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

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Abstract: The 7α and 7β ketones of the 6,14-*endo*-etheno- and -ethanotetrahydrothebaine series I suffer base-catalyzed rearrangement to isomeric bases VIII, though the reaction may be interrupted by other reagents at an intermediate stage II or V. The rearrangement of the esters and nitriles of this series does not proceed beyond the stage X or XII, corresponding to V. All of these products are unstable to acids which readily convert them into derivatives of 5,14-ethanothebainone III, VI, VII, and XII. The catalytic reduction of and the reaction of organometallic compounds with the ketone VIII have been studied. 18-Acetyl-5,14-ethanothebainone (VII, R′ = H) has been shown to undergo base-catalyzed ketolization to the hexacyclic base XXV. The Hofmann degradation of the quaternary salts of certain of the rearranged bases has been shown to proceed normally.

The ketone nepenthone (I, CH_3 = Ph), which is the Diels–Alder adduct of thebaine and phenyl vinyl ketone, readily suffers base-catalyzed rearrangement to isonepenthone (VIII, CH_3 = Ph),[2] and similar rearrangements have been effected with certain other adducts of thebaine bearing electron-withdrawing substituents at C-7. The aldehyde I (CH_3 = H), the ketone I,[2,3] the ester I (CH_3 = OEt),[3] and the 7-nitrile I ($COCH_3$ = CN)[2,3] have all been subjected to base-catalyzed rearrangement as have some of their 6,14-ethano analogs. The reaction is initiated by the removal of the C-7 proton, which is α to the activating group. Although the methyl ketone I is initially enolized by removal of a proton from the methyl group under kinetic control,[3] under reversible conditions removal of the C-7 proton occurs with formation of an enolate ion in which C-7 is no longer asymmetric and both 7α and 7β forms of the reactive species give the same product after rearrangement.

Following the removal of the C-7 proton displacement of the 4,5-oxide bridge by the carbanion occurs to give the phenate ion IV, and the final fate of this ion then depends on the nature of C-7 substituent and on the conditions of the reaction. If no other reagent is present, and if the electron-accepting power of the C-7 substituent is great enough, *i.e.*, if this is a keto group, the cyclopropane ring may be opened under attack at C-5, which would lead to the starting material, or at C-6, which leads to the rearranged base VIII. The examination of models of the molecules of structures I and VIII shows that the ring system, and in particular the oxygen-containing ring, of the latter is appreciably the less strained of the two and, since the reactions are clearly reversible, excellent yields of the rearranged bases are obtained.

If methyl iodide is added to a solution in *t*-butyl alcohol of the phenate anion IV, obtainable from either of the ketones I and VIII, methylation occurs; the cyclopropane ring is not affected, and the product is the base V (R′ = Me). The rearrangement also occurs under the influence of Grignard reagents functioning as bases,[4] and this process competes with the normal attack of the carbonyl group in the reaction of the ketone I and its 7β epimer with these reagents. In this reaction the initially formed phenate anion IV reacts further with the Grignard reagent at the carbonyl group to give a tertiary alcohol, thus effectively blocking the route for opening of the cyclopropane ring; the product is the phenolic alcohol II (R′ = H). This represents only a minor side reaction of the ketone I with Grignard reagents but frequently accounts for as much as 40% of the product of the reaction in the 6,14-ethano series.

Base-catalyzed rearrangements of the ester I (CH_3 = OEt) and the nitrile I ($COCH_3$ = CN) are also easily effected. The products of simple rearrangement are the ester X (R = Et, R′ = H) and the nitrile XII (R′ = H); the electron-accepting power of the C-7 substituent in these cases apparently is insufficient to effect the production of analogs of the ketone VIII. The ester I (CH_3 = OEt) reacts normally with methylmagnesium iodide to give a tertiary carbinol,[4] but with other Grignard reagents the main products are the rearranged ester X (R = Et, R′ = H) and the symmetrical tertiary carbinol II (R′ = H, Me = R) resulting from the reaction of this ester with the reagent. The nitrile I ($COCH_3$ = CN) affords the rearranged base in excellent yield with aliphatic Grignard reagents, though with aromatic reagents some of the product of "normal" attack of the C≡N group is also obtained.[3] The addition of alkyl or acyl halides during the rearrangement results in alkylation or acylation of the phenate ion, the products being the ethers or esters X (R′ = Me) and XII (R′ = Me, Et, Ac). The base-catalyzed rearrangement of the ester I (CH_3 = OEt) can also be combined with ester exchange processes; the products are esters of structure X (R′ = H).

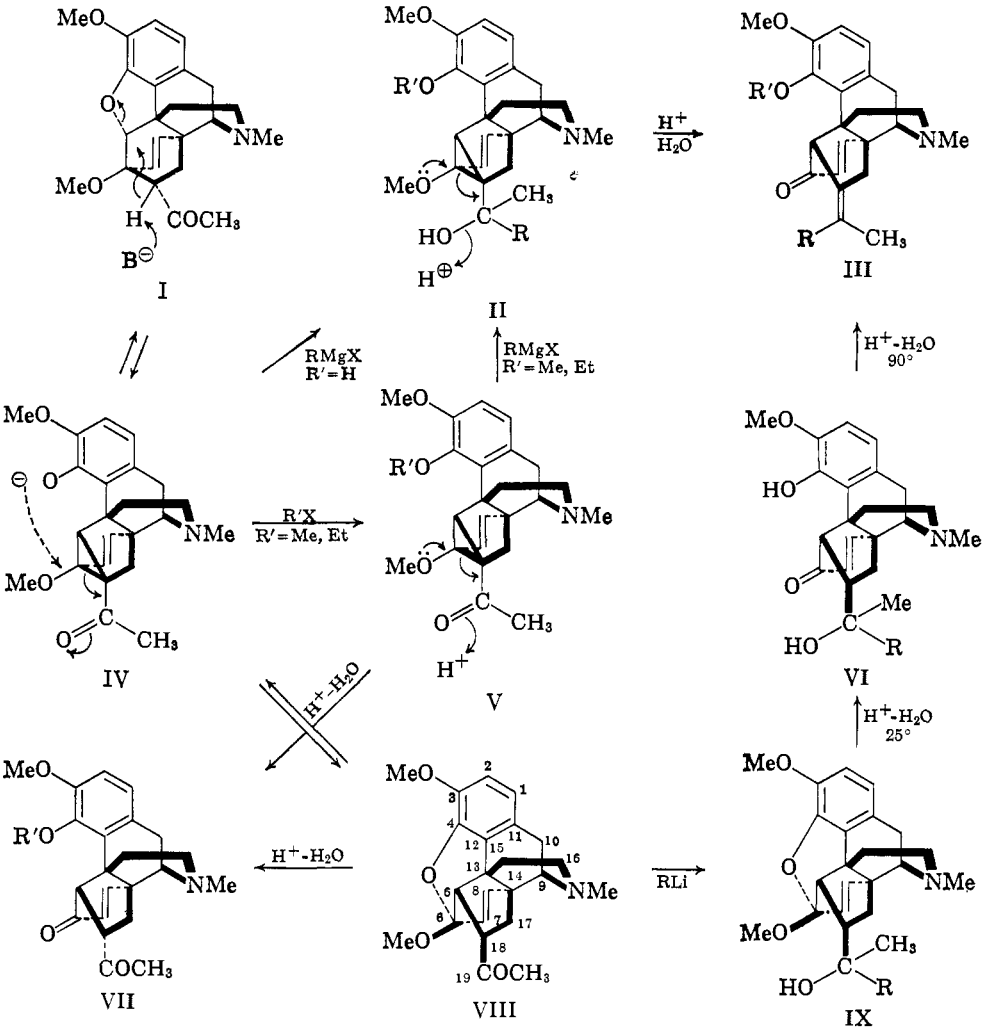
The nmr spectra of representative bases of the various groups are entirely in accord with the assigned structures. The spectrum of isonepenthone (VIII, CH_3 =

