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Synthesis of Thebaine and Oripavine from Codeine and Morphine

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A practical synthesis of thebaine and oripavine has been developed from codeine and morphine, respectively. Attempts to use a codeinone intermediate gave poor yields; however, methylation of the potassium salt of codeine to give codeine methyl ether followed by oxidation with γ-MnO_2 gave thebaine in 67% yield from codeine. Similarly, the potassium salt of the di-O-anion of morphine was selectively alkylated to give morphine 6-methyl ether (heterocodeine) in better than 90% yield. Heterocodeine was then acetylated and oxidized to oripavine 3-acetate which was hydrolyzed to give oripavine in 73% yield from morphine.

Thebaine is the least abundant among the hydrophenanthrene alkaloids in *Papaver somniferum*, and it has no medicinal use in itself. Yet it is singularly important as the key intermediate in the synthesis of many useful opiate derivatives. This is uniquely the case for the naloxone family of opiate antagonists[1] and for the highly potent oripavine derivatives initiated from the Diels–Alder adducts of thebaine.[2]

The significant increase of opiate abuse in the United States, starting in the late 1960's, focused attention on the potential role of antagonists and raised the real danger of a thebaine shortage.[3] This danger was aggravated by the temporary cessation of opium cultivation in Turkey which stimulated the search for new sources of thebaine such as *P. bracteatum*.[4] With the ebb and flow of drug diplomacy[5] now resulting in the resumption of Turkish opium cultivation, *P. somniferum* appears to be restored as the most abundant and efficient source of the medicinal opiates.

We have sought to develop a practical and economic method for the synthesis of thebaine from the more available alkaloids of *P. somniferum*, morphine and codeine. Corollary to this is our objective of devising a ready source of oripavine, which is naturally occurring in very minor amounts in *P. bracteatum*.[4,6] Readily available oripavine is of interest since its use may obviate the final and difficult *O*-3-methyl ether cleavage in the synthesis of the Diels–Alder derived narcotics.[2]

The literature teaches three methods for the synthesis of thebaine (**2a**). The first[7] converts dihydrocodeinone to thebaine in four steps in 27% yield. Considering the preparation of dihydrocodeinone from codeine,[8] this leads to a 20% overall yield from codeine. Although this conversion could undoubtedly be improved, the improvement is limited and the process inconvenient since six steps are involved. The second process[9] involves direct methyl enol ether formation from codeinone and claims a 27% yield of thebaine; further comments on this process are given below.

The third process[10] is a total synthesis in which the key step is the oxidative coupling of a reticuline derivative to a salutaridine derivative. While the yields in this coupling step have been improved dramatically (by a factor of 1000), the overall yield of *dl*-thebaine remains in the 1–2% range, based on isovanillin.

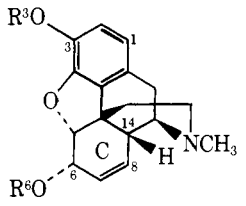
Discussion

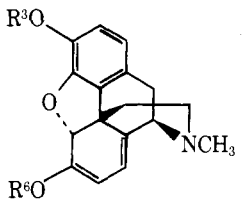
In considering the conversion of codeine (**1b**) to thebaine (**2a**), the two changes which must be effected, both in ring C, are oxidation (removal of two hydrogens) and methylation (formation of a methyl ether at O-6). Our first attempts followed the common pathway, namely, first oxidation to codeinone[11] and then formation of the methyl enol ether directly or via the dimethyl ketal and methanol elimination.[7] This is the same path as followed recently[9] and our

efforts were focused on finding better methods for effecting the second step.

Direct acid-catalyzed enol ether formation gave the best yield with 1-propanol, 37% of codeinone *n*-propyl enol ether. Extensive study and variation of the conditions (time, temperature, acidity, concentration) led to no improvement,[12] and our maximum yields of thebaine (**2a**) were in the 15–20% range.[13] We then explored a variety of different enol ether and ketal forming reagents.

