Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. IV.[1] Acid-Catalyzed Rearrangements of Alcohols of the 6,14-*endo*-Ethenotetrahydrothebaine Series

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Abstract: Alcohols of general structure I have been dehydrated to olefins II which have been further converted into 14-alkenylcodeinones V, themselves transformed by further acid-catalyzed reactions into recyclized products VII and IX and derivatives of 5,14-thebainone (XV). 14-(3-Methylbut-2-enyl)codeine (XXVII) has been converted into a derivative XXIX of (−)-sinomenilan, the structure of which has been demonstrated by spectral studies and by conversion *via* the bases XXX and XXXIII into the olefin XXXIV.

The alcohols of the 6,14-etheno- and -ethanotetrahydrothebaine and -oripavine groups described in the preceding two papers in this series[2] are all unstable in acid media, in which they suffer dehydration and rearrangement, the speed, extent, and course of which depends on the nature of the alcoholic group and the 6,14 bridge and on the conditions of the reaction. In all cases the first product appears to be an olefin. The olefins are generally preparable in good yield by heating the alcohols in 98–100% formic acid, though in some cases further reaction takes place before complete dehydration occurs. In no case was evidence obtained of the production of more than one olefin, and in the cases examined the olefin is the product of dehydration in the side chain rather than toward C-7.

The olefin II ($R^1 = R^2 = H$) on ozonolysis affords formaldehyde and the ketone III, and the olefin II ($R^1 = H$, $R^2 = Et$) yields propionaldehyde, thus confirming the structures assigned to these bases. The structure II ($R^1 = R^2 = H$) for the olefin derived from the alcohol I (R = Me) is further confirmed by its production from the ketone III by the Wittig reaction, and by its nmr spectrum, which shows a two-proton signal at δ 4.80 ($H_2C{=}C<$) and a three-proton signal at δ 1.60 ($={}CCH_3$). The production of the same olefin II ($R^1 = H$, $R^2 = Me$) from two diastereoisomeric alcohols of structure I (R = Et) and of the olefin II ($R^1 = H$, $R^2 = Et$) from two alcohols of structure I (R = *n*-Pr) shows that the alcohols in each case are diastereoisomers at the asymmetric alcoholic carbon atom and do not differ at C-7.[2,3]

Olefins analogous to those of structure II, but bearing a 6,14-ethano bridge are preparable by the dehydration of the 6,14-ethano analogs of the alcohols of structure I. Catalytic reduction of the olefins II in general results in the saturation of the 6,14-etheno bridge, which is appreciably less hindered than in the alcohols I, but in addition the methylene group in the olefin II ($R^1 = R^2 = H$) is also reduced; the more heavily substituted double bond in the olefin II (R = H, R^1 = *n*-Pr) is more resistant to reduction.

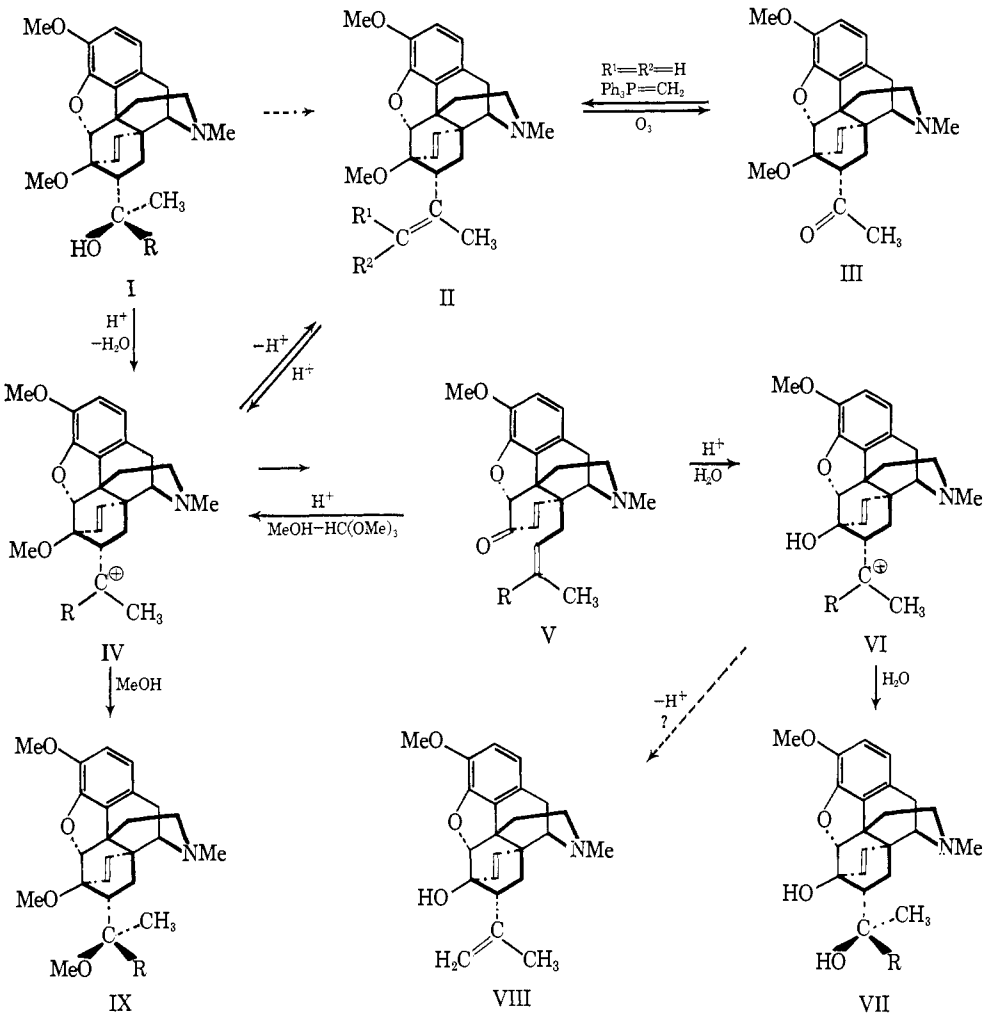
The olefins themselves are unstable under acid conditions, but the ease of rearrangement appears to depend on the degree of substitution of the double bond. For example, the olefin II ($R^1 = R^2 = H$, CH_3 = Ph) is completely rearranged after 10-min boiling in 98–100% formic acid, and the olefin II ($R^1 = R^2 = H$) after 3 hr-boiling, whereas the trisubstituted olefins II ($R^1 = H$) are stable to boiling formic acid and require heating with dilute mineral acid before rearrangement can be effected. Presumably the ease of rearrangement is dependent on the ease of protonation of the double bond to give the carbonium ion IV, which can either revert to the olefin II with the loss of a proton, or can suffer ring fission to give the 14-alkenylcodeinone (V). Compounds of this structure V (R = Me and Ph) have been isolated from the products rearrangement of the alcohols I (R = Me and Ph) and the derived olefins, and the ketone V (R = Ph, CH_3 = Et) has been obtained from the alcohol I (R = Ph, CH_3 = Et). In each of these cases, rearrangement to the codeinone was complete in refluxing 98–100% formic acid. In other cases, the alkenylcodeinones are only obtained when the alcohols or olefins are heated with dilute mineral acid. Under these conditions, however, the unsaturated ketones are themselves susceptible to further rearrangement (see following paper), and hence the yields of the codeinones in these cases are very poor, and the isolation of pure materials from the reaction mixtures is difficult.

The structures assigned to the 14-alkenylcodeinones (V) are in accord with their chemical properties and absorption spectra. They are insoluble in alkalies and do not couple with diazonium salts. Their infrared spectra show carbonyl absorption at 1690 cm^{-1}, and the ultraviolet spectra of the bases V (R = Ph and also R = Ph,CH_3 = Et) are styrenoid. The nmr spectrum of the base V (R = Ph) shows signals (in δ units) at 7.23 (five aromatic H), 6.52 (C-1 and C-2 H), doublets centered at 6.52 (C-8 H) and 6.05 (C-7 H) ($J_{7,8}$ = 10 cps), a triplet centered at 5.58 (CH=CMePh), and singlets at 4.65 (OCH), 3.78 (C-3 OCH_3), 2.40 (NCH_3), and 2.02 ($C{=}CPhCH_3$). The spectrum of the base V (R = Me) is similar to that of the base (R = Ph), but

(1) (a) Part III: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3281 (1967). (b) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963); since the publication of this report some similar work on a simpler system has been reported by A. J. Birch and J. S. Hill, *J. Chem. Soc.*, 419 (1966).

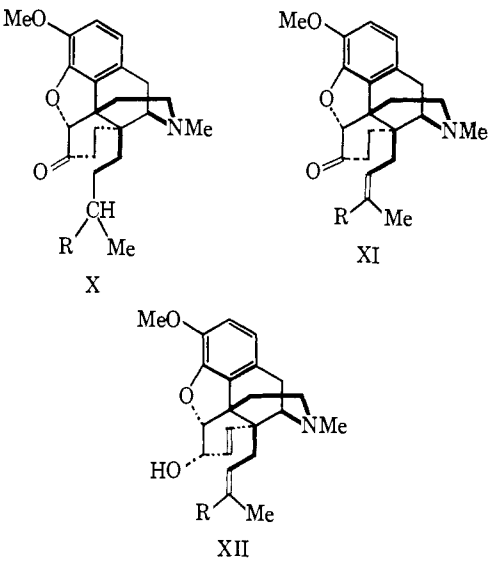
(2) Part II: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3273 (1967).

(3) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1720 (1958).



lacks the signals at 7.23 and 2.02 and shows instead signals at 1.68 (3 H) and 1.47 (3 H) attributed to the methyl groups in the system C=CMe$_2$.