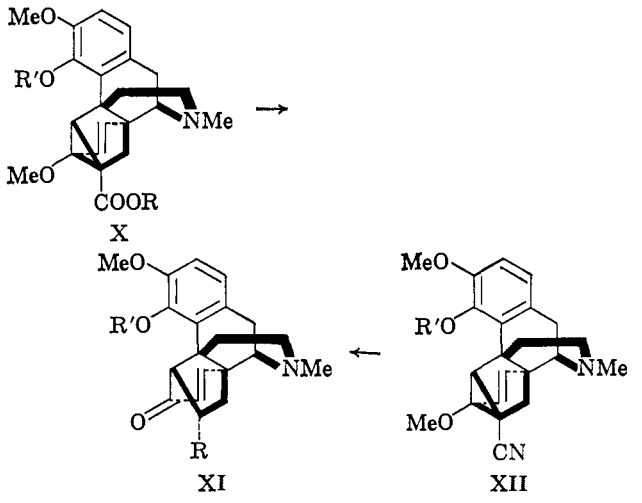
(1) Part V: K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3303 (1967).

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

(3) Part I: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967).

(4) Part II: K. W. Bentley, D. G. Hardy, and B. Meek, *ibid.*, **89**, 3273 (1967).





Ph) shows signals (in δ units) at 8.2–7.2 (complex, five aromatic H), 6.6 (two aromatic H), 6.0 (doublet, C-8 H, $J_{8,7}$ = 9 cps), 5.15 (doublet, C-7 H, $J_{7,8}$ = 9 cps, each peak a doublet, $J_{7,5}$ = 2 cps), 3.82 (C-3 OCH_3), 3.55 (C-6 OCH_3), and 2.30 (NCH_3). The spectrum of the ketone VIII is virtually identical with that of isonepenthone except that it lacks the complex signals at δ 8.2–7.2 due to the phenyl group, and it shows instead a signal at δ 2.22 due to $COCH_3$. The examination of Dreiding models of these ketones shows that disposition of the C-5 and C-7 hydrogen atoms is such as to permit long-range coupling, the two protons and the intervening carbon atom C-6 lying in the same plane, the system being similar to those in which coupling is observed in narwedine and Pummerer's ketone.[5] Neither spectrum shows a signal at *ca.* δ 4.5 which is a feature of the spectrum of the ketone I,[6] attributed to the C-5 hydrogen atom at the end of the 4,5-oxygen bridge.

The spectrum of the ester X (R = Et, R′ = H) in deuteriochloroform containing perdeuteriopyridine[7] showed signals due to the C-17 and C-18 protons (equivalent to C-8 and C-7 in VIII) at δ 5.93 and 5.72 (doublets, $J_{17,18}$ = 9.0 cps) showing no additional coupling. The C-5 hydrogen gave a signal at δ 3.57 as a single peak showing no coupling. The examination of models of the structure X shows that the dispositions of the C-5 and C-18 protons no longer meet the requirement for long-range coupling. The C-8 αH pattern was found as a doublet, coupling occurring only with C-8 βH ($J_{8\alpha,8\beta}$ = 13.0 cps) indicating the absence of a hydrogen atom at C-7. The phenolic hydroxyl proton was signalled at *ca.* δ 8.0 in the presence of deuteriopyridine, but in the absence of this agent the signal appeared partially superimposed upon one line of the C-17 proton doublet at δ 5.82. The other fea-

(5) G. W. Kirby and H. P. Tiwari, *J. Chem. Soc.*, 4655 (1964).
(6) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, 89, 3322 (1967).
(7) We are indebted to W. Fulmor, J. E. Lancaster, and G. O. Morton of Lederle Laboratories, Pearl River, N. Y., for the determination and interpretation of this spectrum.

tures of the spectrum of this ester were entirely consistent with the structure X (R = Et, R′ = H).

The spectrum of the nitrile XII (R = H) was similar in essential features to that of the ester, showing signals due to C-17–C-18 at δ 6.1 and 5.7 (doublets, $J_{17,18}$ = 9.0 cps) and C-8 αH at δ 1.13 ($J_{8\alpha,8\beta}$ = 13.0 cps), as well as signals due to two aromatic H, two different methoxyls, and the N-methyl group. The phenolic hydroxyl group was located by a signal at δ 8.38 in dimethyl sulfoxide. The infrared spectrum of the nitrile, like that of the above ester, but unlike the spectra of the ketone VIII and isonepenthone, in solution showed hydroxyl absorption at 3545 cm^{-1}.

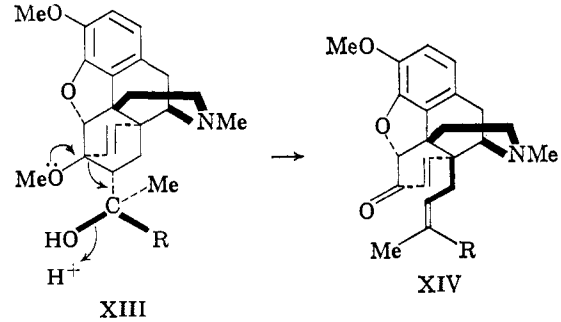
The nmr spectrum of the alcohol II (R′ = H, R = *n*-Pr),[7] isolated as a minor product from the products of the reaction of the ketone I with *n*-propylmagnesium halides, was also similar to that of the ester X (R = Et, R′ = H) showing signals (in δ units) for the following: phenolic OH, 5.93 (exchangeable); C-18 H, C-17 H, 6.00 and 5.64 (doublets, $J_{17,18}$ = 9 cps); alcohols OH 4.72 (exchangeable); C-5 H, 3.0; C-8 αH, 0.70 (doublet, $J_{8\alpha,8\beta}$ = 11 cps), in addition to the expected signals for the other systems present in structure II (R′ = H, R = *n*-Pr).

The products of the rearrangements set out above, *i.e.*, the bases of general structures II, V, VIII, X, and XII, are all unstable to acids and readily suffer hydrolysis. The ketones VIII and VIII (CH_3 = Ph), being both mixed ketals and allylic phenyl ethers, on treatment with acids under mild conditions are converted into the phenolic α,β-unsaturated ketones VII (R′ = H) and VII (R′ = H, CH_3 = Ph, *i.e.*, ψ-nepenthone). Both of the nonphenolic parent ketones, which are prepared under conditions of reversible enolization, may be assumed to be the stable isomers, which are shown by the examination of models to have the $COCH_3$ or COPh group disposed as shown in formula VIII. The examination of models of ψ-nepenthone (VII, R′ = H, CH_3 = Ph), however, suggests that in this base there is little difference in stability between the two C-18 isomers. In support of this view it has been found that ψ-nepenthone produced by the mild acid hydrolysis of isonepenthone (VIII, CH_3 = Ph) is a single substance, presumably the 18β isomer, which can be equilibrated on standing in acid solution to an approximately 1:1 mixture of two bases[8] which can be differentiated on alumina plates. The extraction of the separate zones on the alumina with methanol, however, results in reequilibration of the isomers, and the C-18 epimer of ψ-nepenthone has not been isolated. The examination of models of the epimeric forms of the ketone VII (R′ = H), however, suggests that the 18α isomer will be the more stable of the two, since in this form nonbonded interactions are minimal, whereas in the 18β ketone there is appreciable interaction between the methyl group in the side chain and one of the C-15 hydrogen atoms. The hydrolysis of the ketal VIII takes place without the separation of a hydrochloride, *i.e.*, under conditions similar to those required for the equilibration of ψ-nepenthone, and gives a single substance, which is assigned the 18α structure on the basis of its very ready cyclization to the base XXV (see below).