(1) Transketalization with 2,2-dimethoxypropane, trimethyl orthoformate, or dimethylformamide dimethyl acetal and (2) methyl dienol ether formation with acetimino methyl ether hydrochloride, *O*-methyl-*N,N'*-dicyclohexylisourea, and *O*-methyl-*N,N'*-dicyclohexylisourea hydrochloride were investigated. None of these methods yielded the desired products and in most cases gave either no reaction or underwent 1,4 addition to the α,β-unsaturated ketone.[7]





	R^3	R^6
1a	H	H
b	CH_3	H
c	CH_3	CH_3
d	H	CH_3
e	$COCH_3$	CH_3
f	COC_6H_5	H
g	H	COC_6H_5

	R^3	R^6
2a	CH_3	CH_3
b	$COCH_3$	CH_3
c	H	CH_3

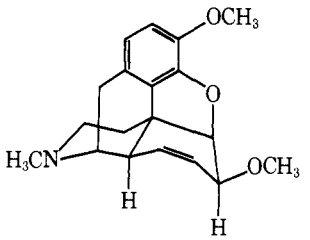
Failure of the oxidation–methylation sequence to achieve a practical conversion of codeine to thebaine led us to investigate the reverse procedure, that is, methylation first followed by oxidation. The requisite codeine methyl ether (**1c**, CME) has been prepared by a method which involves O- and N-methylation followed by dequaternization.[14] A significantly improved method was developed in which the potassium salt of codeine was methylated with methyl iodide to give CME in 83% yield. The yield was less with the sodium salt and zero with the lithium salt.

Oxidation of CME was first attempted by bromination–dehydrobromination. Under a large variety of conditions, neither bromine addition nor allylic bromination occurred; the exclusive product was 1-bromocodeine methyl ether. Direct catalytic dehydrogenation was then attempted by heating with Pd/C, but CME was recovered unchanged.

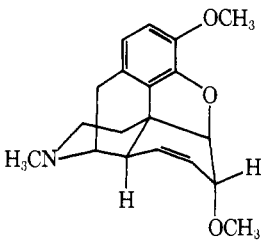
Successful conversions to thebaine were obtained when CME was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or *o*-chloranil. DDQ was the more effective oxidizing agent, and the reaction with it and CME proceeded more rapidly than with *o*-chloranil. The reaction with DDQ requires at least 2 equiv of DDQ, the first equivalent forming a benzene-insoluble complex with CME. Since DDQ is a relatively expensive reagent, especially when used in 300 mol % stoichiometry, and since the reaction yields a crude mixture (about 1:1) of CME and thebaine, we examined some other oxidants such as CrO_3·Py_2,[15] selenium dioxide, and manganese dioxide. Both CrO_3·Py_2 and SeO_2 consumed codeine methyl ether but no thebaine was detected.

Best results have been obtained from the reaction of codeine methyl ether with γ-MnO_2[16] to give thebaine in 80% yield (67% overall from codeine). Manganese dioxide has been used to oxidize benzylic and allylic alcohols to ketones and aldehydes and certain tertiary amines to products containing carbonyl groups but is seldom effective for introducing carbon–carbon double bonds, although such reactions are known.[17] Most of these reactions were performed using the active manganese dioxide as prepared by Attenburrow,[18] and similar results are obtained with MnO_2 on charcoal.[19]

This is the first example of the oxidation of an allylic ether to a dienol ether with manganese dioxide. In seeking other applications for this process, we attempted the oxidation of isocodeine methyl ether (*i*-CME) and geranyl methyl ether. Neither was oxidized to a dienol methyl ether; both were recovered unchanged. Thus, this reaction does not appear to be general, and the reason for its successful use may be steric. In the case of CME, the two hydrogens being removed are 1,4-cis-diaxial; however in *i*-CME, the hydrogens being removed are trans. In this regard, it is interesting that *i*-CME also is not oxidized by DDQ.



codeine methyl ether



isocodeine methyl ether

Isocodeine methyl ether was obtained from isocodeine in a manner analogous to the formation of codeine methyl ether from codeine. Isocodeine was prepared in 71% yield by inversion of codeine via reaction with dimethylformamide dineopentyl acetal and acetic acid to yield isocodeine 6-acetate which was then hydrolyzed. This method for the inversion of saturated secondary alcohols[20] is thus applicable to an allylic alcohol. Preparation of isocodeine by this process is comparable in yield (65–70%) and easier to perform than the procedure via codeine 6-tosylate.[21]

The synthesis of oripavine from morphine was patterned after the synthesis of thebaine from codeine. We first thought that the phenolic group of morphine would have to be protected in order to get selective methylation of the 6-OH; therefore, morphine 3-benzoate (**1f**) was prepared analogously to the reported method for morphine 3-acetate.[22] However, attempts to methylate morphine 3-benzoate gave mostly morphine 6-benzoate (**1g**). The alternatives were either to find another blocking group or to attempt selective methylation of morphine directly. The latter alternative was selected, and the dipotassium salt of the di-O-anion of morphine, when treated with methyl iodide, gave morphine 6-methyl ether (**1d**, heterocodeine) in 92% yield. The phenolic group at C-3 of heterocodeine was then blocked as the acetate. Oxidation with γ-MnO_2 and hydrolysis gave oripavine in an overall yield of 73% from morphine.