Catalytic reduction of the 14-alkenylcodeinones proceeds very sluggishly and affords poor yields of 14-alkyldihydrocodeinones (X), but isolation of pure materials is difficult since mixtures of isomers appear to be formed in most cases. Reduction only of the α,β-unsaturated ketone system of the base V (R = Me) could not be accomplished with zinc and acetic acid or with sodium amalgam, both of which reagents yielded mixtures containing phenols resulting from opening of the 4,5-oxygen bridge. The dihydro compound XI (R = Ph) was, however, obtained, together with the alcohol XII (R = Ph), by the reduction of the unsaturated ketone with sodium borohydride in pyridine.[4] The alkenyldihydrocodeinones XI are not accessible by the rearrangement of the 6,14-ethano alcohols analogous to those of structure I, since they appear to suffer further rearrangement in acid media very much more readily than their α,β-unsaturated counterparts, and the rearrangements only furnish either olefins or phenolic bases. The C-6 carbonyl group in the 14-alkenylcodeinones and their reduction products can be reduced very readily with sodium borohydride to give the related derivatives of codeine, for example, the 14-alkenylcodeines (XII). In this reduction there is no evidence of the production of more than one alcohol, and there is no reason to suppose that the reduction occurs less stereospecifically than does that of codeinone, which gives only codeine,[5] since only one side of the carbonyl group is readily accessible to hydride ion. The corresponding morphinones and morphines are accessible by the rearrangement of alcohols of the tetrahydrooripavine series.



(4) We are indebted to Dr. J. W. Lewis and Mr. M. J. Readhead of this laboratory for details of this reaction, the further implications of which will be discussed in a subsequent publication.

(5) M. Gates, *J. Am. Chem. Soc.*, 75, 4340 (1953).

The 14-alkenylcodeinones and morphinones are, however, only intermediates in the complex rearrangements that the alcohols of structure I and their phenolic analogs undergo in acid media. When the alcohol I (R = Me) is warmed at 45° with 6 *N* hydrochloric acid for 6–7 hr or kept in the same medium at 25° for 3 days, it is converted in good yield into the 6-hydroxy analog VII (R = Me), the infrared spectrum of which is very similar to that of the parent alcohol I (R = Me) and shows no carbonyl absorption. The nmr spectrum shows no band attributable to the C-6 methoxyl group, but does show two bands at δ 4.71 and 4.48 that disappear after shaking the base with deuterium oxide and that must, therefore, be due to two hydroxyl groups, the rest of the spectrum being virtually identical with that of the parent alcohol. Since the ketones III (also CH_3 = Ph) are unaffected under the conditions under which the alcohol I (R = Me) is demethylated, this demethylation may be assumed to proceed through the alkenylcodeinone V (R = Me), by recyclization to the carbonium ion VI (R = Me), which can then either lose a proton to give the 6-hydroxyolefin VIII, or react with a water molecule to give the alcohol VII (R = Me). This process has, indeed, been accomplished separately starting with the codeinone V (R = Me), which on standing in cold 6 *N* hydrochloric acid affords the alcohol VII (R = Me) in good yield. The olefin VIII has not yet been isolated. Further support for this mechanism is forthcoming from the action of methyl orthoformate, methanol, and perchloric acid on the codeinone V (R = Me) which leads, presumably *via* the carbonium ion, to the carbinol methyl ether IX (R = Me) (40%) and the olefin II (R^1 = R^2 = H) (4%).[6] The alcohol VII (R = Me) can be converted back into the alkenylcodeinone V (R = Me) by heating with 100% formic acid.

If the alkenylcodeinone V (R = Me), the alcohols I (R = Me) and VII (R = Me), or the olefin II (R^1 = R^2 = H) is heated with 6 *N* hydrochloric acid at 100° for a short period, further rearrangement occurs, and the major product is a phenolic base isomeric with the codeinone V (R = Me) and, like the latter, an α,β-unsaturated ketone. The phenolic hydroxyl must appear as the result of fission of the 4,5-oxide bridge, in which case a new bond must be formed to C-5, and the base is clearly an analog of flavonepenthone (XV, R = H, R^1 = Ph)[3,7] and may be assigned the structure XV (R = R^1 = Me). This is supported by the nmr spectrum of the base which shows signals (in δ units) at 6.58 (two aromatic H), doublets centered at 6.77 (C-8 H) and 5.67 (C-7 H) ($J_{7,8}$ = 10 cps), singlets at 4.42 (C-5 H), 3.77 (aromatic OCH_3), 2.36 (NCH_3) and 1.86 and 1.70 ($=CMe_2$), and by the ozonolysis of the base, which affords acetone.

The ultraviolet spectrum of the base XV (R = R^1 = Me) further supports the assigned structure, showing as it does the long wavelength absorption band λ_{max} 3350 A, which is a characteristic feature of the spectra of flavothebaone (XIX),[8] benzflavothebaone (XX),[9] and flavonepenthone (XV, R = H, R^1 = Ph),[3] though the intensity of absorption at this wavelength is somewhat less than in these three bases. This absorption band in flavothebaone has been attributed by Meinwald and Wiley[10] to charge transfer between the quinol nucleus and the enone system as shown in formula XXI, but such charge transfer is not possible in bases of general structure XV, in which no oxygen atom is available to supply electrons. Bentley, Dominguez, and Ringe,[8] however, have suggested that this long wavelength absorption band is simply the absorption band of the α,β-unsaturated ketone system, which normally appears in this region but which in normal circumstances is very weak (ϵ_{max} ~50) intensified (ϵ_{max} ~2000) as a result of the perturbation of the enone system by the spatially proximate π orbitals of the unsaturated system, the precise nature of which (quinol, naphthaquinol, styrene, or isolated double bond) appears to be of little importance.

Bases of general structure XV can arise from the 14-alkenylcodeinones by protonation of the oxide bridge, bridge fission, and Markovnikov addition of the resulting carbonium ion to the side-chain double bond, as in XIII → XV.[3] Non-Markovnikov addition, clearly unlikely, would lead to a base of structure XVI, which is demonstrably not that of the product. Alternatively, since the alkenylcodeinone is in equilibrium with the recyclized carbonium ion VI in acid solution, rearrangement may take place by way of such an ion and the olefin XVII, in which concerted bridge fission and migration in a pinacolone type rearrangement can occur. The geometry of the molecule of the olefin XVII is particularly favorable for such a 1,2 shift. In view of the formation of the olefin II from the carbonium ion IV, the ion XIV might be expected to give the olefin XVIII instead of the actual product XV.

Other bases analogous to the base XV (R = R^1 = Me), bearing substituents other than a methyl group on the nitrogen atom, are preparable in about 40–50% yield by the rearrangement of the corresponding analogs of the alcohol I (R = Me), and the related 3-hydroxy compounds may be obtained either by the demethylation of the 3-methoxy bases with 48% hydrobromic acid or by the combined rearrangement and demethylation of the appropriate alcohol with this reagent.

Zinc and acetic acid reduction of the unsaturated ketone XV (R = R^1 = Me) affords the saturated ketone,[11] which is the sole end product of the rearrangement of the 6,14-ethano analog of the alcohol I (R = Me). In this reaction, the 14-alkenyldihydrocodeinone (X, R = Me) has not been detected an an intermediate in the reaction and it may be concluded that this base is rearranged more rapidly than the corresponding codeinone.

During the rearrangement of the alcohol I (R = Me) and the codeinone V (R = Me), a second process competes with the formation of the phenol XV (R = R^1 = Me) giving rise to an isomer of the latter. This process,

(6) We are indebted to Dr. J. J. Brown of Lederle Laboratories, Pearl River, N. Y., for details of this reaction.

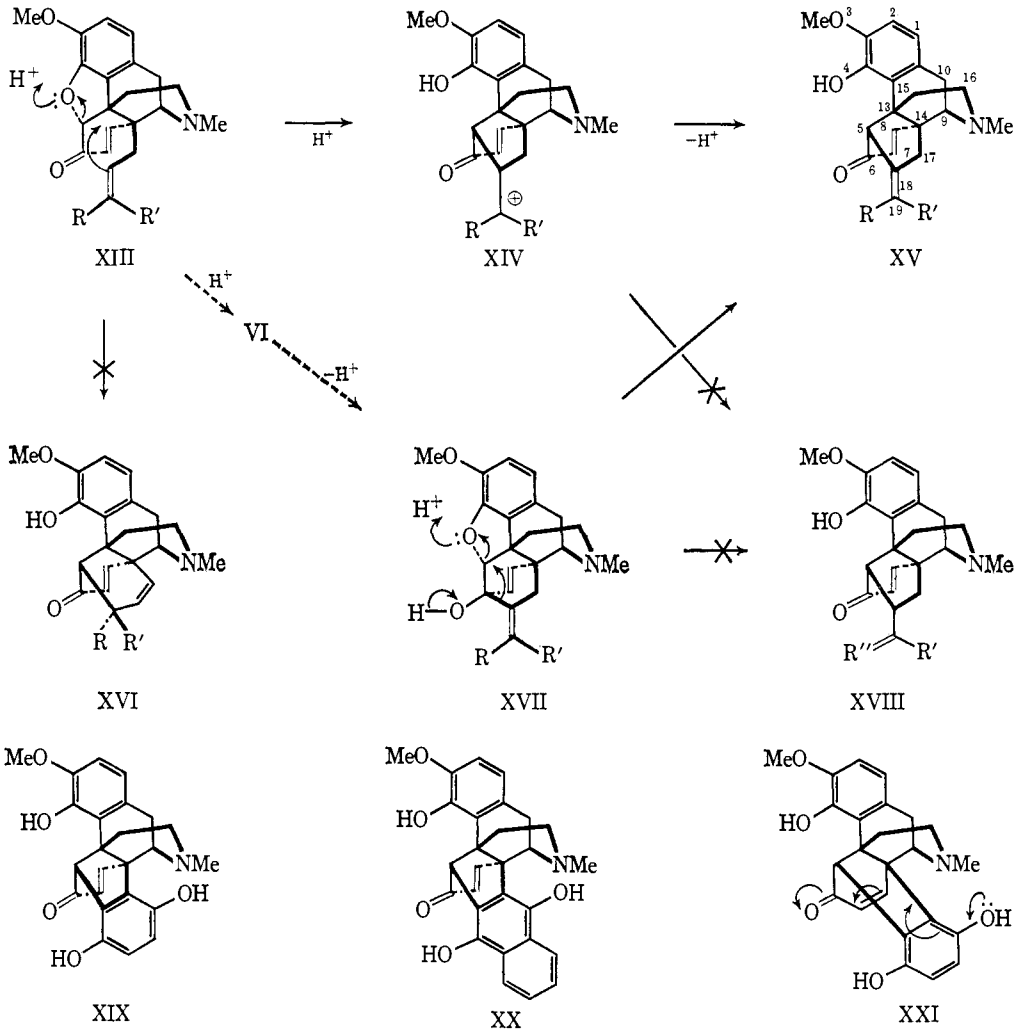
(7) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1725 (1958).