The ketone V (R′ = Me) is an aldol methyl ether as well as a highly strained (cyclopropane) derivative, and is readily hydrolyzed by acids under very mild conditions. Since this reaction must proceed through the enol form of the ketone, the product is the stable C-18 epimer, identical with the product of methylation of the phenol VII (R′ = H).

The rearranged nitriles and esters of general structures XII and X are likewise very readily hydrolyzed with production of the corresponding α,β-unsaturated ketones XI (R = CN) or XI (R = COOR). The ease with which the hydrolysis of the bases V, X, and XII occurs contrasts markedly with the stability of the ketones I and also I (CH_3 = Ph) and the ester I (CH_3 = OEt) under acid conditions.[9] This may be the result of strain in the cyclopropane ring, but it may be noted that a similar difference in stability has been observed in the enol ether systems of thebaine and dihydrothebaine, in which the 4,5-oxygen bridge is intact, which form stable hydrochlorides, and the phenolic bases dihydrothebaine-φ,[10] β-dihydrothebaine, thebainone-A enol methyl ether,[10] and the Δ^5- and Δ^6-enol methyl ethers of dihydrothebainone,[10] all of which are extremely rapidly hydrolyzed, even by cold acetic acid.

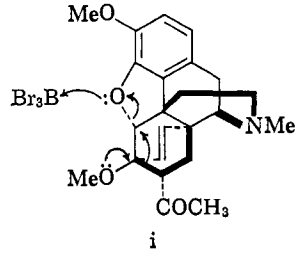
The ketone V (R′ = Me), which is stable to bases, reacts normally with Grignard reagents, giving tertiary alcohols of general structure II (R′ = Me), and these, like the corresponding phenols II (R′ = H), on treatment with acid very readily suffer dehydration and hydrolysis to give the olefinic ketones III. This reaction is essentially the same as that involved in the conversion of alcohols of structure XIII into 14-alkenylcodeinones (XIV),[11] but occurs under much milder conditions. The bases III (R = Me, R′ = H) and III (R = R′ = Me), obtained in this way, are identical with the stable phenolic end product of acid-catalyzed rearrangement of the alcohol XIII (R = Me) or the alkenylcodeinone XIV (R = Me) and its methyl ether.[11]



XIII XIV

(8) This observation was made by Dr. J. W. Lewis and Mr. M. J. Readhead of this laboratory.

(9) This phenolic, α,β-unsaturated ketone VII (R = H) is the product of the action of boron tribromide on the ketone I at 5°. The reaction can be rationally represented by the mechanism set out in i, which involves no disturbance of stereochemistry at C-7 [becoming C-18 in the diketone VIII (R = H)], and is analogous to the flavothebaone rearrangement.



i

(10) L. F. Small and G. L. Browning, *J. Org. Chem.*, 3, 618 (1939); K. W. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, 58, 958 (1952).

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

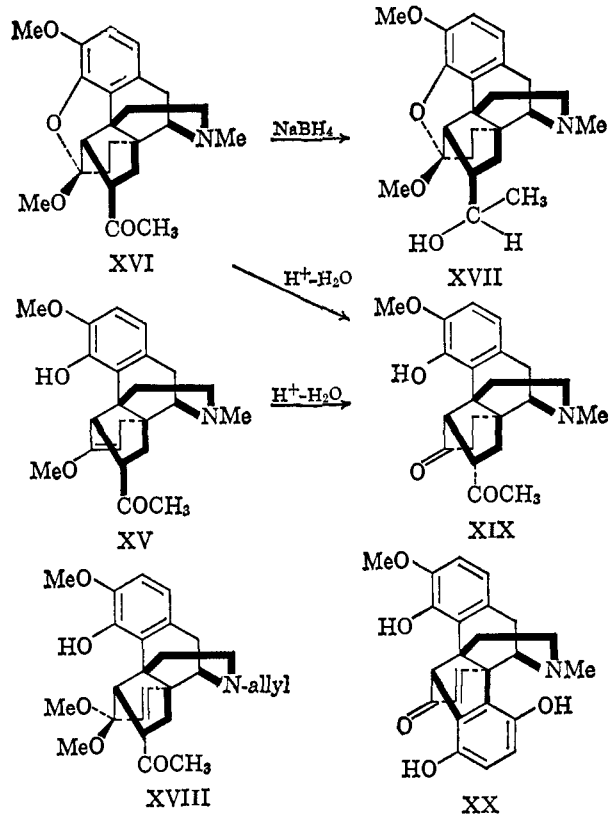
The nitrile XII (R′ = Me), which contains no readily removed proton, reacts normally with methylmagnesium iodide and the initial product on hydrolysis yields the ketone VII (R′ = Me), identical with that prepared from the ketones V (R′ = Me), and VIII. The ester X (R = Et, R′ = H) in part reacts further with Grignard reagents, when generated by these from the ester I (CH_3 = OEt), giving the tertiary carbinols II (R′ = H, Me = R).

The reaction of the ketones VIII and also VIII (CH_3 = Ph) with Grignard reagents is more complex, since they contain more than one reactive system. As well as being ketones they are allylic phenyl ethers, and bases of this type in the morphine–thebaine group (dihydrothebaine,[12] dihydrocodeinone enol acetate,[13] deoxycodeine-C,[14] ψ-codeine methyl ether[13]) readily undergo competing 1,2 and 1,4 addition of Grignard reagents to the allylic ether system to give nuclear alkylated phenolic bases. In this event the ketone VIII reacted vigorously with methylmagnesium iodide to give nonketonic phenolic matter, together with unchanged starting material, both of which must be obtained *via* the phenate ion IV.

The reaction with methyllithium, however, afforded a good yield of the tertiary alcohol IX (R = Me), which was hydrolyzed by cold dilute hydrochloric acid to the ketonic alcohol VI (R = Me) and by hot hydrochloric acid to the olefinic ketone III (R = Me, R′ = H), identical with the product of hydrolysis of the alcohol II (R = Me, R′ = H) and of rearrangement of the alkenylcodeinone XIV (R = Me) and alcohol XIII (R = Me).[11] Other lithium alkyls, however, reacted sluggishly with the ketone VIII, and the process does not provide an attractive route to a series of alcohols of structures IX and VI. The ketone VIII is readily reduced with sodium borohydride to the secondary alcohol IX (R = H), which is hydrolyzed by acids to the ketone VI (R = H), also obtainable by the reduction of the diketone VII (R′ = H) with sodium borohydride, during which process the hindered C-6 carbonyl group is unaffected.