Experimental Section[23]

Codeine Methyl Ether (1c). An excess of potassium hydride (300 mol %, 35% dispersion in oil) was washed with hexane (3 × 50 ml, distilled from CaH_2) and then suspended in THF (50 ml, distilled from $LiAlH_4$). With stirring under a nitrogen atmosphere, a solution of codeine (1.00 g, 2.33 mmol) in 50 ml of THF was added to the KH suspension over a period of 2 hr and stirred for an additional hour. Methyl iodide (0.43 ml, 6.66 mmol) was added to the mixture rapidly and the reaction was quenched after 90 sec with 20 ml of 1 *N* $NaOC_2H_5$ in ethanol. Water (50 ml) was added and the solution evaporated to remove organic solvents. The resulting aqueous mixture was extracted with chloroform (4 × 50 ml), and the chloroform extracts were washed with a small portion of water, dried over $MgSO_4$, and evaporated to give a crude solid which was crystallized from ethanol to give 0.87 g (83%), mp 138–139° (lit.[14]

mp 140–141°), identical with an authentic sample of codeine methyl ether by TLC, GC, mass spectrum [*m/e* 313 (M^+)], and NMR.

Thebaine (2a). A. By Oxidation with DDQ. To a stirred solution of codeine methyl ether (156 mg, 0.5 mmol) in 5 ml of benzene under a nitrogen atmosphere was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (119 mg, 0.525 mmol) and the dark green precipitate (272 mg) which formed was collected by filtration. The filtrate yielded 7 mg of CME. When 50 mg of the precipitate was partitioned between chloroform and aqueous $NaHCO_3$, 28 mg of CME was recovered from the chloroform layer. The green precipitate (50 mg) was suspended in 5 ml of benzene and another portion of DDQ (22 mg, 0.097 mmol) was added and the mixture was boiled overnight. The precipitate (64 mg), now red brown, was collected by filtration and was partitioned between chloroform and aqueous $NaHCO_3$ to give in the $CHCl_3$ phase 26 mg of an oil which by TLC and GC contained CME and thebaine in a 1:1 ratio.

B. By Oxidation with Chloranil. Codeine methyl ether (159 mg, 0.508 mmol) was refluxed with o-chloranil (131 mg, 0.535 mmol) in 5 ml of benzene under a nitrogen atmosphere for 6 hr. After the usual work-up GC analysis showed 70% CME remaining and a small portion of thebaine.

C. By Oxidation with γ-MnO_2. A solution of codeine methyl ether (313 mg, 1.00 mmol) in THF (10 ml, distilled from $LiAlH_4$) was shaken vigorously with γ-MnO_2 (440 mg, 5.0 mmol) under a nitrogen atmosphere at room temperature. Further portions of γ-MnO_2 (440 mg, 5.0 mmol) were added at intervals of 1, 3, 5, and 10 hr. After 24 hr the black mixture was filtered through a fine sintered glass funnel, the residue was washed with THF (4 × 50 ml), and the washings were combined with the original filtrate and evaporated to give 207 mg of crude thebaine. The MnO_2 was then washed with methanol (4 × 30 ml) which yielded an additional 119 mg of crude thebaine. The two fractions were combined and crystallized from ethanol to give thebaine (251 mg, 80%) identical with an authentic sample by mp (191–192°), TLC, GC, mass spectrum [*m/e* 311 (M^+)], and NMR.

Morphine 6-Methyl Ether (Heterocodeine, 1d). Potassium hydride (57.0 g, 331 mmol, 27% dispersion in oil) was washed with dry hexane, suspended in THF (1000 ml, distilled from $LiAlH_4$), and cooled in an ice bath under a nitrogen atmosphere. A solution of morphine monohydrate (11.4 g, 37.5 mmol) in 1 l. of THF was added slowly, and the resulting white suspension was stirred for 6 hr and allowed to warm to room temperature. Methyl iodide (2.7 ml, 43.4 mmol) was added and an aliquot of the reaction was analyzed after 25 min by GC; no morphine remained and only heterocodeine was present. The reaction was quenched by slowly adding water and cooling in an ice bath. The solution was neutralized to pH 7, the THF was evaporated, the pH of the solution was readjusted to 12.5, and it was extracted with chloroform to remove any phenolic methyl ether. The pH was then adjusted to 8.6 and the solution extracted with chloroform–2-propanol (3:1). This extract was evaporated to give a brown oil from which heterocodeine (9.44 g) was crystallized from ethyl acetate. The mother liquor was chromatographed on thin layer ($CHCl_3$–CH_3OH–NH_4OH, 3:1:1%) to give additional heterocodeine (0.82 g): total yield, 91.6%; mp 242–243° (lit.[24] mp 242°); NMR δ 2.5 (s, 3 H), 3.5 (s, 3 H), 4.9 (d, 1 H, *J* = 3 Hz), 5.5 (m, 2 H), 6.5 (q, 2 H, *J* = 4 Hz); mass spectrum *m/e* 299 (M^+).

