacement of the cyano group by hydrogen can be accomplished using lithium aluminum hydride,[15] but this also leads to hydrogenolysis of the allylic oxide ring.[16] Acid hydrolysis was not applicable, and the drastic conditions required for alkaline hydrolysis[17] destroyed the molecule.

Therefore we turned to an alternative route *via* N-cyanonorcodeinone dimethyl ketal (XIX). Since the oxide ring is not allylic in XIX, it is stable to lithium aluminum hydride which only removes the cyano group and gives norcodeinone dimethyl ketal (XX). Now methanol elimination with phosphorus oxychloride in pyridine gives northebaine (XXI) in 63% yield. This



sequence thus provides a practical synthesis of northebaine.[18]

Experimental Section[19]

Bisulfite Experiments. A bisulfite–sulfite solution at pH 7 was prepared by adding three volumes of 1 *M* sodium sulfite to one volume of 1 *M* sodium bisulfite and adjusting the pH to 7 with either additional sulfite or bisulfite solution. This was the standard bisulfite–sulfite solution used in separating ketonic from nonketonic alkaloidal material.

Optical rotations were measured at pH 5 in 1 *M* acetate buffer and 1 *M* sodium bisulfite. In acetate buffer, thebaine, codeine, and Δ^6-dihydrothebaine had $[\alpha]$'s of -204, -133, and $-254°$, respectively; in all three cases the rotations were within $\pm 2°$ of these values in 1 *M* sodium bisulfite. Dihydrocodeinone showed $[\alpha]$ -143 (acetate) and $-163°$ (bisulfite); codeinone had $[\alpha]$ -195 (acetate) and $-100°$ (bisulfite).

Apparent partition coefficients were measured at pH 7 between benzene and (a) 1 *M* phosphate buffer and (b) 1 *M* sulfite–bisulfite. The *P*'s (benzene–aqueous) for Δ^6-dihydrothebaine and codeine were 13.3 ± 0.3 and 0.93 ± 0.1, respectively. Dihydrocodeinone had $P'_{\text{phosphate}} = 3.0$, $P'_{\text{sulfite}} = 0.2$; codeinone had $P'_{\text{phosphate}} = 7.4$, $P'_{\text{sulfite}} = 0.3$.

8-Methoxy-Δ^6-dihydrothebaine (IV). A solution of 6 g (20 mmoles) of codeinone (I), 192 ml of methanol, 576 ml of fractionally distilled trimethyl orthoformate (bp 99–100°; $n^{24}D$ 1.3782), and 2 ml of concentrated sulfuric acid was heated at 70° for 3 hr. After the cooled solution was treated with 300 ml of 2 *N* sodium hydroxide, it was extracted with two 300-ml portions of benzene. The combined benzene extracts were then washed with 2 *N* sodium hydroxide, water, and four 200-ml portions of 1 *N* acetic acid, each acidic wash being added immediately to the same 200-ml portion of 6 *N* sodium hydroxide. The alkaline aqueous solution was extracted with benzene; the benzene phase was washed with water, dried, and evaporated. The residue (6.8 g), dissolved in 200 ml of benzene, was washed with three 200-ml portions of bisulfite–sulfite buffer (pH 7). After the combined bisulfite extracts were adjusted to pH 10 with sodium carbonate, they were extracted with benzene, the benzene was added to the previous benzene phase, and the combined benzene solution was dried and evaporated. Crystallization of the residue from hexane and then from 2-propanol and sub-

(12) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

(13) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **74**, 1109 (1952); **78**, 1380 (1956); D. Elad and D. Ginsburg, *ibid.*, **76**, 312 (1954); *J. Chem. Soc.*, 3052 (1954).

(14) J. von Braun, *Ber.*, **47**, 2312 (1914); E. Speyer and H. Rosenfeld, *ibid.*, **58**, 1125 (1925).

(15) A. C. Currie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 4693 (1961).

(16) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **33**, 863 (1950).

(17) H. Mishima, M. Kurabayashi, and I. Iwai, *J. Org. Chem.*, **28**, 2621 (1963).

(18) Following essentially the principles presented in our original communication, a synthesis of northebaine has recently been effected [Belgian Patent 638,369; *Chem. Abstr.*, **62**, 14751 (1965); J. R. Bartels-Keith, *J. Chem. Soc., Org.*, 617 (1966)]. This method proceeds from dihydronorcodeinone to northebaine in exceedingly poor yield.