(8) K. W. Bentley, J. Dominguez, and J. P. Ringe, *ibid.*, **22**, 418 (1957).

(9) K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *ibid.*, **23**, 941 (1958).

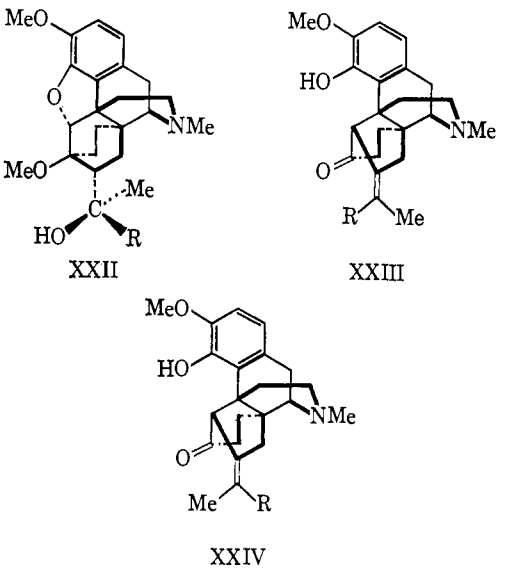
(10) J. Meinwald and G. A. Wiley, *J. Am. Chem. Soc.*, **79**, 2569 (1957).

(11) 14-Hydroxycodeinone undergoes bimolecular coupling during reduction with zinc and acetic acid [L. J. Sargent and U. Weiss, *J. Org. Chem.*, **25**, 987 (1960)], but the enone system present in the bases of general structure XV is so shielded by the other parts of the molecule that bimolecular coupling is very seriously hindered. In the 14-alkenylcodeinones of structure V the enone system is much less hindered, and bimolecular coupling may be assumed to be involved in part in the formation of the very complex product of reduction of these bases with zinc and acetic acid.



which is discussed in the following paper,[12] becomes the dominant one in the rearrangement of alcohols I in which R is not a methyl group, with the result that bases of structure XV then become minor products of the reaction. For example, the rearrangement of the alcohol I (R = Ph) affords only 1.6% of the phenol XV (R = Me, R¹ = Ph). This competing reaction, however, involves the 14-alkenylcodeinone (V) as an essential intermediate and is not operative in the rearrangement of the 6,14-ethano alcohols. Rearrangement of the alcohols XXII (R = *n*-Pr), XXII (R = *n*-Bu), XXII (R = *n*-Am), however, affords mixtures in each case of two isomeric phenols. The products from the alcohol XXII (R = *n*-Bu) have identical infrared spectra, and these are presumably *cis–trans* isomers XXIII and XXIV, which could obviously arise from the intermediate carbonium ion, whether this be of the type XIV or VI.

The presence of the carbonyl group in the alkenylcodeinone V (R = Me) is essential for the rearrangement of this base to the phenol XV (R = R¹ = Me) by recyclization to the carbonium ion VI and concerted oxide bridge opening and rearrangement as in XVII, and may be necessary for activation of the 4,5-oxide bridge if the rearrangement proceeds as shown in formulas XIII → XV. The reaction of the 14-alkenyl-

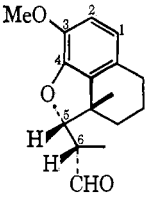


codeine (XII, R = Me), which contains no carbonyl group, with hot concentrated hydrochloric acid was accordingly examined. This reaction yielded a complex mixture of products from which a crystalline base "A," mp 200°, was recovered in 25% yield. Base "A" is isomeric with the codeine XII (R = Me), and its infrared spectrum shows carbonyl absorption at 1730 cm^{-1} but no hydroxyl absorption. It is very sparingly soluble in ethanol but dissolves readily on the addition

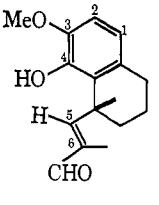
(12) Part V: K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3303 (1967).

of sodium ethoxide to give a deep yellow solution, which couples readily with diazotized sulfanilic acid to give a blood red solution. Base "A" is recovered from the yellow ethoxide solution on the addition of water, but the addition of an excess of ammonium chloride solution results in the precipitation of a new base "B," which is isomeric with base "A" and shows phenolic hydroxyl absorption and carbonyl absorption at 1690 cm^{-1} in the infrared. Base "B" is readily soluble in ethanol, and the solution rapidly deposits base "A" on the addition of a small amount of aqueous sodium hydroxide. The reduction of base "A" with sodium borohydride in neutral solution affords a nonphenolic alcohol, whereas reduction in the presence of sodium ethoxide yields a phenolic alcohol, and both of these products are stable to alkalis.

Base "A" reacts relatively slowly with bromine and, hence, cannot contain an olefinic center, and this is confirmed by the failure of ozonolysis to yield either acetone or formaldehyde. The nmr spectra of bases "A" and "B" show that both of these bases are aldehydes. Both spectra show signals attributable to the C-1 C-2 aromatic protons and protons of the OCH_3, NCN_3, and two CCH_3 groups. The two CCH_3 peaks appear at δ 1.0 and 0.77 in the spectrum of base "A" and at δ 1.16 and 1.03 in the spectrum of base "B," indicating that neither base contains the system $=CMe_2$, and that some change in the distant environment of the two methyl groups occurs in the conversion of base "A" into base "B." The aldehyde proton signal in the spectrum of base "A" is a doublet at δ 9.35, J = 2 cps, suggesting that the system >CHCHO is present in this base, whereas the corresponding signal in the spectrum of base "B" is a singlet at δ 9.76, which is consistent with the presence in this base of the system C=CCHO. This interpretation is consistent with the shift of carbonyl absorption frequency from 1730 to 1690 cm^{-1} in the conversion of base "A" into base "B." The reversible conversion of the system CCHCHO into C=CCHO with the simultaneous appearance of a phenolic hydroxyl group suggests that base A and base B are related as shown in part structures XXV and XXVI, and in agreement with this the C-5 proton of XXV is revealed in the nmr spectrum of base A by a doublet centered at δ 5.15, $J_{5,6}$ = 9 cps, which is absent from the spectrum of base B. The spectrum of base B, however, shows a one-proton signal at δ 7.68, which is absent from the spectrum of base A and is attributable to the C-5 proton in XXVI.

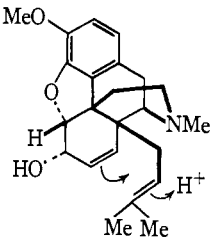


XXV

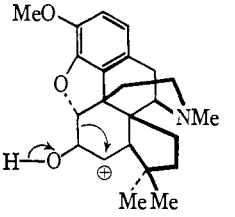


XXVI

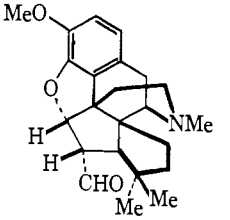
The spectrum of base A shows no signal attributable to an olefinic proton and, hence, both of the double bonds in the base XII (R = Me) must be involved in a cyclization process, in which case the side-chain methyl groups would appear as a *gem*-dimethyl group in the product. The appearance of an aldehyde group in base A indicates the contraction of ring C of XII and all of these requirements are met by the mechanism shown in formulas XXVII → XXIX. The resulting structures for base A XXIX and base B XXX are in agreement with all of the known facts about these bases. A model of the structure XXIX, which can be constructed with very little strain, shows that steric hindrance is least with the CHO group disposed on the same side of the molecule as the oxide bridge, and it may be noted that the infrared spectrum of the alcohol XXXI derived from base A shows a band attributable to a hydrogen-bonded hydroxyl group and that hydrogen bonding is easily accommodated in the structure XXXI but is impossible in the epimeric structure XXXII.



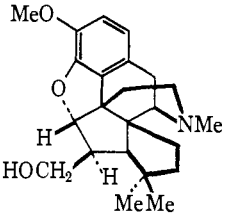
XXVII



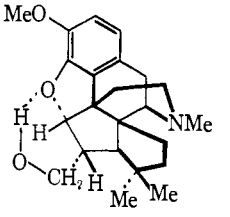
XXVIII



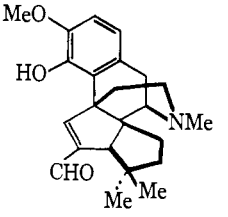
XXIX



XXXII



XXXI



XXX

The primary alcohol XXXIII, obtained by the reduction of base A in sodium ethoxide solution, might be expected to suffer dehydration in acids by the mechanism shown, with 4,5-oxide ring closure, to give the olefin XXXIV, by analogy with the way in which both isomers of the dienol XXXV are cyclized to thebaine.[13-16]

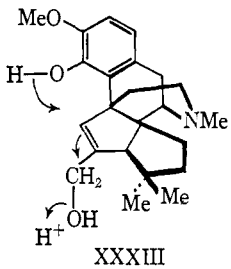
(13) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 2423 (1965).

(14) A. Matthiessen and C. R. A. Wright, *Proc. Roy. Soc.*, (London), 18, 83 (1869); A. Matthiessen and C. R. A. Wright, *Ann. Suppl.*, 7, 364 (1870); L. Knorr and H. Horlein, *Ber.*, 40, 4883 (1907).

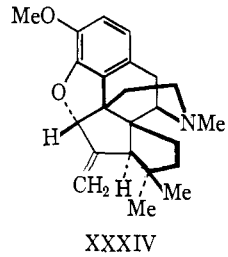
(15) L. Knorr and H. Horlein, *ibid.*, 41, 969 (1908).

(16) The numbering of the ring system is given in structure XV. The 5,14-ethano bridge is on the same side of the molecule as are the hydrogen atoms at C-5 and C-14 in thebainone, as is implied by the nomenclature used.