Catalytic reduction of the ketone VIII is not a simple process, and the composition of the product depends on the nature of the catalyst. The allylic ether system present in the ketone readily undergoes 1,4 addition of hydrogen to give the phenolic base XV. Simple saturation of the olefinic bond has also been observed, the product being the nonphenolic base XVI, which is also accessible by the base-catalyzed rearrangement of the 6,14-ethano analog of the ketone I. The phenolic base XV is an enol ether and is very rapidly hydrolyzed by acids to the saturated diketone XIX, also accessible by the hydrolysis of the base XVI and by the catalytic reduction of the unsaturated ketone VII (R′ = H). The reduction of the ketone XVI with sodium borohydride yields the corresponding secondary alcohol XVII, which may be hydrolyzed to a saturated ketone, which is the dihydro derivative of the base VI (R = H).

Several analogs of the ketone VIII have been prepared by the base-catalyzed rearrangement of the appropriate ketone I (NMe = NR). In one case in methanolic potassium hydroxide solution, two products were obtained: the expected ketone VIII (NMe = N·CH_2-CH=CH_2) and a phenolic base containing the elements



of added methanol. Since both bases yielded the same α,β-unsaturated ketone on hydrolysis with acids, and since each of the pure compounds was converted into an approximately 1:1 mixture of the two on heating with methanolic potassium hydroxide, the phenolic product, which is a ketone but not an enol ether (infrared spectrum), is assigned the structure XVIII. This base presumably arises through the phenate ion IV (NMe = N-allyl) by competitive opening of the cyclopropane ring by the phenate oxygen and by a methoxide ion. An analogous product has previously been isolated from the base-catalyzed rearrangement of nepenthone (I, CH_3 = Ph).[2]

The 5,14-bridged thebainones of general structure III and VIII are quaternized more readily than the 6,14-*endo*-ethenotetrahydrothebaines I and XIII,[3,4] but less easily than flavothebaone (XX), and this difference may be attributed to hindrance to approach of the quaternizing halide to the nitrogen by the C-17β hydrogen. The methiodides of the bases III (R = R′ = Me) and VII (R′ = Me) readily suffer Hofmann degradation to the methine bases XXI and XXII. The last of these, subjected to further Hofmann degradation, afforded a very poor yield of a nitrogen-free product, containing CH_2 less than the simple Hofmann degradation product and showing no infrared absorption band characteristic of a vinyl group, and was assigned the structure XXIII.[15] An attempt to confirm this assignment by the preparation of the ether XXIII by the exhaustive methylation of the phenol VII (R′ = H) led in the first

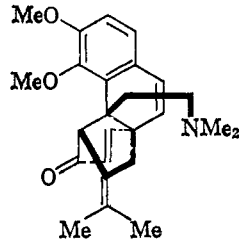
(12) L. F. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936).

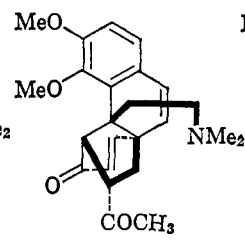
(13) L. F. Small, S. G. Turnbull, and H. M. Fitch, *J. Org. Chem.*, **3**, 204 (1938).

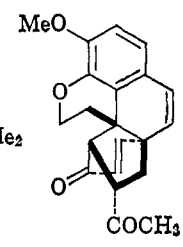
(14) L. F. Small and K. C. Yuen, *J. Am. Chem. Soc.*, **58**, 192 (1936).

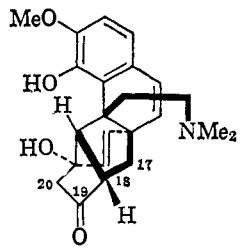
(15) The tendency to form the thebenone cyclic ether system is so strong that a C-4 methoxyl group is split during Hofmann degradation: W. Bralley, Dissertation, University of Virginia, 1941, quoted by L. J. Sargent and L. F. Small, *J. Org. Chem.*, **16**, 1032 (1951).

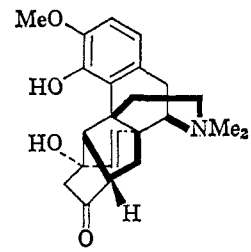
Hofmann degradation to a base showing styrenoid ultraviolet absorption and carbonyl absorption in the infrared only at 1740 cm^{-1}.


XXI


XXII


XXIII


XXIV


XXV

The nmr spectrum of this base in deuteriochloroform showed signals (in δ units) at 6.70 (two aromatic H), 6.45 (doublet, C-9 CH=, $J_{9,10}$ = 9.0 cps), 5.97 (doublet, C-10 CH=, $J_{9,10}$ = 9.0 cps), 5.42 (two olefinic H), 3.92 (C-3 OCH_3), and 2.30 ($2NCH_3$). This spectrum, which clearly shows that the $COCH_3$ system of the phenol VII (R′ = H) is no longer present in the new base, coupled with the infrared spectrum which shows the absence of an α,β-unsaturated ketone system, and the presence of a carbonyl group very probably in a five-membered ring, leads to the structure XXIV for the new base. Further examination of the nmr spectrum in deuteriochloroform containing deuteriobenzene[7] resulted in resolution of the two aromatic proton signals and also of the signal at δ 5.42, which was resolved into a barely defined double doublet with centers at δ 5.63 and 5.40 (J = *ca.* 9.0 cps), attributed to the C-7 and C-8 protons. In this spectrum the C-5 proton was located as a doublet at δ 3.50 ($J_{5,18}$ = 9.0 cps), and the C-20 protons were located as doublets at δ 2.95 and 2.58 ($J_{20,20}$ = 16 cps). The base XXIV obviously results from the Hofmann degradation of the methiodide of the base VII (R′ = H) and base-catalyzed ketolization of the $COCH_3$ and C-6 carbonyl groups.

A model of XXIV can be constructed without strain, and as the parent base containing an intact nitrogen-containing ring is also strain-free, the action of alkalis on the diketone VII (R′ = H) was studied. This results in the production of the base XXV, Hofmann degradation of the methiodide of which yields the methine base XXIV. The ketolization can only occur with one arrangement of the $COCH_3$ group, and the stable ketone VII (R′ = H) may confidently be assumed to be the 18α form shown. The phenol VII (R′ = H) and its methyl ether VII (R′ = Me) give deep orange solutions in alkalis and this color fades as the cyclization of the ketone VII (R′ = H) proceeds. The color is, therefore, assumed to be that of the enolate ion, in which some interaction between the enone and enol systems must occur, and it may be noted that the color is similar to that of flavothebaone in alkaline solution.[16]

(16) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, 22, 418 (1957).

The methyl ether VII (R′ = Me) of the phenol VII (R′ = H) is recovered unchanged from alkaline solution, and methylation of the ketol XXV in alkali results in deketolization and the production of the diketone VII (R′ = Me). The examination of a model of the base XXV shows that the hydroxyl groups at C-4 and C-6 are in very close proximity and the stability of the phenol in alkalis may be attributed to inhibition by the phenate anion of the removal of a proton from the C-6 hydroxyl group, which is an essential first step in the deketolization. Indeed, the proton of the C-6 hydroxyl may be expected to form a very firm hydrogen bond with the C-4 oxygen atom when the latter acquires a negative charge in alkaline solution. In the methyl ether of the phenol XXV, however, there will be no electrostatic inhibition of the removal of the proton of the C-6 hydroxyl group and deketolization can proceed.