(19) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California. Optical rotations were measured using the sodium D-line at 25° on 1% solutions; the solvent was ethanol unless otherwise specified. Ultraviolet spectra were taken in ethanol. The adsorbent for the thin layer plates was prepared by mixing a slurry of 2 g of silica gel in 3.5 ml of chloroform with 3.5 ml of 10% methanolic potassium hydroxide; development was with chloroform–methanol (1:1) and visualization with iodoplatinate spray.

limation at 100° (10 μ) gave 2.2 g (32% yield) of 8-methoxy-Δ⁶-dihydrothebaine (IV), mp 190–191°, [α] −133°.

Anal. Calcd for $C_{20}H_{25}O_4N$: C, 70.2; H, 7.1; OCH_3, 27.5. Found: C, 70.0; H, 7.3; OCH_3, 27.1.

The **methiodide** was prepared in methanol and was crystallized from ethanol, mp 212–213°, [α] −86°.

Anal. Calcd for $C_{21}H_{28}O_4NI \cdot H_2O$: C, 50.1; H, 6.0; I, 25.2. Found: C, 50.3; H, 5.8; I, 24.8.

8-Methoxy-Δ⁶-dihydrothebaine Methine (VII). To a solution of 2.07 g (4.27 mmoles) of 8-methoxy-Δ⁶-dihydrothebaine (IV) methiodide in 20 ml of water was added 20 ml of 30% aqueous potassium hydroxide, and the mixture was boiled in a nitrogen atmosphere for 20 min. It then was cooled and extracted with three 100-ml portions of benzene, the combined benzene extracts were washed with water and then extracted with four 50-ml portions of cold, 1 *N* acetic acid, and the combined acetic acid extracts were adjusted to pH 12 and extracted with four 100-ml portions of benzene. Evaporation of the combined, dried benzene left 1.47 g of residue which was crystallized from hexane and sublimed at 60° (5 μ) to give 1.27 g, 84% yield of methine (VII), mp 124–125°, [α] −119°.

Anal. Calcd for $C_{21}H_{27}O_4N$: C, 70.5; H, 7.6; OCH_3, 26.1. Found: C, 70.4; H, 7.5; OCH_3, 25.6.

N-Cyano-8-methoxy-Δ⁶-dihydronorthebaine (IX). A solution of 106 mg (1.0 mmole) of cyanogen bromide and 240 mg (0.7 mmole) of 8-methoxy-Δ⁶-dihydrothebaine (IV) in 4 ml of chloroform was heated under reflux for 2 hr, the chloroform was evaporated to dryness, and 5 ml of water was added. The mixture was heated to reflux, cooled, and filtered. The precipitate was dissolved in 25 ml of chloroform, and the chloroform was washed with three 25-ml portions of 1 *N* acetic acid, dried over potassium carbonate, and evaporated leaving 220 mg, 90% yield, of the N-cyano compound, mp 225–230°. Crystallization from absolute ethanol and sublimation at 100° (50 μ) gave 120 mg of material, mp 228–231°, [α] −185° (pyridine).

Anal. Calcd for $C_{20}H_{22}O_4N_2$: C, 67.8; H, 6.3; N, 7.9. Found: C, 68.0; H, 6.4; N, 7.9.

Acid Hydrolysis of 8-Methoxy-Δ⁶-dihydrothebaine (IV). Codeinone (I) and 8-Methoxydihydrocodeinone (X). A solution of 1 g (2.9 mmoles) of 8-methoxy-Δ⁶-dihydrothebaine in 75 ml of 1 *M* potassium acid sulfate was allowed to stand at room temperature for 4 hr. The cooled solution was made alkaline with 40 ml of 2 *N* sodium hydroxide, the alkaline solution was extracted with four 50-ml portions of benzene, and the combined benzene extracts, after being concentrated to 75 ml, were subjected to a four-stage, counter-current extraction using benzene (75-ml portions) and 1 *M* bisulfite–sulfite buffer (pH 7, 75-ml portions).

From the combined benzene phases, on evaporation, was recovered 424 mg, 42%, of **8-methoxy-Δ⁶-dihydrothebaine.**

The combined bisulfite phases were adjusted to pH 9 with 6 *N* sodium carbonate and extracted with four 100-ml portions of benzene. Evaporation of the combined, dried benzene extracts gave 200 mg, 20% yield, of the saturated ketone. After crystallization from 2-propanol and sublimation at 140° (10 μ), **8-methoxydihydrocodeinone (X)**, mp 195–197°, was obtained. It was stable to further treatment with potassium acid sulfate as above.