Morphine 3-Acetate 6-Methyl Ether (Heterocodeine 3-Acetate, 1e). Acetic anhydride (0.35 ml, 3.70 mmol) was added to a solution of heterocodeine (0.97 g, 3.25 mmol) in pyridine (7.5 ml, distilled from BaO) at room temperature and under a nitrogen atmosphere. After 2.5 hr the reaction was complete (TLC and GC) and it was quenched with ice and water (125 ml). The resulting aqueous solution was extracted with chloroform (4 × 100 ml), and the chloroform extracts were washed with water, dried over Na_2SO_4, and evaporated to give 1.08 g (97%) of heterocodeine 3-acetate (1e): mp 133.5–134.0° on crystallization from ethanol; NMR δ 3.5 (6-OCH_3), 2.5 (NCH_3), 2.18 ($OCOCH_3$); mass spectrum *m/e* 341 (M^+). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

Oripavine 3-Acetate (2b). Portions of γ-MnO_2 (5 × 440 mg, 5 × 5.0 mmol) were added to a solution of heterocodeine 3-acetate (1e, 341 mg, 1.0 mmol) in THF (50 ml, distilled from sodium benzoketyl) at intervals of 1, 2, 3, and 4 hr at room temperature with shaking. After a total of 24 hr of shaking the reaction mixture was filtered and the precipitate was washed with fresh THF (4 × 50 ml) which was combined with the filtrate and evaporated to give a tan foam of 264 mg, homogeneous by TLC. The precipitate was then washed with methanol 4 × 50 ml) to give an additional 82 mg which contained a trace of 1e. The two residues were combined and crystallized from ethanol to give oripavine 3-acetate (2b) in 88% yield: mp 173°; NMR showed the expected quintet in the 5–6-ppm region for the 5, 7, and 8 protons; mass spectrum *m/e* 339 (M^+); homogeneous by TLC. Anal. ($C_{20}H_{21}NO_4$) C, H, N.

Oripavine (2c). Oripavine 3-acetate (2b, 224 mg, 0.67 mmol) was dissolved in methanol–water (4:1, 25 ml) and 2 *N* NaOH (2 ml) was added. Reaction was complete in less than 2 min (TLC), 14 ml of water was added, the pH was lowered to 8, and the methanol was evaporated. The resulting aqueous solution was adjusted to pH 8.9 and extracted with chloroform–2-propanol (3:1, 5 × 50 ml). The extracts were combined, washed with aqueous $NaHCO_3$ (saturated, 2 × 75 ml), dried over Na_2SO_4, and evaporated to give 184 mg (93%) of oripavine (2c): homogeneous by TLC; mass spectrum *m/e* 297 (M^+); mp 199–200° (lit.[4] mp 200–201°); NMR, same as thebaine minus 3-OCH_3.

Isocodeine. A mixture of dimethylformamide dineopentyl acetal (17.3 ml, 60.0 mmol) and glacial acetic acid (3.6 ml, 60.0 mmol) in toluene (60 ml, dried over Na) was added in two portions 3 hr apart to a solution of codeine (3.00 g, 10.0 mmol) in toluene (250 ml) heated to 80° under a nitrogen atmosphere with stirring. The reaction solution was then stirred and heated at 80° for an additional 21 hr, after which 100 ml of *o*-xylene was added and the mixture evaporated at 80°. *o*-Xylene was added and evaporated twice more to give crude isocodeine 6-acetate. The crude isocodeine acetate was hydrolyzed with aqueous methanolic NaOH to give a crude solid which was crystallized from ethanol yielding 2.12 g (71%) of isocodeine: mp 173.5–174.5° (lit.[21] mp 173–174°); homogeneous by TLC and GC; mass spectrum *m/e* M^+ 297; and NMR consistent with the literature.[21]

Isocodeine Methyl Ether. Isocodeine (297 mg, 1.00 mmol) was treated in a similar fashion as in the preparation of codeine methyl ether to give 283 mg of an oil which contained isocodeine and isocodeine methyl ether. This mixture was separated by preparative thin-layer chromatography to give 167 mg of isocodeine methyl ether (mp 94.5–95° from ethanol) and 32 mg of isocodeine, each homogeneous by TLC and GC. The isocodeine methyl ether had a mass spectrum *m/e* 313 (M^+); its NMR was the same as that of isocodeine except for the presence of 6-*O*-methyl absorption at δ 3.6 (s, 3 H). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

Geraniol Methyl Ether. Geraniol (1.00 g, 6.5 mmol) was treated in a similar fashion with KH and methyl iodide as in the preparation of codeine methyl ether to give an oil: 0.56 g (51%); bp 85–88° (8 mm) [lit.[25] bp 100–105° (10 mm)]; NMR same as geraniol plus an *O*-methyl absorption at δ 3.3 (s, 3 H).