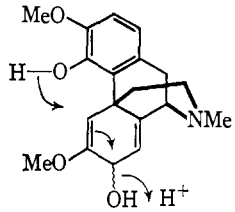
The alcohol is recovered unchanged from hot dilute hydrochloric acid but on heating with concentrated hydrochloric acid is converted into a crystalline base that shows no hydroxyl absorption in the infrared but does show nmr signals (in δ units) at 6.67 (two aromatic H), 3.92 (C-3 OCH_3), 2.46 (NCH_3), 1.07 (6 H, $2CH_3$), a complex one-proton signal at 5.60 (C-5 H, split by the methylene protons), and a two-proton doublet at 4.95 showing further splitting, due to the system $CHC(=CH_2)CH$. There is little doubt that this base has the structure XXXIV.



XXXIII



XXXIV

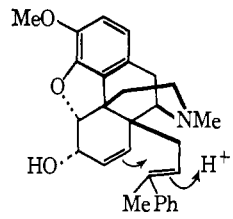


XXXV

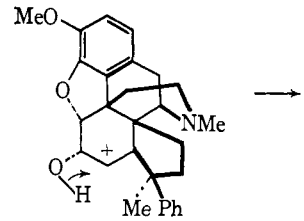
The alkenylcodeine XXXVI, which is an analog of the base XXVII, on heating with concentrated hydrochloric acid gave a mixture from which about 10% of a crystalline solid was easily isolated. This base was isomeric with the codeine XXXVI, but the infrared spectrum showed no carbonyl group absorption. It did not react readily with bromine, and the nmr spectrum showed no signal attributable to an olefinic proton. This spectrum showed signals (in δ units) at about 7.2 (phenyl group protons), 6.72 (C-1 and C-2 H), 4.70 (doublet, C-5 H, $J_{5,6}$ = 9 cps), 3.92 (C-3 OCH_3), 3.05 (2 H), 2.40 (NCH_3), and 1.39 ($PhCCH_3$). It is clear from this spectrum that both of the double bonds present in the codeine XXXVI have disappeared with the conversion of the system CH=CMePh into C—(C—)-CMePh during the production of this new base, and a rational interpretation of this is that the reaction proceeds through the cyclized carbonium ion XXXVII, which is an analog of the ion XXVIII.

This carbonium ion could be converted into a neutral product in several ways, *e.g.*, by the loss of a proton from C-6 or C-8, by reaction with a water molecule to give a glycol, by ring contraction to give an aldehyde similar to the aldehyde XXIX, or by the loss of a proton from the hydroxyl group with the formation of an epoxide ring XXXVIII. Since the infrared spectrum of the base shows neither carbonyl nor hydroxyl group absorption, and the nmr spectrum shows no signal attributable to olefinic or hydroxyl protons, only the structure XXXVIII seems tenable for this compound. The complex two-proton signal at about δ 3.05 in the nmr spectrum of the base may be attributed to the protons at C-6 and C-7.

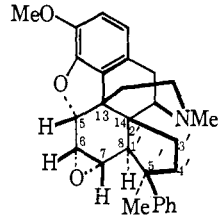
The base is recovered unchanged after treatment with lithium aluminum hydride or acetic anhydride, and is



XXXVI



XXXVII



XXXVIII

attacked only very slowly by potassium periodate in 2 *N* sulfuric acid. The examination of models of the structure XXXVIII and its C-5′ diastereoisomer shows that in both structures attack from above the molecule at C-7 by a hydride ion (which gives an axial C-6 hydroxyl group in the product) is very severely hindered by the methyl or phenyl group at C-5′. Also, although the oxygen atom of the epoxide ring may be attacked by a solvated proton, completion of the reaction with the formation of a *trans*-diaxial 6,7-glycol is very severely hindered by the C-5′ substituent. The stability of the base to the reagents cited above is thus explicable on the basis of the structure XXXVIII.

It may be assumed that the acid-catalyzed rearrangements of the codeines XXVII and XXXVI are complex processes leading to a variety of products, the aldehyde XXIX and the epoxide XXXVIII simply being the most easily crystallized reaction products in the two cases.

The dehydration of the alcohols I to the olefins II and rearrangement to the 14-alkenylcodeinones (V) results in a substantial decrease in analgesic potency, but further transformation into the analogs of flavonepenthone results in the production of bases of high potency. For example, the base XV (R = R′ = Me) is about twice as potent and its methyl ether is about 15 times as potent as morphine.

Experimental Section

6,14-*endo*-Etheno-7α-isopropenyltetrahydrothebaine (II, R^1 = R^2 = H) (Anhydro-19-methylthevinol). a. 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (I, R = Me, 19-methylthevinol) (10 g) was boiled under reflux with 98–100% formic acid (25 ml) for 45 min. The mixture was diluted with ice–water (100 ml) and basified with ammonia, and the product was isolated by ether extraction. The dried extract was evaporated, and the residue was dissolved in benzene (250 ml) and passed down a column of grade 1 neutral alumina (75 g). A yellow band rapidly developed on the column, which was eluted with benzene until this band just reached the foot of the column. The eluate was concentrated and rechromatographed on alumina with elution again only of material running in front of the (narrow) yellow band. Evaporation of the eluate *in vacuo* gave a crystalline residue (3.8 g) which was recrystallized from methanol when the olefin was obtained as white irregular plates, mp 151°.

Anal. Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.7. Found: C, 75.7; H, 7.5.

The hydrochloride, prepared in ethanol–ether had mp 198–200°. Elution of the yellow band on the alumina column with benzene containing 5% of chloroform gave 3.8 g of 14-(3-methylbut-2-enyl)codeinone (V, R = Me) (see below).

b. Methyltriphenylphosphonium bromide (3.6 g, 0.01 mole) was added to a solution of butyllithium (0.01 mole) in hexane–ether under an atmosphere of nitrogen, and the mixture was stirred at room temperature for 4 hr. 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (III, 3.8 g) in dry ether (100 ml) was added to the resulting orange solution, and the mixture was then stirred at room temperature overnight. Solid matter was removed from the mixture by filtration and washed well with ether; the filtrate and washings were then washed with water, dried, and evaporated. The oily residue was crystallized from petroleum ether (bp 40–60°), and the product was shown by thin layer chromatography to consist of approximately a 3:1 mixture of the olefin II ($R^1 = R^2 = H$) and the ketone III. Chromatographic separation of the two was achieved in ether on a silica column, from which the olefin was eluted first and was obtained on recrystallization from methanol as white prisms, mp 151°, alone or mixed with material prepared from the alcohol I (R = Me) as in a above. Use of a 50% excess of the ylide resulted in no improvement in the yield of olefin, and when the ylide was generated with sodium hydride in dimethyl sulfoxide the yield of olefin was reduced, since base-catalyzed rearrangement of the ketone also took place.

Ozonolysis of Anhydro-19-methylthevinol (II, $R^1 = R^2 = H$). Ozonized oxygen, with an ozone delivery rate of 0.5 mmole of ozone/min, was passed into a solution of anhydro-19-methylthevinol (0.38 g, 1 mmole) in 4 *N* acetic acid (50 ml) cooled in ice water. After 12 min, when 2.1 mmoles of ozone had been absorbed, zinc dust was added to the solution, which was shaken for 5 min, filtered, and neutralized with sodium bicarbonate, and then warmed. All of the evolved gas was drawn through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, in which a precipitate of formaldehyde-2,4-dinitrophenylhydrazone, mp and mmp (with an authentic specimen) 166°, was formed.

In a second ozonolysis ozone uptake was limited to 1 mmole and after the neutralization with sodium bicarbonate the mixture was extracted with ether. The ether extract on evaporation afforded a solid from which on chromatographic separation on silica the olefin, mp 151°, and 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine, mp 121°, were recovered. The aqueous phase after the ether extraction on treatment with dimedone gave the formaldehyde derivative, mp 186°, undepressed on mixing with an authentic specimen.

6,14-*endo*-Etheno-7α-(1-phenylvinyl)tetrahydrothebaine (Anhydro-19-phenylthevinol, II, $R^1 = R^2 = H$, $CH_3 = Ph$). 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (I, R = Ph) (10 g) was dissolved in boiling 98–100% formic acid (25 ml), and the solution was boiled for 1.5 min and poured into ice–water. The solution was basified with ammonia; the product was isolated by ether extraction and was chromatographed on grade 1 neutral alumina in benzene solution. The column was eluted with benzene, and the eluate was collected until a yellow band reached the foot of the column. Evaporation of the eluate *in vacuo* and recrystallization of the product from methanol afforded the olefin (1.8 g) as pale fawn plates, mp 145–146°.

Anal. Calcd for $C_{29}H_{31}NO_3$: C, 79.0; H, 7.1. Found: C, 79.1; H, 7.1.

Elution of the yellow band from the alumina column with benzene containing 5% of chloroform afforded 5.3 g of 14-(3-phenylbut-2-enyl)codeinone, mp 168–169° (see below).

6,14-*endo*-Ethano-7α-isopropenyltetrahydrothebaine (Anhydrodihydro-19-methylthevinol, II, $R^1 = R^2 = H$, 6,14-ethano). 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (dihydro-19-methylthevinol, 2.0 g) was boiled under reflux with 98–100% formic acid for 10 min. The mixture was diluted with water, basified with ammonia, and extracted with ether. The dried ether extract on evaporation gave a viscous residue which was chromatographed on alumina in benzene solution with elution with benzene containing 5% of ethyl acetate until the presence of a second base in the eluate was just detectable by thin layer chromatography. The eluate was then evaporated, and the residue was crystallized and recrystallized from petroleum ether (bp 40–60°), when the olefin (0.8 g) was obtained as prisms, mp 127°.

Anal. Calcd for $C_{24}H_{31}NO_3 \cdot 0.5H_2O$: C, 73.9; H, 8.2. Found: C, 73.7; H, 8.2.