Experimental Section

18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) (Isothevinone). a. 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (50 g) was boiled under reflux with potassium hydroxide (50 g) in methanol (500 ml) and water (100 ml) for 1 hr, during which time crystalline material separated. The mixture was diluted with water (100 ml) and cooled, and the solid was collected, when isothevinone (VIII) (40 g) was obtained as pale cream prisms, mp 168° raised to 170° on recrystallization from ethanol, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.4; H, 7.1. Found: C, 72.3; H, 7.1.

The base was alkali insoluble and the alkaline suspension gave only a pale pink coloration with diazotized sulfanilic acid.

b. The same base was obtained in the same way by the rearrangement of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine.

7-Acetyl-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (V, R′ = Me). a. 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (10 g) in dry *t*-butyl alcohol (20 ml) was added to a solution of potassium (1.1 g) in dry *t*-butyl alcohol (30 ml) and the mixture heated at 50° for 10 min. Methyl iodide (3.5 g, 0.95 mole) was then added and the mixture stirred for 15 min, after which it was poured into water and the product isolated by ether extraction. Evaporation of the dried extracts yielded a viscous yellow gum that crystallized on standing. Recrystallization of the product from petroleum ether (bp 80–100°) afforded the base V (R′ = Me) as pale cream prisms, mp 116°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_4$: C, 73.0; H, 7.3. Found: C, 73.1; H, 7.3.

Acid hydrolysis of this base afforded 18-acetyl-5,14-ethano-4-O-methylthebainone (VII, R′ = Me) (see below).

b. 18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) (32 g) (prepared by the alkaline rearrangement of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine) in *t*-butyl alcohol (100 ml) was added to a solution of potassium (12 g) in *t*-butyl alcohol (200 ml), and the mixture was stirred for 10 min at 50°. Methyl iodide (40 g) was added to the mixture which was stirred for 2 hr. The precipitated sodium iodide was removed by filtration, and the mixture was evaporated to dryness, the residue being thoroughly extracted with ether. The ether extract on evaporation afforded a viscous oil, which crystallized on standing. Recrystallization of the product from petroleum ether (bp 80–100°) afforded 7-acetyl-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (V R′ = Me) as pale cream prisms, mp 115–116°, identical (mixture melting point and infrared spectrum) with material prepared as described above.

18-Acetyl-5,14-ethanothebainone (VII, R′ = H) (ψ-Thevinone). 18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (isothevinone, VIII) (20 g) was dissolved in 2 *N* hydrochloric acid (100 ml) and the solution was basified with ammonia, when the diketone VII (R′ = H) (18 g) was precipitated. The product was collected, washed, and recrystallized from methanol, when it was obtained as white prisms, mp 200°, ν_{max} 1715 and 1690 cm^{-1}.

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.9; H, 6.8. Found: C, 71.1; H, 6.9.

From aqueous 2-ethoxyethanol the hydrated base separated as prisms, mp 169–170°.

Anal. Calcd for $C_{22}H_{25}NO_4 \cdot H_2O$: C, 68.6; H, 7.0. Found: C, 68.7; H, 6.9.

This base was readily soluble in alkali to give a yellow solution which gave a blood red color with diazotized sulfanilic acid.

The methiodide, prepared from the base, methyl iodide, and methanol under reflux for 2 days, was precipitated with ether and crystallized from methanol–ether and then from ethanol, when it was obtained as white prisms, mp 202–205°.

Anal. Calcd for $C_{22}H_{25}NO_4 \cdot CH_3I \cdot H_2O$: C, 52.3; H, 5.7. Found: C, 52.1; H, 6.0.

The oxime was obtained as prisms, mp 253–255°, from ethanol.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.1; H, 6.9; N, 7.2. Found: C, 68.6; H, 7.1; N, 7.2.

18-Acetyl-5,14-ethano-4-O-methylthebainone (VII, R′ = Me). a. Methyl sulfate (40 g) was slowly added to a vigorously stirred hot solution of 18-acetyl-5,14-ethanothebainone (VII, R′ = H) (50 g) and potassium hydroxide (20 g) in water. The product separated as a cream solid (48 g) which was collected and recrystallized from aqueous 2-ethoxyethanol, when the methyl ether V (R′ = Me) (35 g) was obtained as white prisms, mp 183°, ν_{max} 1715 and 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.4; H, 7.1. Found: C, 72.1; H, 7.2.

The base was insoluble in alkali.

The methiodide was prepared by boiling the base in methyl iodide under reflux for 4 days, and was obtained from ethanol as prisms, mp 245°.

Anal. Calcd for $C_{23}H_{27}NO_4 \cdot CH_3I \cdot 0.5H_2O$: C, 54.1; H, 5.8. Found: C, 54.0; H, 5.7.

The oxime was obtained as prisms, mp 247–248°, from ethanol.

Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.7; H, 7.1; N, 7.1. Found: C, 69.9; H, 7.4; N, 7.1.

b. 7-Acetyl-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (V, R′ = Me) (1 g) was dissolved in 2 *N* hydrochloric acid (10 ml) and the solution basified with ammonia. The precipitated solid was collected and recrystallized from aqueous 2-ethoxyethanol, when 18-acetyl-5,14-ethano-4-O-methylthebainone (VII, R′ = Me), mp 183°, was obtained identical with material prepared as in the preceding paragraph (mixture melting point and infrared spectrum).

5,14-Ethano-4(O)-6-dehydro-18-(1-hydroxyethyl)-6-O-methylthebainol (IX, R = H) (Isothevinol). Sodium borohydride (0.5 g) was added to a solution of 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) (10 g) in 2-ethoxyethanol (20 ml), and the mixture was heated at 100° for 30 min. The resulting solution was cooled, and the solid (9 g) was collected and recrystallized from aqueous 2-ethoxyethanol, when the secondary alcohol IX (R = H) was obtained as white prisms, mp 215°.

Anal. Calcd for $C_{23}H_{29}NO_4 \cdot H_2O$: C, 68.8; H, 7.7. Found: C, 68.7; H, 7.8.

No carbonyl absorption showed in the infrared. The base was alkali insoluble, and the suspension in alkali gave no color with diazotized sulfanilic acid.

5,14-Ethano-18-(1-hydroxyethyl)thebainone (VI, R = H). a. 5,14-Ethano-4-(O)-6-dehydro-18-(1-hydroxyethyl)-6-O-methylthebainol (IX, R = H) (10 g) was dissolved in 2 *N* hydrochloric acid (100 ml), and the resulting solution was basified with ammonia. The precipitated base was collected (9 g) and recrystallized from aqueous 2-ethoxyethanol, when the keto alcohol VI (R = H) was obtained as white prisms, mp 248°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot H_2O$: C, 68.3; H, 7.5. Found: C, 68.5; H, 7.3.

The base was readily soluble in alkali, and the solution gave a blood red color with diazotized sulfanilic acid.

b. Sodium borohydride (0.1 g) was added to a suspension of 18-acetyl-5,14-ethanothebainone (2 g) in ethanol (10 ml) and the solution stirred at 25° for 15 min. Water (50 ml) was added, and the mixture was stirred until crystallization was complete, and the solid was then collected. Recrystallization of the product from aqueous ethanol afforded the secondary alcohol VI (R = H) identical with material prepared as above, mp and mmp 248°, ν_{max} 1690 cm^{-1}.