Anal. Calcd for $C_{19}H_{23}O_4N$: C, 69.3; H, 7.0; OCH_3, 18.9. Found: C, 69.4; H, 6.8; OCH_3, 19.4.

The sulfite solution then was made strongly alkaline with 10 *N* sodium hydroxide and shaken mechanically with 250 ml of chloroform, the chloroform phase being removed and fresh chloroform (250 ml) being added at intervals of 2, 4, 8, and 21 hr. Evaporation of the combined, dried chloroform extracts gave 240 mg, 24% of **codeinone,** identical with an authentic sample.

7-Hydroxy-8-methoxydihydrocodeinone (VIII). A solution of 2 g (5.8 mmoles) of 8-methoxy-Δ⁶-dihydrothebaine (IV) and 0.94 ml of pyridine in 25 ml of benzene was added to a solution of 1.48 g (5.83 mmoles) of osmium tetroxide in 25 ml of benzene, and the mixture was kept at room temperature for 2 hr. It then was added to a solution of 11.2 g of sodium bicarbonate, 11.2 g of sodium sulfite, 100 ml of methanol, and 50 ml of benzene in 140 ml of water. The resulting suspension was stirred vigorously for 16 hr, 50 ml of chloroform was added, and the precipitate was removed by filtration through filter aid and washed with hot chloroform (four 50-ml portions), and the aqueous phase of the filtrate was extracted with two 100-ml portions of chloroform. Evaporation of the combined, dried chloroform phases left 1.9 g, 95% yield of the amorphous hydroxymethoxy ketone. It gave a positive Fehling test, a positive periodic acid test, and a red precipitate with 2,3,4-triphenyl-2H-tetrazolium chloride; infrared absorption, $\lambda_{max}^{CHCl_3}$ 2.91 and 5.79 μ.

Anal. Calcd for $C_{19}H_{23}O_5N$: C, 66.1; H, 6.7. Found: C, 66.1; H, 7.1.

The **oxime** was prepared by treating a solution of 345 mg (1.0 mmole) of the ketone in 5 ml of absolute ethanol with 174 mg (2.5 mmoles) of hydroxylamine hydrochloride and heating under reflux overnight. The solution was cooled, the oxime hydrochloride was collected by filtration, and the free base was obtained by dissolving the oxime hydrochloride in 10 ml of water, adjusting the pH to 8.5, and extracting with chloroform (four 25-ml portions). Evaporation of the combined chloroform extracts left a crystalline residue which was recrystallized from absolute ethanol to give oxime, mp 251–253° dec, [α] −204° (pyridine).

Anal. Calcd for $C_{19}H_{24}O_5N_2$: C, 63.3; H, 6.7; N, 7.8; OCH_3, 17.2. Found: C, 62.9; H, 6.9; N, 7.9; OCH_3, 16.9.

7-Bromodihydrocodeinone Dimethyl Ketal (XII). To a suspension of 10 g (32 mmoles) of Δ⁶-dihydrothebaine (XI) in 125 ml of methanol, maintained at 15°, was added a solution of 4.5 g (32 mmoles) of N-bromoacetamide[20] in 80 ml of methanol, maintained at 0°. Addition was over a 2-hr period with the reaction mixture protected from light and maintained at 15°, after which it was allowed to stand at room temperature for 3 hr. Water (325 ml) then was added, and the mixture was cooled in an ice bath for 1 hr and then filtered. The precipitate was washed with 50% aqueous methanol and crystallized from hexane to give 7-bromodihydrocodeinone dimethyl ketal (XII) in 62% yield, mp 116–117°, [α] −170°.

Anal. Calcd for $C_{20}H_{26}NO_4Br$: C, 56.6; H, 6.2; Br, 18.9; OCH_3, 21.9. Found: C, 56.8; H, 6.3; Br, 18.9; OCH_3, 21.7.

Codeinone Dimethyl Ketal (III). 7-Bromodihydrocodeinone dimethyl ketal (XII) (13.1 g, 31.4 mmoles) was added to a solution of 2.45 g (62.8 g-atoms) of potassium in 130 ml of dry *t*-amyl alcohol and the solution was boiled for 24 hr in a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*; 100 ml of water was added. The concentration was repeated, and the mixture was filtered after addition of 300 ml of benzene. The benzene phase in the filtrate was removed, washed with water (two 50-ml portions), dried, and evaporated. Chromatography of the residue on alumina (Merck) and elution with 50% benzene–hexane followed by sublimation at 130° (0.5 mm) gave 8.6 g (80% yield) of codeinone dimethyl ketal (III), mp 138–139°, [α] −233°, ultraviolet absorption λ_{max} 284 mμ (ε 1480).