6,14-*endo*-Ethano-7α-isopropyltetrahydrothebaine (Dihydro-19-methylthevinan). 6,14-*endo*-Etheno-7α-isopropylpenyltetrahydrothebaine (anhydro-19-methylthevinol, 1.0 g) was shaken under hydrogen at 22° (760 mm) in the presence of 5% palladium on charcoal (250 mg) until absorption of hydrogen (130 ml, 2 moles) ceased (3 hr). The solution was filtered from catalyst and evaporated, when the saturated base was obtained as an uncrystallizable viscous gum characterized as the picrate, which was obtained as yellow needles, mp 194°, from 2-ethoxyethanol.

Anal. Calcd for $C_{24}H_{33}NO_3 \cdot C_6H_3N_3O_7$: C, 58.9; H, 5.9; N, 9.2. Found: C, 58.9; H, 5.9; N, 9.4.

6,14-*endo*-Etheno-7α-(1-methylprop-1-enyl)-tetrahydrothebaine (Anhydro-19-ethylthevinol, II, $R^1 = H$, $R^2 = Me$). **a.** 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-methylpropyl)tetrahydrothebaine (19-ethylthevinol, I, R = Et) (1 g) was heated at 100° with 98–100% formic acid (10 ml) for 2 hr. The solution was diluted with ice–water and basified with ammonia. The product was isolated by ether extraction and crystallized and recrystallized from aqueous methanol when the olefin (II, $R^1 = H$, $R^2 = Me$) (0.6 g) was obtained as white irregular plates, mp 120–121°.

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.4; H, 7.9. Found: C, 76.7; H, 8.0.

b. 6,14-*endo*-Etheno-7α-(1-(*S*)-hydroxy-1-methylpropyl)tetrahydrothebaine (I, R = Me; Me = Et) (1 g) was dehydrated in the same way and gave the same olefin, melting point and mixture melting point with material prepared as in part **a**, 120–121°.

6,14-*endo*-Etheno-7α-(1-methylbut-1-enyl)tetrahydrothebaine (Anhydro-9-propylthevinol, II, $R^1 = H$, $R^2 = Et$). 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylbutyl)tetrahydrothebaine (19-propylthevinol, I, R = *n*-Pr) (10 g) was boiled under reflux with 98–100% formic acid (50 ml) for 3 hr. The mixture was diluted with ice–water and basified with ammonia, and the product was isolated by ether extraction. On crystallization and recrystallization from aqueous methanol, the olefin II ($R^1 = H$, $R^2 = Et$) (6.8 g) was obtained as white plates, mp 110°.

Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.7; H, 8.2. Found: C, 76.7; H, 8.3.

The same olefin was obtained by the dehydration in the same way of 6,14-*endo*-etheno-7α-(1-(*S*)-hydroxy-1-methylbutyl)tetrahydrothebaine, which is the C-19 epimer of the alcohol I (R = *n*-Pr).

Ozonolysis of Anhydro-19-propylthevinol (II, $R^1 = H$, $R^2 = Et$). Ozonized oxygen, delivering 0.6 mmole of ozone/min, was passed into a solution of anhydro-19-propylthevinol (0.41 g, 1 mmole) in 4 *N* acetic acid (50 ml). The reaction was stopped when 2 mmoles of ozone had been absorbed (8 min), and the reaction mixture was reduced with zinc dust, filtered, and neutralized with sodium bicarbonate. The neutralized solution was divided into two parts, one of which was warmed, and the evolved gas was passed through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, when a 2,4-dinitrophenylhydrazone, mp 146°, was obtained. This depressed the melting point of pentan-2-one dinitrophenylhydrazone (mp 142°) but did not depress the melting point of propionaldehyde dinitrophenylhydrazone (mp 146°). The second portion of the neutralized reaction mixture was treated with dimedone, when the propionaldehyde derivative was obtained, mp 154° undepressed on mixing with an authentic specimen (mp 155°).

6,14-*endo*-Etheno-7α-(1-methylbut-1-enyl)tetrahydrothebaine (Anhydro-19-propyldihydrothevinol, II, $R^1 = H$, $R^2 = Et$, 6,14-etheno). **a.** 6,14-*endo*-Ethano-7α-(1-(*R*)-hydroxy-1-methylbutyl)-tetrahydrothebaine (5 g) and 98–100% formic acid (100 ml) were boiled together under reflux for 20 min. The solution was diluted with ice–water and basified with ammonia, and the product was isolated by ether extraction and chromatographed on neutral alumina in benzene solution. Elution of the column with benzene:ethyl acetate, 95:5, gave the olefin (3 g) as white plates, mp 65–67°, from petroleum ether (bp 40–60°) characterized as the hydrochloride, mp 218–219°.

Anal. Calcd for $C_{26}H_{33}NO_3 \cdot HCl$: C, 70.0; H, 8.1; Cl, 7.95. Found: C, 69.6; H, 8.1; Cl, 8.3.

b. 6,14-*endo*-Etheno-7α-(1-methylbut-1-enyl)tetrahydrothebaine (1 g) was hydrogenated at 20° (760 mm) over 5% palladium on charcoal (0.25 g) in ethanol. Hydrogen (50 ml, 1 mole) was absorbed over 90 min. Evaporation of the solution afforded an oil giving a hydrochloride, mp 218–219°, identical in melting point, mixture melting point, and infrared absorption with that obtained as in part a above.

Other Olefins. The following olefins were prepared by the same process as the one described above for the preparation of 6,14-*endo*-etheno-7α-(1-methylbut-1-enyl)tetrahydrothebaine: 6,14-*endo*-etheno-7α-(1-methylpent-1-enyl)tetrahydrothebaine (anhydro-19-butylthevinol, II, $R^1 = H$, $R^2 = n$-Pr, white plates, mp 75°, from methanol. *Anal.* Calcd for $C_{27}H_{35}NO_3$: C, 77.0; H, 8.4. Found: C, 76.9; H,8.4); 6,14-*endo*-etheno-7α-(1-methylhex-1-enyl)tetrahydrothebaine (anhydro-19-amylthevinol, II, $R^1 = H$, $R^2 = n$-Bu, white plates, mp 180°, from methanol. *Anal.* Calcd for $C_{28}H_{37}NO_3 \cdot 0.5H_2O$: C, 75.7; H, 8.6. Found: C, 75.6; H, 8.3); 6,14-*endo*-etheno-7α-(1,4-dimethylpent-1-enyl)-

tetrahydrothebaine (anhydro-19-isoamylthevinol, II, R^1 = H, R^2 = *i*-Bu, noncrystalline, hydrochloride, white prisms, mp 170°, from water. *Anal.* Calcd for $C_{28}H_{37}NO_3 \cdot HCl \cdot H_2O$: C, 71.5; H, 8.5. Found: C, 71.4; H, 8.4); N-(2-methylallyl)-6,14-*endo*-etheno-7α-(1-methylprop-1-enyl)tetrahydronorthebaine (N-methylallylanhydro-19-ethylnorthevinol, II, R^1 = H, R^2 = Me, NMe = $NCH_2CMe{=}CH_2$, white plates, mp 110°, from methanol. *Anal.* Calcd for $C_{28}H_{33}NO_3$: C, 77.6; H, 8.2. Found: C, 77.5; H, 8.2); N-propargyl-6,14-*endo*-etheno-7α-(1-methylpent-1-enyl)tetrahydronorthebaine (N-propargylanhydro-19-butylnorthevinol, II, R^1 = H, R^2 = *n*-Pr, NMe = $NCH_2C{\equiv}CH$, white plates, mp 108°, from methanol. *Anal.* Calcd for $C_{29}H_{35}NO_3 \cdot 0.5H_2O$: C, 76.7; H, 7.9. Found: C, 76.7; H, 7.9); and, 6,14-*endo*-ethano-7α-(1-methylprop-1-enyl)tetrahydrothebaine (anhydro-19-ethyldihydrothevinol, II, R^1 = H, R^2 = Me, 6,14-CH_2CH_2, noncrystalline, hydrochloride white prisms, mp 222–223°, from ethanol. *Anal.* Calcd for $C_{25}H_{33}NO_3 \cdot HCl \cdot 0.5H_2O$: C, 69.5; H, 7.9; Cl, 8.2. Found: C, 68.2; H, 8.1; Cl, 8.4).

N-Cyano-6,14-*endo*-etheno-7α-(1-methylbut-1-enyl)tetrahydronorthebaine (N-Cyanoanhydro-19-propylnorthevinol, II, R^1 = H, R^2 = Et, NMe = NCN). The olefin II (R^1 = H, R^2 = Et) (5 g), cyanogen bromide (2 g), and methylene chloride (100 ml) were boiled together under reflux for 24 hr. Evaporation of the solvent and crystallization of the residue from methanol afforded the N-cyanonor compound (4 g) as prisms, mp 138°.

Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.7; H, 7.2. Found: C, 75.0; H, 7.2.

6,14-*endo*-Etheno-7α-(1-methylbut-1-enyl)tetrahydrooripavine. 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)tetrahydrooripavine (19-propylorvinol, I, R = *n*-Pr, 3OMe = 3OH) (2 g) was heated at 100° with 98–100% formic acid (20 ml) for 2 hr. The mixture was diluted with ice–water and basified with ammonia and the product collected. It was not immediately soluble in dilute aqueous sodium hydroxide, and the infrared spectrum showed a carbonyl absorption band at 1730 cm^{-1}. It was evidently the 3-O-formyl ester of the phenol and was hydrolyzed by heating to boiling for 2 min with potassium hydroxide (0.25 g) in ethanol (10 ml). The solution was diluted with water, and the phenol was precipitated with aqueous ammonium chloride and isolated by ether extraction. The resulting viscous gum was dissolved in ethanol (5 ml) made acid with ethanolic hydrogen chloride and diluted with ether when the hydrochloride crystallized. This was collected and recrystallized from ethanol–ether and was obtained as prisms, mp 122°.

Anal. Calcd for $C_{25}H_{31}NO_3 \cdot HCl \cdot 0.5H_2O$: C, 68.5; H, 7.6. Found: C, 68.2; H, 7.7.