5,14-Ethano-18-(1-hydroxyethyl)-4-O-methylthebainone. 18-Acetyl-5,14-ethano-4-O-methylthebainone (VII, R′ = Me) (10 g) was reduced as above with sodium borohyride (0.5 g) in methanol. Evaporation of the solvent left a yellow oil that crystallized on standing. The product was recrystallized from methanol, when it was obtained as white prisms, mp 271°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}NO_4 \cdot 0.5H_2O$: C, 70.4; H, 7.7. Found: C, 70.7; H, 7.5.

The same base was obtained by the O-methylation of the phenol VI (R = H) in aqueous methanolic potassium hydroxide, with methyl sulfate, as an oil on removal of most of the methanol *in vacuo*.

Catalytic Reduction of 18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII). a. A suspension of the ketone VIII (20 g) in 2-ethoxyethanol (200 ml, distilled from sodium) was shaken under hydrogen at 20° (55 psi) in the presence of 5% rhodium on alumina (1 g) for 3 hr. By the end of that time the base had dissolved and uptake of hydrogen had ceased. The solution was filtered and evaporated, and the residual solid was recrystallized from ethanol (100 ml), when 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methyldihydrothebainol (XVI) (14 g) was obtained as white prisms, mp 158–160°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7. Found: C, 72.0; H, 7.6; N, 3.8.

The base was insoluble in alkali and the suspension gave only a pale pink coloration with diazotized sulfanilic acid.

b. A suspension of the ketone VIII (10 g) in 2-ethoxyethanol (200 ml) was shaken under hydrogen at 20° (55 psi) in the presence of 10% palladized charcoal (0.5 g) for 2 hr after which time hydrogen absorption had ceased. Evaporation of the filtered solution gave an oil which was dissolved in ether (50 ml), when a crystalline solid separated (6.2 g). This was found to be a mixture of the dihydro compound XVI (see above) and 18-acetyl-5,14-ethanodihydrothebainon-Δ^6-enol methyl ether (XV) from which the latter (3.4 g) was recovered by recrystallization from ethanol, rapid washing of the crystals with two 20-ml portions of ether, and further recrystallization from ethanol. In this way it was obtained as white prisms, mp 161–163°, ν_{max} 1700 and 1675 cm^{-1} (C=O enol ether).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6. Found: C, 72.1; H, 7.4.

An alkaline solution of the base gave a blood red color with diazotized sulfanilic acid.

Rearrangement of 7α-Acetyl-6,14-*endo*-ethanotetrahydrothebaine (I, CH=CH = CH_2CH_2). Potassium hydroxide (8.8 g) was added to a hot solution of 7α-acetyl-6,14-*endo*-ethanotetrahydrothebaine (8.8 g) in methanol (88 ml), and the mixture was boiled under reflux for 1 hr, evaporated to 45 ml, and poured into ice–water (350 ml). The precipitated solid (8.2 g) was collected and recrystallized from petroleum ether (bp 40–60°) to give 18-acetyl-4-(O)-6-dehydro-5,14-methyldihydrothebainol (XVI) (4.5 g) as prisms, mp 155–157° raised to 158–160° on recrystallization from methanol. This base was identical in melting point, mixture melting point, and infrared absorption with that obtained by the catalytic reduction of 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) over rhodium on alumina.

18-Acetyl-5,14-ethanodihydrothebainone (XIX). a. 18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methyldihydrothebainol (XVI) (5 g) was dissolved in 1 *N* hydrochloric acid (100 ml) and after 1 hr crystalline 18-acetyl-5,14-ethanodihydrothebainone hydrochloride was collected, mp 197–198°.

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot HCl \cdot H_2O$: C, 62.3; H, 7.1; Cl, 8.4; N, 3.3. Found: C, 61.7; H, 7.6; Cl, 8.0; N, 3.2.

The free base was recovered by treating the salt with sodium bicarbonate solution and extracting with chloroform. On recrystallization from ethanol it was obtained as white prisms, mp 205–207°, ν_{max} 1720 and 1705 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8. Found: C, 71.3; H, 7.5; N, 3.8.

b. The same base, mp 205–207°, undepressed on mixing with material prepared as in a, was obtained in the same way by the hydrolysis of 18-acetyl-5,14-ethanodihydrothebainone-Δ^6-enol methyl ether (XV) with 1 *N* hydrochloric acid. It is most convenient to prepare the base by the hydrolysis of the mixture of bases XV and XVI obtained by the reduction of 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol over palladized charcoal.

18-Acetyl-5,14-ethano-4-O-methyldihydrothebainone (XIX, OH = OMe). The mixture of bases (5 g) from the hydrogenation of the ketone VIII was dissolved in the minimum amount of 2 *N* hydrochloric acid, and the solution was diluted to 70 ml. Sodium hydroxide solution (2 *N*) was added until the precipitate redissolved followed by a further 50 ml. Dimethyl sulfate (5 ml) was then added and the mixture shaken for 1 hr, after which the solid was collected, washed with water, and recrystallized from ethanol, when the diketone XIX (OH = OMe) (2 g) was obtained as white prisms, mp 165–166°. *Anal.* Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7. Found: C, 71.8; H, 7.7; N, 3.7.

4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxyethyl)-6-O-methyl dihydrothebainol (XVII). Sodium borohydride (3 g) was added in portions over 15 min to a solution of 18-acetyl-4(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (XVI) (5 g) in 2-ethoxyethanol (50 ml) at 20°. The mixture was heated at 100° for 15 min, cooled, diluted with 2 *N* ammonia solution, and extracted with chloroform. The chloroform extract was evaporated and the residue recrystallized from ethanol, when the secondary alcohol XVII was obtained as white prisms, mp 165–166°.

Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.7; H, 8.1. Found: C, 71.8; H, 8.3.

5,14-Ethano-18-(1-hydroxyethyl)dihydrothebainone (VI, R = H, CH=CH = CH_2CH_2). 4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxyethyl)-6-O-methyldihydrothebainol (XVII) (0.5 g) was dissolved in 2 *N* hydrochloric acid (5 ml), and the solution was kept at room temperature for 30 min and in the refrigerator overnight. The solid was collected and recrystallized from water, when 5,14-ethano-18-(1-hydroxyethyl)dihydrothebainone hydrochloride was obtained as white prisms, mp 257° dec, ν_{max} 1720 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}NO_4 \cdot HCl \cdot 3H_2O$: C, 57.2; H, 7.9. Found: C, 57.0; H, 8.0.

Rearrangement of N-Allyl-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (I, NMe = $NCH_2CH=CH_2$) (N-Allylnorthevinone). A solution of potassium hydroxide (4.8 g) in methanol (50 ml) was added slowly to a boiling solution of N-allyl-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine hydrochloride (11 g) in methanol (50 ml) and the mixture then boiled under reflux for 1 hr. The solution was diluted with water and extracted with chloroform to give a mixture of two bases (11 g). The product (8 g) was crystallized from methanol to give N-allyl-18-acetyl-5,14-ethanonorthebainone dimethyl ketal (XVIII) (2.6 g) as prisms, mp 106–107°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.0; H, 7.6; N, 3.2. Found: C, 70.6; H, 7.7; N, 3.5.