Anal. Calcd for $C_{20}H_{25}O_4N$: C, 70.0; H, 7.3; OCH_3, 27.1. Found: C, 69.8; H, 7.3; OCH_3, 27.2.

The **methiodide** was prepared by heating under reflux for 10 min a solution of codeinone dimethyl ketal and excess methyl iodide in ethyl acetate. Cooling gave a quantitative yield of codeinone dimethyl ketal methiodide, mp 193–195° dec.

Anal. Calcd for $C_{21}H_{28}O_4NI$: C, 52.0; H, 5.8; I, 26.2; OCH_3, 19.2. Found: C, 5.18; H, 6.0; I, 26.4; OCH_3, 19.5.

The **hydrolysis** of codeinone dimethyl ketal was effected by allowing a solution of codeinone dimethyl ketal in 3 *N* acetic acid to stand at room temperature for 3 hr. Benzene then was added followed by excess concentrated aqueous ammonia, the benzene layer was separated, and the aqueous phase was extracted with two equal-volume portions of benzene. Evaporation of the combined, dried benzene extracts left a crystalline residue which was recrystallized from benzene and was identical with an authentic sample of codeinone.

Dihydrocodeinone Dimethyl Ketal (XIV). A. From Hydrogenation of Codeinone Dimethyl Ketal (III). A solution of codeinone dimethyl ketal (343 mg, 1 mmole) in 10 ml of absolute ethanol absorbed 100 mole % of hydrogen in 3 hr at room temperature and atmospheric pressure in the presence of 100 mg of 5% palladium-on-carbon catalyst. The mixture was filtered, the filtrate was evaporated, and the residue, dissolved in 25 ml of benzene, was washed with 1 *N* sodium hydroxide and water. Drying and evaporating the benzene left a residue which was crystallized from hexane; 286 mg, mp 122–123°, [α] −151°.

Anal. Calcd for $C_{20}H_{27}O_4N$: C, 69.6; H, 7.9; OCH_3, 26.9. Found: C, 69.7; H, 8.0; OCH_3, 26.5.

B. From Ketalization of Dihydrocodeinone (XIII). To 193 ml of trimethyl orthoformate and 64 ml of methanol, 2 g of dihydrocodeinone was added, the solution was heated to reflux (internal temperature 68–72°), and 0.64 ml of concentrated sulfuric acid was added. After 3 hr at reflux, the solution was poured into 100 ml of cold 2 *N* sodium hydroxide and 200 ml of benzene. The sepa-

(20) Purified by dissolving in chloroform (1 g/50 ml) at room temperature and crystallizing by addition of an equal volume of hexane; mp 105–108°.

rated benzene phase was washed with 100 ml of 2 *N* sodium hydroxide and then with cold 1 *N* acetic acid (200-ml portions) until the acetic acid extracts gave a negative Mayer's test. Each acid extract was added immediately to excess 2 *N* sodium hydroxide, and the crude alkaloidal material was extracted into benzene. The benzene solution was dried, filtered, and evaporated to give 2.2 g of residue, which then was dissolved in cyclohexane and chromatographed on alumina (Merck). From a detailed chromatography, dihydrocodeinone dimethyl ketal (XIV), identical with the material from hydrogenation of codeinone dimethyl ketal, was isolated as the first fraction. Δ^6-Dihydrothebaine (XI), identical with an authentic sample, was isolated as the last fraction, and the intermediate fraction consisted of a mixture of dihydrocodeinone dimethyl ketal and Δ^6-dihydrothebaine.

Codeinone Dimethyl Ketal Methine (XV). A solution of 4.75 g (9.8 mmoles) of codeinone dimethyl ketal methiodide (prepared above) in 56 ml of water was boiled for 15 min in a nitrogen atmosphere after the addition of 56 ml of hot, 30% aqueous potassium hydroxide. The cooled mixture was extracted with three 200-ml portions of benzene, and the combined benzene extracts were washed with water, dried, and evaporated to leave 3.09 g, 88% yield, of the crystalline methine, mp 71–72°, $[\alpha]$ −328°, ultraviolet absorption λ_{max} 274 mμ (ϵ 8500).