14-(3-Methylbut-2-enyl)codeinone (V, R = Me). a. 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (19-methylthevinol, I, R = Me) (10 g) was boiled under reflux for 3 hr with 98–100% formic acid (30 ml). The solution was diluted with ice–water and basified with ammonia. The product was collected, washed well with water, air dried, and recrystallized from methanol, when the codeinone (6.5 g) was obtained as pale cream prisms, mp 139–140°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.6; H, 7.5. Found: C, 75.4; H, 7.4.

The hydrochloride formed prisms, mp 286–288°. The base was insoluble in aqueous sodium hydroxide, and in methanolic sodium hydroxide solution gave no color with diazotized sulfanilic acid.

b. 6,14-*endo*-Etheno-7α-isopropenyltetrahydrothebaine (II, R^1 = R^2 = H) (1 g) was boiled with 98–100% formic acid (15 ml) for 3 hr. Isolation of the product as in part a gave 0.75 g of the same codeinone, mp 139–140°.

N-Propargyl-14-(3-methylbut-2-enyl)norcodeinone (V, R = Me, NMe = $NCH_2C{\equiv}CH$). Prepared as above from N-propargyl-6,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)tetrahydronorthebaine (N-propargyl-19-methylnorthevinol, I, R = Me, NMe = $NCH_2C{\equiv}CH$) this base was obtained as prisms, mp 126°, from methanol.

Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.2; H, 7.2. Found: C, 77.2; H, 7.0.

N-(3,3-Dimethylallyl)-14-(3-methylbut-2-enyl)norcodeinone (V, R = Me, NMe = $NCH_2CH{=}CMe_2$). Prepared as above from N-(3,3-dimethylallyl)-19-methylnorthevinol (I, R = Me, NMe = $NCH_2CH{=}CMe_2$) this base was obtained as prisms, mp 123°, from methanol.

Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.4; H, 7.9. Found: C, 77.5: H, 7.8.

Ozonolysis of 14-(3-Methylbut-2-enyl)codeinone (V, R = Me). Ozonized oxygen, delivering 0.5 mmole of ozone/min was passed into a solution of 14-(3-methylbut-2-enyl)codeinone (0.365, 1 mmole) in 4 *N* acetic acid (50 ml). The reaction was stopped when 2 mmoles of ozone had been absorbed, and the mixture was reduced with zinc dust, filtered, neutralized with sodium bicarbonate, and warmed. The evolved gas was passed through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, when acetone 2,4-dinitrophenylhydrazone (0.182 g, 0.765 mmole) was obtained, mp 125° undepressed on mixing with an authentic specimen.

14-(3-Methylbut-2-enyl)codeine (XII, R = Me). Sodium borohydride (0.5 g), 14-(3-methylbut-2-enyl)codeinone (V, R = Me) (10 g), and 2-ethoxyethanol (30 ml) were boiled together under reflux for 15 min. Water was added to the hot solution until separation of crystalline material began. A small amount of a sticky solid separated initially but dissolved as more water was added. The mixture was cooled in ice–water; the solid was collected and recrystallized from aqueous 2-ethoxyethanol, when the codeine (8.9 g) was obtained as white plates, mp 168–169°.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.3; H, 8.0. Found: C, 75.5; H, 8.0.

7,8-Dihydro-14-(3-methylbutyl)codeinone (X, R = Me). 14-(3-Methylbut-2-enyl)codeinone (V, R = Me) (1.9 g) was shaken under hydrogen at 22° (750 mm) in ethanol (100 ml) over 5% palladium on charcoal (250 mg). Hydrogen (250 ml, 2 moles) was absorbed over 75 min. Filtration and evaporation of the solution afforded the dihydrocodeinone as a viscous gum that crystallized on keeping for several weeks. Trituration of the partly crystallized mass with ice-cold methanol afforded prisms, mp 125–126°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.8; H, 8.4. Found: C, 74.6; H, 8.2.

14-(3-Phenylbut-2-enyl)codeinone (V, R = Ph). 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (I, R = Ph) (10 g) was heated under reflux with 98–100% formic acid (50 ml) for 30 min. The solution was diluted and basified with ammonia. The precipitated base was crystallized from aqueous 2-ethoxyethanol, when the codeinone was obtained as white prisms, mp 156–157°, ν_{max} 1690 cm^{-1}, λ_{max} 240 and 295 mμ, ϵ_{max} 20,000 and 4000.

Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.6; H, 6.8. Found: C, 78.6; H, 6.7.

The picrate formed yellow prisms, mp 160–161°, from 2-ethoxyethanol.

Anal. Calcd for $C_{28}H_{29}NO_3 \cdot C_6H_3N_3O_7$: C, 62.4; H, 4.8; N, 8.5. Found: C, 63.0; H, 5.0; N, 8.2.

The oxime formed white prisms, mp 182°, from 2-ethoxyethanol.

Anal. Calcd for $C_{29}H_{30}N_2O_3$: C, 76.1; H, 6.8. Found: C, 76.4; H, 7.0.

The same base was obtained by heating the alcohol I (R = Ph) at 100° with 2 *N* hydrochloric acid for 5 min and also by heating the olefin II (R^1 = R^2 = H, CH_3 = Ph) with formic acid for 30 min.

14-(3-Phenylbut-2-enyl)codeine (XII, R = Ph). Sodium borohydride (0.5 g), 14-(3-phenylbut-2-enyl)codeinone (V, R = Ph) (10 g), and 2-ethoxyethanol (50 ml) were boiled together under reflux for 30 min. Water was added to the hot solution until the initially sticky precipitate dissolved and until separation of crystalline material began. The mixture was then cooled in ice–water, and the product was collected and recrystallized from aqueous 2-ethoxyethanol, when the codeine (8.5 g) was obtained as off-white plates, mp 172°.

Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.3; H, 7.2. Found: C, 78.2; H, 7.3.

7,8-Dihydro-14-(3-phenylbut-2-enyl)codeinone (XI, R = Ph). 14-(3-Phenylbut-2-enyl)codeinone (9.5 g) was added to a solution of sodium borohydride (4 g) in anhydrous pyridine (150 ml), and the mixture was kept at the room temperature for 4 hr. It was then poured slowly with vigorous stirring into water (1200 ml) and the precipitated base was collected, washed well with water, and dried. The dried solid (8.5 g) in benzene was chromatographed on alumina, and elution of the column with benzene gave starting material (0.2 g) whereas elution with 2% ethyl acetate in benzene gave the dihydro ketone XI (R = Ph) (1.1 g) which was obtained from methanol as white elongated plates, mp 160–162°, ν_{max} 1720 cm^{-1}.

Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.3; H, 7.2. Found: C, 78.4; H, 7.1.

Elution of the column with 50% ethyl acetate in benzene afforded 14-(3-phenylbut-2-enyl)codeine (XII, R = Ph) (1.2 g), mp 168–170° undepressed on mixing with an authentic specimen.

14-(3-Phenylpent-2-enyl)codeinone (V, =C(—Me)—Ph = =C(—Et)—Ph). 6,14-*endo*-Etheno-7α-(1-(*S*)-hydroxy-1-phenylpropyl)-tetrahydrothebaine (1 g) was heated at 100° with 98–100% formic

acid (8 ml) for 30 min. The base isolated in the usual way was recrystallized from aqueous 2-ethoxyethanol, when it was obtained as white prisms, mp 176–177°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.9; H, 7.0. Found: C, 78.3; H, 7.2.

6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)dihydrocodeine (VII, R = Me). a. 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (I, R = Me) (20 g) was heated at 45° with 6 *N* hydrochloric acid (160 ml) for 6 hr. The mixture was diluted, and the base was precipitated with ammonia, collected, and recrystallized from ethanol, when the dihydrocodeine derivative (13.3 g) was obtained as white prisms, mp 265°.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7; OMe (1), 8.1. Found: C, 72.0; H, 7.6; N, 3.7; OMe, 8.0.

The hydrochloride was obtained as white prisms, mp 262°, from ethanol.

Anal. Calcd for $C_{23}H_{29}NO_4 \cdot HCl \cdot H_2O$: C, 63.1; H, 7.4. Found: C, 62.6; H, 7.5.

b. 14-(3-Methylbut-2-enyl)codeinone (V, R = Me) (1 g) was heated at 45° with 6 *N* hydrochloric acid (10 ml) for 6 hr. The base recovered as above was obtained as white prisms, mp 262° alone or mixed with material prepared as in a. The bases prepared by both methods had identical infrared spectra.

6,14-*endo*-Etheno-7α-(1-methoxy-1-methylethyl)tetrahydrothebaine (IX, R = Me). a. Perchloric acid (1.5 ml, 72%) was added dropwise to a stirred solution of 14-(3-methylbut-2-enyl)codeinone (V, R = Me) (500 mg) in methylene chloride (10 ml), methanol (10 ml), and trimethyl orthoformate (10 ml), and the mixture was kept at room temperature for 20 hr. Methylene chloride was added, and the mixture was washed with aqueous sodium bicarbonate and water and dried. Thin layer chromatography showed the product to consist of one major and one minor, less polar, component. The gum obtained by the removal of solvent was dissolved in *n*-hexane, and the solution was chromatographed on alumina (20 g, Woelm, activity II). Fractions of 10 ml were collected and examined by thin layer chromatography. The column was eluted first with 5% and then with 10% chloroform in *n*-hexane, when the less polar component was eluted. The material (12 mg, *c* 2.5%) was identical in melting point (143–145°) and infrared absorption with 6,14-*endo*-etheno-7α-isopropenyltetrahydrothebaine (II, $R^1 = R^2 = H$) obtained by the dehydration of the alcohol (I, R = Me). Continued elution of the column gave a mixture of the two components followed by the more polar component. The column was then eluted with 25 and 50% methylene chloride in *n*-hexane. Evaporation of appropriate fractions gave a gum which was crystallized from aqueous methanol to give 6,14-*endo*-etheno-7α-(1-methoxy-1-methylethyl)tetrahydrothebaine (130 mg), mp 97–99°. A further 90 mg was obtained from the mother liquors making a total yield of 39%. The compound showed no carbonyl absorption in the infrared and had nmr signals (in δ units) at 6.57 and 6.51 (C-1 H and C-2 H; doublets, $J_{1,1} = 9$ cps), 5.72 and 5.37 (C-18 H and C-17 H; doublets $J_{17,18} = 10$ cps), 4.56 (C-5 H), 3.82 (C-3 OMe), 3.58 (C-6 OMe), 3.18 (C-19 OMe), 2.36 (NMe), 1.30 and 0.95 (C-19 methyls).