Bromination of Codeine Methyl Ether. 1-Bromocodeine Methyl Ether. To a stirred solution of 500 mg of codeine methyl ether in 60 ml of methylene chloride in a nitrogen atmosphere and cooled in a Dry Ice–acetone bath was added, over 0.5 hr, a cooled solution of 368 mg of bromine in 30 ml of methylene chloride. Potassium hydrosulfite (1.0 g) and saturated potassium carbonate solution (50 ml) were added, the mixture was removed from the cooling bath, and the organic phase was separated. Evaporation of the methylene chloride after washing and drying gave a residue (631 mg) which was chromatographed on silica gel, eluting with methanol–chloroform (1:3). Recovered codeine methyl ether and 1-bromocodeine methyl ether were obtained; crystallization from methanol gave the 1-bromo compound of mp 159°. Anal. ($C_{19}H_{22}BrNO_3$) C, H, N.

Bromination in carbon tetrachloride gave the same result as did the use of tetramethylammonium tribromide and free-radical bromination with *N*-bromosuccinimide.[26]

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Cardiovascular Activity of Aromatic Guanidine Compounds

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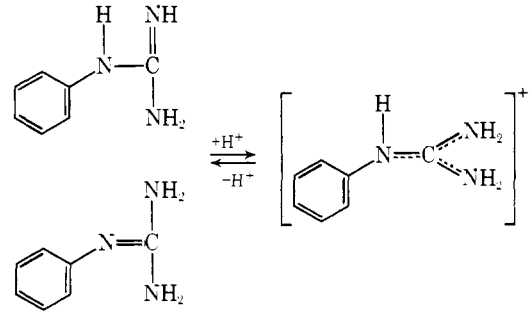
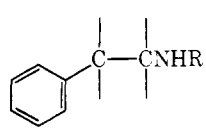
A series of aromatic guanidines and several 1-phenylbiguanides was prepared and tested for cardiovascular (CV) effects in anesthetized dogs measuring heart rate, blood pressure, carotid artery blood flow, and myocardial force changes. The predominant CV effect at minimally effective dose was vasoconstriction unassociated with cardiac stimulation. The structure–activity relationships of the compounds were discussed comparing their structural similarities to the β-phenylethylamines. The most potent members of the series were phenylguanidines substituted in the 3 and 4 positions on the aromatic nucleus with hydroxy or chloro groups. Preliminary mechanism studies indicated that the 3,4-dihydroxyphenylguanidines act at least partially by a direct α-adrenergic mechanism.

During a general screening program of organic compounds several phenylguanidine compounds were found to exhibit biological activity similar to the familiar adrenergic action of the β-phenylethylamine series. Examination of the two significant tautomeric structures and the protonated species of phenylguanidine I, which would be expected to exist at physiologic pH, reveals obvious structural similarity to the β-phenylethylamine series II.



I



II

Both structures I and II have aromatic groups and basic amino groups separated by similar distances. The bond distance between the central carbon and each nitrogen of the guanidine nucleus has been reported to be 1.32 Å[1] in contrast to 1.46 Å for an aliphatic carbon to carbon bond. The guanidine compounds would, however, be planar and thus more rigid than the aliphatic portion of the β-phenylethylamine series. Using these considerations as a rationale, a large series of aromatic guanidine and several 1-phenylbiguanide compounds were prepared. The pharmacological actions of these compounds were investigated to determine if they possessed potentially useful cardiovascular effects.

Chemistry. The guanidine and biguanide moieties of the compounds described in Tables I and II were prepared using five different methods. The method selected for each compound was dependent upon the location and number of substituents on the guanidine or biguanide nitrogens. For the preparation of the monosubstituted guanidine compounds and the 1,1-disubstituted compounds in Tables I and II, the well-known reaction of an aromatic amine mineral acid salt and hydrogen cyanamide in a refluxing solution of water or aqueous ethanol was used (method 1).[2]

The aromatic amines were obtained commercially or