Anal. Calcd for $C_{21}H_{27}O_4N$: C, 70.6; H, 7.6; OCH_3, 26.0. Found: C, 70.7; H, 7.5; OCH_3, 26.2.

Neopinone Dimethyl Ketal Methine (XVI). Codeinone dimethyl ketal methine (XV) (1 g, 2.8 mmoles) in 5 ml of water and 7 ml of ethanol containing 1.1 g of potassium hydroxide was heated under reflux in a nitrogen atmosphere for 24 hr. Water (85 ml) and methylene chloride (30 ml) were added, the phases were separated, and the aqueous layer was extracted with three 50-ml portions of methylene chloride. The combined methylene chloride extracts were washed (water), dried, and evaporated to leave an oily residue of neopinone dimethyl ketal methine. This was distilled onto a cold-finger at 125° (0.1 mm), yield 890 mg, 89%, $[\alpha]$ +301°, ultraviolet absorption λ_{max} 318 mμ (ϵ 9000).

Anal. Calcd for $C_{21}H_{27}O_4N$: C, 70.6; H, 7.6; OCH_3, 26.0. Found: C, 70.6; H, 7.5; OCH_3, 25.8.

Conversion of Codeinone Dimethyl Ketal (III) to Thebaine (XVII). A. Using *p*-Toluenesulfonic Acid. A standard solution was prepared containing 13.5 μl of water in 66.7 ml of methylene chloride (dried over magnesium sulfate and distilled) diluted to 100 ml with benzene (distilled from calcium hydride). A standard solution of *p*-toluenesulfonic acid was prepared by drying a sample of the acid hydrate by means of the benzene azeotrope, and adding enough dry methylene chloride to keep the acid in solution. An aliquot of this solution was evaporated and titrated to determine its concentration (0.04 *M* in 2:1 methylene chloride–benzene). Each of the 10-mg portions of codeinone dimethyl ketal was treated with 2 molar equiv of acid solution in the presence of appropriate amounts of the water solution for 30 min at room temperature. The product was isolated by shaking with potassium carbonate, then adding water, and removing the organic phase. The aqueous layer was extracted with chloroform, and the combined organic phase was analyzed by tlc. In all cases the product consisted solely of codeinone and thebaine.

An experiment under anhydrous conditions was carried out by placing 50 mg of freshly sublimed codeinone dimethyl ketal in a dry, 30-ml syringe and drawing 20 ml of chloroform, freshly distilled from phosphorus pentoxide, into the syringe. This solution was injected through a serum cap into a solution of 2 equiv of *p*-toluenesulfonic acid in 10 ml of benzene, dried by azeotropic distillation of 20 ml of benzene, which removed the water of hydration of the acid as well as any other moisture present. After 1 min, the alkaloidal product was isolated as above. Analysis by tlc showed only codeinone, with no thebaine or codeinone dimethyl ketal, present.

B. Using Phosphorus Oxychloride. Codeinone dimethyl ketal (52 mg) was dissolved in 14 ml of toluene, and to this was added a solution of 150 μl of pyridine and 30 μl of freshly distilled phosphorus oxychloride. The solution was heated at 90° under nitrogen with vigorous stirring for 95 min, cooled to room temperature, and washed into a separatory funnel with 15-ml portions of water and chloroform. The aqueous layer was brought to pH 11 by addition of 10% potassium hydroxide solution and extracted with three 30-ml portions of chloroform. The chloroform layers were combined, dried over sodium sulfate, and evaporated to a residue which was purified by chromatography on preparative thin layer plates of silica gel G which had been treated with potassium hydroxide.[19] The thebaine fraction was removed (38.7 mg, 82% yield). Analytical tlc showed this material to be pure thebaine. A portion was recrystallized from methanol and sublimed to yield thebaine identical with an authentic sample in melting point and mixture melting point (192–194°), ultraviolet [λ_{max} 283 mμ (ϵ 7500)] and infrared absorption, and tlc.