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 73.0; H, 8.1; N, 3.4. Found: C, 72.5; H, 7.9; N, 3.5.

b. 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (19-methylthevinol, I, R = Me) (1 g) was added to a solution of potassamide (from 0.2 g of potassium) in liquid ammonia (~100 ml), and the mixture was stirred for 15 min. Methyl iodide (1 ml) was then added and the mixture stirred for 10 min more and poured cautiously into water (200 ml). The precipitated product was isolated by ether extraction and shown by thin layer chromatography to consist of approximately 30% of starting material (I, R = Me) and 70% of a less polar compound. The mixture was dissolved in a 1:1 mixture of benzene and *n*-hexane and chromatographed on a column of alumina (Woelm, activity II). The column was eluted with benzene, and 25-ml samples were collected, the composition of these being followed by thin layer chromatography. The first material to be eluted from the column (500 mg) was obtained as a gum, which crystallized on keeping for several hours. On recrystallization from aqueous methanol it was obtained as white prisms, mp 96–98°, identical in infrared absorption with material prepared as in part a above.

5,14-Ethano-18-isopropylidenethebainone (XV, R = R^1 = Me). a. 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (19-methylthevinol, I, R = Me) (50 g) was heated at 100° with 10 *N* hydrochloric acid (150 ml) for 45 min, during which time crystalline material separated. The mixture was diluted with water (150 ml) and cooled in ice, and the hydrochloride (27 g) was collected. This was dissolved in aqueous methanol, and the base was precipitated with ammonia. It was recrystallized readily only from methanol, from which it separated as off-white solvated prisms, mp 138°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_3 \cdot 0.5CH_3OH$: C, 73.0; H, 7.6. Found: C, 72.8; H, 7.8.

The hydrochloride was obtained as white prisms, mp 320°, from water.

Anal. Calcd for $C_{23}H_{27}NO_3 \cdot HCl$: C, 68.7; H, 7.0. Found: C, 68.4; H, 7.2.

The picrate was obtained as yellow needles, mp 224°, from aqueous 2-ethoxyethanol.

Anal. Calcd for $C_{23}H_{27}NO_3 \cdot C_6H_3N_3O_7 \cdot 1.5H_2O$: C, 56.0; H, 5.2. Found: C, 55.8; H, 5.2.

b. The same base was obtained from 6,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)dihydrocodeine (VII, R = Me), from 6,14-*endo*-etheno-7α-isopropenyltetrahydrothebaine (II, $R^1 = R^2 = H$), and from 14-(3-methylbut-2-enyl)codeinone (V, R = Me) by the same process as in a above, the yields being comparable with that in a in all cases.

The base was almost insoluble in aqueous alkalis but dissolved readily in aqueous methanolic potassium hydroxide to give an orange solution that readily coupled with diazotized sulfanilic acid to give a blood red solution. The alkaline solution was readily methylated and ethylated with methyl and ethyl sulfate, respectively.

The 4-O-methyl ether was prepared most conveniently from the hydrochloride obtained directly from the acid-catalyzed rearrangement of the alcohol (I, R = Me). The hydrochloride (20 g) was suspended in methyl sulfate (50 ml), and the mixture was cooled in ice. A solution of potassium hydroxide (40 g) in water (80 ml) was slowly added to the vigorously stirred suspension at a rate sufficient to keep the temperature of the mixture between 15 and 20°. When all of the alkali had been added, the mixture was stirred at 20° for 2 hr. Water (150 ml) was added, and the solid base was collected, washed, and recrystallized from methanol, when it was obtained as off-white prisms, mp 176–177°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.7. Found: C, 76.0; H, 7.8.

The 4-O-ethyl ether was obtained from aqueous methanol as white prisms, mp 126–127°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.4; H, 8.0. Found: C, 76.4; H, 7.9.

Ozonolysis of 5,14-Ethano-18-isopropylidenethebainone (XV, R = R^1 = Me). Ozonized oxygen, delivering 0.5 mmole of ozone/min was passed into a solution of 5,14-ethano-18-isopropylidenethebainone (0.365 g, 1 mmole) in 4 *N* acetic acid (50 ml). After 26 min, when 2 mmoles of ozone had been absorbed, the mixture was reduced with zinc dust, filtered, neutralized with sodium bicarbonate, and warmed. The evolved gas was passed through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, when acetone 2,4-dinitrophenylhydrazone (0.192 g, 0.807 mmole) was obtained, mp 125° alone or mixed with an authentic specimen.

7,8-Dihydro-5,14-ethano-18-isopropylidenethebainone (XXIII, R = Me). a. 6,14-*endo*-Ethano-7α-(1-hydroxy-1-methylethyl)-tetrahydrothebaine (dihydro-19-methylthevinol, XXII, R = Me) (2 g) was heated with 10 *N* hydrochloric acid (20 ml) for 2 hr at 100°. The mixture was diluted with water, and the base was precipitated with ammonia, collected, and recrystallized from methanol, when it was obtained as white prisms, mp 142°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.2; H, 7.9. Found: C, 75.2; H, 7.8.

The hydrochloride formed prisms, mp 245°, from water.

Anal. Calcd for $C_2H_{29}NO_3 \cdot HCl \cdot 1.5H_2O$: C, 64.1; H, 7.7. Found: C, 64.1; H, 7.5.

b. Zinc dust (2 g) was added to a vigorously stirred boiling solution of 5,14-ethano-18-isopropylidenethebainone (V, R = R^1 = Me) in glacial acetic acid (25 ml) and water (2 ml). The mixture was stirred and heated under reflux for 2 hr, filtered, diluted with aqueous ammonium chloride, and basified with ammonia. The precipitated base was collected and recrystallized from methanol, when it was obtained as prisms identical in melting point, mixture melting point, and infrared absorption with material prepared as in part a above.

The 4-O-methyl ether, prepared by methylation of the phenol and by reduction of the corresponding thebainone methyl ether with zinc dust and acetic acid, was obtained as off-white prisms, mp 168–169°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.6; H, 8.1. Found: C, 75.8; H, 8.0.

N-Allyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = R¹ = Me, NMe = $NCH_2CH{=}CH_2$). N-Allyl-7,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)tetrahydronorthebaine (1 g) was heated 100° with 10 *N* hydrochloric acid (10 ml) for 2 hr. The mixture was diluted with water; the hydrochloride (0.38 g) was collected and recrystallized from aqueous methanol, when it was obtained as white prisms, mp 186–188°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}NO_3 \cdot HCl$: C, 70.1; H, 7.0. Found: C, 70.2; H, 7.2.

The base could not be crystallized.

The following hydrochlorides were prepared from the appropriate N-substituted 6,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)tetrahydronorthebaines, and hot concentrated hydrochloric acid with isolation of the sparingly soluble salt: N-propargyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = Me, NMe = $NCH_2C{\equiv}CH$, prisms, mp 155°. *Anal.* Calcd for $C_{25}H_{27}NO_3 \cdot HCl \cdot H_2O$: C, 67.6; H, 6.8. Found: C, 68.0; H, 6.7); N-(3,3-dimethylallyl)-5,14-ethano-18-isopropylidenenorthebainone (XV, R = Me, NMe = $NCH_2CH{=}CMe_2$, prisms, mp 196°. *Anal.* Calcd for $C_{27}H_{33}NO_3 \cdot HCl \cdot H_2O$: C, 68.3; H, 7.6. Found: C, 68.3; H, 8.0); and N-cyclopropylmethyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = Me, NMe = N-cyclopropylmethyl, white prisms, mp 206°. *Anal.* Calcd for $C_{26}H_{31}NO_3 \cdot HCl \cdot H_2O$: C, 67.9; H, 7.4. Found: C, 67.8; H, 7.4).

3-O-Desmethyl-5,14-ethano-18-isopropylidenethebainone (XV, R = R¹ = Me, OMe = OH). a. 5,14-Ethano-18-isopropylidenethebainone (5 g) was boiled under reflux with 48% hydrobromic acid (50 ml) for 1 hr. Solid material that separated was dissolved by the addition of water (10 ml) and methanol (50 ml), and the solution was then basified with ammonia and the solid collected and recrystallized from methanol, when it was obtained as prisms (3 g), mp 268°.

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.2; H, 7.1. Found: C, 75.6; H, 7.0.

The hydrochloride was obtained as prisms, mp 342°, from aqueous methanol.

Anal. Calcd for $C_{22}H_{25}NO_3 \cdot HCl$: C, 68.1; H, 6.7. Found: C, 68.0; H, 6.8.

b. The same base (2 g, identical in melting point and infrared absorption with the above) was obtained by the direct rearrangement and demethylation of 6,14-*endo*-ethano-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (5 g) with 48% hydrobromic acid (45 ml). The hydrobromide was separated and dissolved in aqueous ethanol, and the base was precipitated with ammonia.

N-Allyl-3-O-desmethyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = R¹ = Me, OMe = OH, NMe = $NCH_2CH{=}CH_2$). N-Allyl-6,14-*endo*-etheno-7-(1-hydroxy-1-methylethyl]tetrahydronororipavine (N-allyl-19-methylnororvinol) (6 g) was heated under reflux with 4 *N* hydrochloric acid (40 ml) for 3 hr. The solid hydrochloride was collected, dissolved in aqueous methanol, and converted to the base with ammonia, the base being obtained from methanol as white prisms, mp 260° dec.

Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.4; H, 7.3. Found: C, 76.2; H, 7.2.

5,14-Ethano-18-(methylbenzylidene)thebainone (XV, R = Me, R¹ = Ph, Methylflavonepenthone). 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (I, R = Ph) (20 g) was heated with concentrated hydrochloric acid (75 ml) and ethanol (10 ml) at 100° for 30 min, during which time a crystalline hydrochloride separated. The mixture was diluted with water (100 ml) and thoroughly cooled in ice. The crystalline solid was collected. This consisted of the hydrochlorides of 7,8-dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeinone and the cyclohex-5′-eno isomer (see following paper), and a solution in aqueous methanolic sodium hydroxide gave only a pale pink color with diazotized sulfanilic acid.