The mother liquor from this crystallization was diluted with water, and the precipitated solid was recrystallized from aqueous methanol, when N-allyl-18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylnorthebainol (VIII, NMe = $NCH_2CH=CH_2$) (1.1 g) was obtained as white prisms, mp 129–130°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.7; H, 7.2; N, 3.4. Found: C, 73.3; H, 7.0; N, 3.7.

N-Allyl-18-acetyl-5,14-ethanonorthebainone (VII, R′ = H, NMe = $NCH_2CH=CH_2$). The above two bases XVIII (R = $CH_2CH=CH_2$) and VIII (NMe = $NCH_2CH=CH_2$) obtained by the rearrangement of the ketone I (NMe = $NCH_2CH=CH_2$), separately or together, on hydrolysis with 2 *N* hydrochloric acid followed by precipitation with ammonia and recrystallization of the product from ethanol, afforded the diketone VII (R′ = H, NMe = $NCH_2CH=CH_2$) as prisms, mp 110–112°, ν_{max} 1715 and 1690 cm^{-1}.

Anal. Calcd for $C_{24}H_{27}NO_4 \cdot 0.5H_2O$: C, 71.4; H, 6.8; N, 3.6. Found: C, 71.6; H, 7.0; N, 3.5.

Rearrangement of N-Propargyl-7α-acetyl-6,14-*endo*-ethenotetrahydronorthebaine (I, NMe = $NCH_2C\equiv CH$). The hydrochloride of the ketone I (NMe = $NCH_2C\equiv CH$) (10 g) was boiled with potassium hydroxide (4.8 g) in methanol (100 ml) for 1 hr. The product was isolated by chloroform extraction and crystallized from methanol, when N-propargyl-18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylnorthebainol (VIII, NMe = $NCH_2C\equiv CH$) was obtained as prisms, mp 177–179°

Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.0; H, 6.7. Found: C, 73.7; H, 6.7.

N-Propargyl-18-acetyl-5,14-ethanonorthebainone (VII, R′ = H, NMe = $NCH_2C\equiv CH$). N-Propargyl-18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylnorthebainol (VIII, NMe = $NCH_2C\equiv CH$) (2 g) was dissolved in warm 2 *N* hydrochloric acid, and after 5 min the solution was basified with ammonia. The product was collected and recrystallized from methanol when the diketone VII (R′ = H, NMe = $NCH_2C\equiv CH$) was obtained as prisms, mp 114°, ν_{max} 1715 and 1690 cm^{-1}.

Anal. Calcd for $C_{24}H_{25}NO_4 \cdot H_2O$: C, 70.4; H, 6.6; N, 3.4. Found: C, 70.4; H, 6.7; N, 3.9.

Base-Catalyzed Rearrangements Accompanying Normal Grignard Reactions with the Ketone I and Its 6,14-Ethano Analog. a. 7β-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (0.5 g) in anhydrous ether (100 ml) was added to a solution of methylmagnesium iodide (from 0.17 g of magnesium) in ether (25 ml), and the mixture was heated under reflux for 1 hr. The mixture was then poured into aqueous ammonium chloride, and the ether layer was separated, dried over magnesium sulfate, and evaporated, to leave a crude product (0.5 g) shown by thin layer chromatography to consist of two components. These were separated on alumina plates using ether as developing solvent. The less polar material (125 mg) was recovered from the plate and obtained as white prisms, mp 215°, from methanol, ν_{max} 3545, 3490 cm^{-1}, and identified as 5,7-dehydro-6,14-*endo*-etheno-7-(1-hydroxy-1-methylethyl)-6-O-methyldihydrothebainol (II, R = Me, R′ = H), by hydrolysis with cold 2 *N* hydrochloric acid to 5,14-ethano-18-isopropylidenethebainone (III, R = Me, R′ = H), identical in melting point, mixture melting point, and infrared absorption with an authentic specimen.

b. The product of the reaction between 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (38 g) and *n*-propylmagnesium iodide was dissolved in methanol and cooled, and the crystalline 6,14-*endo*-etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)tetrahydrothebaine (XIII, R = *n*-Pr)[4] was collected. The mother liquors were concentrated to yield 11.1 g of a glass, a sample of which (1.08 g) was subjected to partition chromatography on Celite using a methanol–heptane system, with observation of the extinction of the eluate at 230 mμ. Three main fractions were obtained, yielding 0.15 g (A), 0.25 g (B), and 0.65 g (C) of product on evaporation. Fraction A consisted of the tertiary alcohol XIII (R = *n*-Pr) and fraction C consisted of the secondary alcohol XIII (R = H), resulting from Grignard reduction of the ketone I.[4]

Fraction B was dissolved in benzene and rechromatographed on alumina (25 g) which was eluted successively with 100-ml portions of 1, 5, 20, 50, and 100% ethyl acetate in benzene. Fractions of 20 ml were collected and examined by thin layer chromatography, similar fractions being combined. Fractions 11–13 gave 96 mg of a mixture of 7α- and 7β-acetyl-6,14-*endo*-ethenotetrahydrothebaine and fractions 18–22 gave 176 mg of an oil, which on trituration with methanol gave 5,7-dehydro-6,14-*endo*-etheno-7-(1-hydroxy-1-methylbutyl)-6-O-methyldihydrothebainol (II, R = *n*-Pr, R′ = H) (36 mg), mp 192–198°, raised to 202–203° on recrystallization from methanol.

Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.4; H, 8.3; N, 3.3. Found: C, 73.1; H, 8.35; N, 3.8.

c. The crude product of the reaction between 7α-acetyl-6,14-*endo*-ethanotetrahydrothebaine (I, 6,14-CH_2CH_2) (140 g) and isopropylmagnesium chloride (from 48.6 g of magnesium), in ether and benzene solution, which was noncrystalline, was triturated with cold methanol. The solid so formed was collected, and extracted with boiling ethanol (300 ml), and the undissolved matter was crystallized from chloroform. In this way 5,7-dehydro-6,14-*endo*-ethano-7-(1-hydroxy-1,2-dimethylpropyl)-6-O-methyldihydrothebainol (II, R = *i*-Pr, R′ = H, 6,14-CH_2CH_2) was obtained as white prisms, mp 253–256°.

Anal. Calcd for $C_{26}H_{37}NO_4$: C, 73.1; H, 8.7; N, 3.3. Found: C, 72.7; H, 8.3; N, 3.5.

d. In like manner to that described in part c above, the following were isolated from the products of reaction of 7α-acetyl-6,14-*endo*-ethanotetrahydrothebaine and the appropriate Grignard reagent: 5,7-dehydro-6,14-*endo*-ethano-7-(1-hydroxy-1-methylpentyl)-6-O-methyldihydrothebainol (II, R = *n*-Bu, R′ = H, 6,14-CH_2CH_2, prisms, mp 169–170°. *Anal.* Calcd for $C_{27}H_{39}NO_4$: C, 73.4; H, 8.9; N, 3.2. Found: C, 72.9; H, 8.7; N, 3.3); 5,7-dehydro-6,14-*endo*-ethano-7-(1-hydroxy-1-methylpropyl)-6-O-methyldihydrothebainol (II, R = Et, R′ = H, 6,14-CH_2-CH_2, white prisms, mp 215–216°. *Anal.* Calcd for $C_{25}H_{35}NO_4$: C, 72.6; H, 8.5; N, 3.4. Found: C, 72.8; H, 8.5; N, 3.4); and 5,7-dehydro-6,14-*endo*-ethano-7-(1-hydroxy-1,4-dimethylpentyl)-6-O-methyldihydrothebainol (II, R = *i*-Am, R′ = H, 6,14-CH_2CH_2, white prisms, mp 178–179°. *Anal.* Calcd for $C_{28}H_{41}NO_4$: C, 73.8; H, 9.1; N, 3.1. Found: C, 73.5; H, 8.9; N, 3.2).