N-Cyanonorthebaine (XVIII). A solution of 270 mg (0.8 mmole) of codeinone dimethyl ketal (III) and 116 mg (1.1 mmoles) of cyanogen bromide in 5 ml of chloroform (dried by shaking briefly with magnesium sulfate) was boiled for 2.5 hr in a nitrogen atmosphere and then evaporated to dryness. Water (5 ml) was added to the residue; the mixture was heated to a boil, cooled, and filtered; and the insoluble material was dissolved in 25 ml of chloroform. Washing with two 25-ml portions of cold 1 *N* acetic acid, drying over potassium carbonate, and evaporating the chloroform left a crystalline residue which was recrystallized from absolute ethanol, giving 200 mg (0.6 mmole, 75% yield) of N-cyanonorthebaine, mp 223–234°, $[\alpha]$ −212° (pyridine), ultraviolet absorption λ_{max} 285 mμ (ϵ 8000).

Anal. Calcd for $C_{19}H_{18}O_3N_2$: C, 70.8; H, 5.6; N, 8.7; OCH_3, 19.2. Found: C, 70.8; H, 5.7; N, 8.7; OCH_3, 19.2.

N-Cyanonorcodeinone Dimethyl Ketal (XIX). The reaction of codeinone dimethyl ketal (III) and cyanogen bromide was carried out as described above in the preparation of N-cyanonorthebaine except that 2 g of anhydrous potassium carbonate was added to the chloroform solution. The mixture was filtered prior to evaporation of the chloroform, and the product was isolated as above, giving a 65% yield of N-cyanonorcodeinone dimethyl ketal, mp 163–164°, ultraviolet absorption λ_{max} 286 mμ (ϵ 1600).

Anal. Calcd for $C_{20}H_{22}O_4N_2$: C, 67.8; H, 6.3; N, 7.9; OCH_3, 26.3. Found: C, 67.8; H, 6.4; N, 8.0; OCH_3, 26.7.

Norcodeinone Dimethyl Ketal (XX). A 2.59-g sample (7.3 mmoles) of N-cyanonorcodeinone dimethyl ketal (XIX) was dissolved in 150 ml of dry tetrahydrofuran and dropped slowly into a suspension of 1.5 g of lithium aluminum hydride in 150 ml of tetrahydrofuran. The reaction mixture was stirred under dry nitrogen, heated at reflux for 3 hr, and then allowed to stand overnight at room temperature. A 20-ml portion of ethyl acetate was slowly added to decompose the excess hydride, and then 35 ml of saturated potassium sodium tartrate solution was added to complex the aluminum salts. Evaporation at reduced pressure of the supernatant solution left a residue which was taken up in ether and filtered. The dissolved alkaloid was precipitated by the addition of petroleum ether to yield 1.81 g (75%) of white powder, mp 69–70°, followed by solidification and remelting at 105°. This material was suitable for use in the following reaction; its melting point increased to 117–118° upon recrystallization and sublimation (lit.[18] mp 113–114°).

Anal. Calcd for $C_{19}H_{23}O_4N$: C, 69.3; H, 7.0; N, 4.3. Found: C, 69.5; H, 7.0; N, 4.2.

Northebaine (XXI). To 200 mg (0.61 mmole) of norcodeinone dimethyl ketal (XX) in 14 ml of dry toluene was added a suspension of 600 μl (7.45 mmoles) of pyridine and 114 μl (1.25 mmoles) of phosphorus oxychloride in 14 ml of toluene. The reaction mixture was stirred vigorously and maintained at 80° for 45 min; then it was washed into a separatory funnel with a 50-ml portion of water, a 10-ml portion of 10% potassium hydroxide solution, and two 25-ml portions of chloroform. The aqueous layer was brought to pH 11 by the addition of solid potassium hydroxide, and the organic phase was removed. The aqueous layer was further extracted by two 50-ml portions of chloroform and the organic layers were washed once with 10% potassium hydroxide solution, combined, and dried over sodium sulfate. Evaporation at reduced pressure provided a residue of 152 mg which was distributed between 50 ml of 0.5 *N* acetic acid and methylene chloride. The acetic acid solution was washed with another 50-ml portion of methylene chloride, and both organic phases were washed with a fresh 50-ml portion of 0.5 *N* acetic acid solution. The combined aqueous phase was brought to pH 11 by addition of solid potassium hydroxide and then extracted with three 50-ml portions of methylene chloride, which were combined, dried over sodium sulfate, and evaporated to yield 114 mg (63%) of essentially pure northebaine. A portion of this material was recrystallized from methanol and sublimed at 120° (0.05 mm) to yield pure northebaine (XXI), mp 158–159°, λ_{max} 285 mμ (ϵ 7100) (lit.[18] mp 157–159°, λ_{max} 286 mμ (ϵ 7490)).