The filtrate from the collection of this hydrochloride, which gave an intense diazo coupling reaction in alkaline solution, was basified with ammonia and the relatively small amount of gummy base produced was extracted rapidly with ether. The extract was shaken for 15 sec with magnesium sulfate and filtered. Rosettes of needles quickly separated from the ether solution and these were collected, washed well with ether, and recrystallized from aqueous 2-ethoxyethanol, when the thebainone derivative (320 mg) was obtained as off-white needles, mp 290°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.8; H, 6.8. Found: C, 78.7; H, 6.7.

The O-methyl ether was obtained as a crystalline precipitate on the addition of methyl sulfate (0.25 ml) to a solution of the phenol (100 mg) in methanol (3 ml), water (1 ml), and potassium hydroxide (200 mg), and on recrystallization from aqueous 2-ethoxyethanol was recovered, as almost white needles, mp 168–169°.

Anal. Calcd for $C_{29}H_{31}NO_3$: C, 79.0; H, 7.1. Found: C, 79.3; H, 7.0.

The O-ethyl ether, prepared in an analogous manner using ethyl sulfate, was obtained from aqueous ethanol as white needles, mp 144°.

Anal. Calcd for $C_{30}H_{33}NO_3$: C, 79.2; H, 7.3. Found: C, 79.3; H, 7.4.

6α-Formyl-5′5′-dimethylcyclopentano[1′,2′:8,14]-(−)-sinomenilan (Base A; XXIX). 14-(3-Methylbut-2-enyl)codeine (XII, R = Me) (5 g) was heated at 100° with concentrated hydrochloric acid (10 ml) for 45 min. The solution turned first pale yellow, then pink, and finally dark red brown. The solution was diluted with water (40 ml) and basified with ammonia. The sticky precipitate was washed three times with water by decantation and triturated with hot methanol (35 ml), when a white crystalline solid separated. The suspension was cooled, and the solid was collected, washed with cold methanol, and recrystallized from aqueous 2-ethoxyethanol when "base A" (1.5 g) was obtained as large irregular prisms, mp 200°, ν_{max} 1730 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.3; H, 8.0. Found: C, 75.8; H, 7.9.

The base was very sparingly soluble in cold ethanol, but dissolved readily in the presence of sodium ethoxide to give a deep yellow solution.

The perchlorate formed prisms, mp 241–242°, from aqueous ethanol.

Anal. Calcd for $C_{23}H_{29}NO_3 \cdot HClO_4$: C, 59.15; H, 6.5. Found: C, 59.15; H, 6.4.

6-Formyl-5′,5′-dimethylcyclopentano[1′,2′:8,14]-(−)-dihydrosinomenil-5-ene (Base B; XXX). Base A (XXIX) (1 g) was dissolved in ethanol (10 ml) containing sodium ethoxide (from 0.25 g of sodium), and the yellow solution was boiled for 1 min and cooled. The solution was poured into an excess of 1 *N* hydrochloric acid, and the base was precipitated with ammonia, collected, washed with water, and recrystallized from aqueous methanol, when it was obtained as white felted needles, mp 157–158°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.3; H, 8.0. Found: C, 75.6; H, 7.9.

The same base was obtained, less conveniently, when the sodium ethoxide solution of base A was poured into aqueous ammonium chloride. The base was readily soluble in aqueous sodium hydride, and the solution gave a deep red color with diazotized sulfanilic acid.

Conversion of Base B (XXX) into Base A (XXIX). Base B (50 mg) was dissolved in methanol (1 ml) and one drop of 2 *N* aqueous sodium hydroxide was added. The solution became yellow and on warming rapidly deposited base A (40 mg), mp 200° alone or mixed with an authentic specimen.

Reduction of Base A with Sodium Borohydride. Base A (XXIX, 500 mg) and sodium borohydride (50 mg) were stirred together in cold ethanol (10 ml) until all the base had dissolved and then for a further 15 min. The product was precipitated with water and isolated by ether extraction, when 6-hydroxymethyl-5′,5′-dimethylcyclopentano[1′,2′:8,14]-(−)-sinomenilan (XXXI) (500 mg) was obtained as a viscous oil, characterized as the 3,5-dinitrobenzoate, which was obtained as yellow needles, mp 190°.

Anal. Calcd for $C_{30}H_{33}N_3O_8$: C, 64.0; H, 5.9; N, 7.5. Found: C, 64.3; H, 6.0; N, 7.8.

Reduction of Base A with Sodium Borohydride and Sodium Ethoxide. Sodium borohydride (150 mg) was added to a solution of base A (XXIX) (1 g) in ethanolic sodium ethoxide solution (20 ml), and the mixture was warmed until the yellow color disappeared. The almost colorless solution was poured into aqueous ammonium chloride and the product isolated by ether extraction, when 6-hydroxymethyl-5′,5′-dimethylcyclopentano[1′,2′:8,14]-(−)-dihydrosinomenil-5-ene (XXXIII) (1 g) was obtained as a viscous oil which could not be crystallized. On distillation a portion was obtained as a colorless glass, bp 190–200° (bath temp) (0.2 mm).

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.8; H, 8.1. Found: C, 74.7; H, 8.0.

6-Methylene-5′,5′-dimethylcyclopentano[1′,2′:8,14]-(−)-sinomenilan (XXXIV). 6-Hydroxymethyl-5′,5′-dimethylcyclopentano-[1′,2′:8,14]-(−)-dihydrosinomenil-5-ene (XXXIII) (250 mg) was boiled with concentrated hydrochloric acid (5 ml) for 2 min, and the mixture was diluted with water and basified with ammonia. The product, isolated by ether extraction, was a viscous oil that crystallized in part on trituration with 80% methanol. The crystals so obtained dissolved readily in petroleum ether (bp 40–60°),

in which the noncrystalline matter was virtually insoluble. Concentration of the petroleum solution afforded the olefin XXXIV (75 mg) as white elongated prisms, mp 107–108°.

Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.6; H, 8.3. Found: C, 78.2; H, 8.2.

Rearrangement of 14-(3-Phenylbut-2-enyl)codeine (XXXVI). 14-(3-Phenylbut-2-enyl)codeine (XXXVI) (2 g) was heated at 100° in the water bath with concentrated hydrochloric acid (20 ml) for 45 min. The pink solution was then diluted with 50% aqueous ethanol, cooled in ice, and basified under ether with ammonia. The ether extract was set aside overnight, and the crystalline matter that separated during that time was collected, washed with methanol, and recrystallized from 2-ethoxyethanol, when 8,14-dihydro-6,7α-epoxy-5′-methyl-5′-phenylcyclopentano[1′,2′:8,14]deoxycodeine-D (XXXVIII) was obtained as white prisms, mp 234° (0.3 g).

Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.3; H, 7.2. Found: C, 78.2; H, 7.2.

The ether solution after removal of this base was evaporated to leave a brown viscous gum, part of which was chromatographed in ether solution on alumina plates. From the plates a nonphenolic α,β-unsaturated ketone XIII (R = Me, R′ = Ph), a nonphenolic saturated ketone, and a nonphenolic aldehyde were obtained as well as a phenolic saturated ketone. Chromatographic separation of a further part of the same viscous gum on silica plates resulted in the separation of the material into a nonphenolic fraction and six nonphenolic bases which on recovery from the plate showed almost identical infrared absorption lacking any band attributable to a carbonyl group. The amounts of material recovered in this way were too small to permit further study.

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Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. V.[1] Derivatives of 7,8-Dihydrocyclohexeno[1′,2′:8,14]codeinone

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Abstract: The acid-catalyzed rearrangement of alcohols of the 6,14-*endo*-ethenotetrahydrothebaine series of general structure I has been shown to proceed in most cases *via* the 14-alkenylcodeinones (II) to 7,8-dihydrocyclohex-4′-eno- and -cyclohex-5′-eno[1′,2′:8,14]codeinones of general structures X and XI. The structures of typical bases have been elucidated by nmr spectral studies and by chemical means. Analogous derivatives of dihydromorphinone and a series of nor bases and N-substituted nor bases have also been prepared. The mechanisms of the rearrangements are discussed.

In the preceding paper it is shown that the alcohols of general structure I can be rearranged to 14-alkenylcodeinones (II), which may be further transformed by concentrated hydrochloric acid into 5,14-bridged thebainone derivatives III. The last of these transformations, however, competes with an alternative process, which in general represents the major reaction, the thebainone derivative III being the major product only in special cases. The alternative rearrangement of the codeinone II affords a nonphenolic nonconjugated ketone as the stable end product, which is, of course, obtained also by the complete rearrangement of the alcohol I under the same conditions, and from the olefin which is an intermediate in the conversion of the alcohol into the codeinone II (see preceding paper). As would be expected, since carbonium ion intermediates are clearly involved in the dehydration and rearrangement of the alcohol I to the codeinone II, diastereoisomeric pairs of alcohols afford the same ketonic end product, in all cases studied. The rearrangement of the alcohol I (R = H, R′ = Ph) is a particularly rapid process; in cold concentrated hydrochloric acid the product is almost entirely the codeinone II (R = H, R′ = Ph), and this is completely converted into stable end products after only 4-min boiling. The nonphenolic nonconjugated ketones obtained in this way are isomeric with the alkenylcodeinones II and the thebainone derivatives III prepared from the same alcohols.

One possible process by which the alkenylcodeinone II could be converted into a nonconjugated ketone involves the protonation of the enone system and non-Markovnikov addition of the resulting carbonium ion to the double bond in the side chain, followed by expulsion of a proton to give the ketone VI. However, the codeinone II (R = H, R′ = Me) is known to suffer recyclization in acid solution, by a process involving Markovnikov addition to the isolated double bond, to give the alcohol V (R = H, R′ = Me),[1] and the rearrangement of such a recyclized base to the noncon-

(1) Part IV: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3293 (1967).

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