5,14-Ethano-18-(3′-methylbut-2′-ylidene)dihydrothebainone (III, R = *i*-Pr, R′ = H, 7,8-dihydro). 5,7-Dehydro-6,14-*endo*-ethano-7-(1-hydroxy-1,2-dimethylpropyl)-6-O-methyldihydrothebainol (II, R = *i*-Pr, R′ = H, 6,14-CH_2CH_2) (0.1 g) was dissolved in 1.5 *N* hydrochloric acid (2.5 ml), and the solution was heated on the water bath for 10 min. A crystalline hydrochloride separated and was collected and recrystallized from water, when it was obtained as white prisms, mp 199–201°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{25}H_{33}NO_3 \cdot HCl \cdot 3H_2O$: C, 61.7; H, 8.3. Found: C, 61.2; H, 8.3.

4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxy-1-methylethyl)-6-O-methylthebainol (IX, R = Me) (Methylisothevinol). A solution of methyllithium (4 g) in ether (125 ml) was slowly added to a vigorously stirred solution of 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) (35 g) in ether (200 ml), under nitrogen,

at a rate sufficient to maintain boiling. The mixture was finally heated under reflux for 30 min and then diluted cautiously with water (250 ml). The ether layer on evaporation afforded 34.9 g of solid matter, still containing some ketone (infrared spectrum), and this was treated under the same conditions with a further 4 g of methyllithium. Evaporation of the ether layer then gave non-ketonic material from which the tertiary alcohol IX (R = Me) (27.8 g) was recovered on recrystallization from ethanol as white prisms, mp 217–218°.

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.5; H, 7.9; N, 3.5. Found: C, 72.2; H, 8.1; N, 3.4.

Hydrolysis of 4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxy-1-methylethyl)-6-O-methylthebainol (Methylisothevinol, IX, R = Me). a. The tertiary alcohol IX (R = Me) (3 g) was dissolved in 1 *N* hydrochloric acid (100 ml), and the solution was kept at 25° for 10 min. Neutralization of the solution with sodium bicarbonate and isolation of the product by ether extraction gave 5,14-ethano-18-(1-hydroxy-1-methylethyl)thebainone (VI, R = Me) (2.2 g), which was obtained from aqueous ethanol as rosettes of white needles, mp 129–132°, ν_{max} (CCl_4 solution) 3615 (free tertiary OH), 3547 (phenolic OH), 3450 (bonded OH), and 1670 cm^{-1} (α,β-unsaturated carbonyl).

Anal. Calcd for $C_{23}H_{29}NO_4 \cdot H_2O$: C, 68.8; H, 7.8. Found: C, 68.9; H, 7.7.

b. The tertiary carbinol IX (R = Me) (1.5 g) was boiled under reflux for 30 min with 5 *N* hydrochloric acid (25 ml), and the mixture was cooled and diluted with water (25 ml). The crystalline solid so obtained was collected (1.4 g) and recrystallized from water, when 5,14-ethano-18-isopropylidenethebainone (III, R = Me, R′ = H) hydrochloride was obtained as white prisms, mp 320°.

Anal. Calcd for $C_{23}H_{27}NO_3 \cdot HCl$: C, 68.7; H, 7.0; Cl, 8.8. Found: C, 68,4; H, 7.0; Cl, 8.7.

The free base crystallized readily only from methanol, when it was obtained as solvated prisms, mp 138–139°, ν_{max} (CCl_4 solution) 3640 (methanol), 3532 (phenolic OH), and 1690 cm^{-1} (α,β-unsaturated carbonyl). The base coupled with diazotized sulfanilic acid in alkalis. The base and its hydrochloride were identical in infrared absorption and in behavior on thin layer chromatography with 5,14-ethano-18-isopropylidenethebainone and its hydrochloride prepared by the acid-catalyzed rearrangement of 6,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (XIII, R = Me).[11]

Dehydration of 5,14-Ethano-18-(1-hydroxy-1-methylethyl)thebainone (VI, R = Me). The tertiary alcohol VI (R = Me) (120 mg) was boiled under reflux with 5 *N* hydrochloric acid (5 ml) for 30 min. The solution was cooled; the crystalline solid was collected and shaken with sodium bicarbonate solution and ether. Evaporation of the ether and crystallization of the product from methanol gave 5,14-ethano-18-isopropylidenethebainone (III, R = Me, R′ = H), identical in infrared absorption with material prepared by the acid-catalyzed rearrangement of the tertiary alcohol XIII (R = Me).[11]

5,7-Dehydro-6,14-*endo*-etheno-7-(1-hydroxy-1-methylethyl)-4,6-O-dimethyldihydrothebainol (II, R = R′ = Me). A solution of 7-acetyl-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (V, R′ = Me) (3.79 g) in dry ether (50 ml) was added to a vigorously stirred boiling solution of methylmagnesium iodide (from 0.96 g of magnesium and 5.64 g of methyl iodide) in ether (150 ml). The mixture was heated under reflux for 3 hr, and poured into saturated ammonium chloride solution. The ether layer was separated, dried, and evaporated, to leave a viscous gum (3.8 g) that crystallized on standing. Recrystallization of the solid from methanol afforded the tertiary alcohol II (R = R′ = Me) as white prisms, mp 140°.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 73.0; H, 8.0. Found: C, 73.4; H, 7.8.

5,14-Ethano-18-isopropylidene-4-O-methylthebainone (III, R = R′ = Me). 5,7-Dehydro-6,14-*endo*-etheno-7-(1-hydroxy-1-methylethyl)-4,6-O-dimethyldihydrothebainol (II, R = R′ = Me) (2 g) was dissolved in 2 *N* hydrochloric acid (10 ml) and after 5 min the solution was basified with ammonia, and the precipitated solid was collected. After recrystallization from methanol the unsaturated ketone III (R = R′ = Me) was obtained as off-white prisms, mp 178°, ν_{max} 1690 cm^{-1}, identical in melting point, mixture melting point, and infrared absorption with the 4-O-methyl ether of the base III (R = Me, R′ = H) obtained by the acid-catalyzed rearrangement of the alcohol XIII (R = Me).[11]

Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.9; H, 7.7. Found: C, 75.6; H, 8.1.

5,14-Ethano-4-O-methyl-18-pent-2′-ylidenethebainone (III, R = *n*-Pr, R′ = Me). 7-Acetyl-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (V, R′ = Me) (3.8 g) was treated with *n*-propylmagnesium chloride, and the noncrystalline reaction product was dissolved in 2 *N* hydrochloric acid. Basification of the acid solution with ammonia, isolation of the product by ether extraction, and crystallization from aqueous methanol afforded the unsaturated ketone III (R = *n*-Pr, R′ = Me) as prisms, mp 70°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{26}H_{33}NO_3 \cdot 0.5H_2O$: C, 75.0; H, 8.2. Found: C, 74.9; H, 8.1.

5,14-Ethano-4-O-methyl-18-(1′-methyl-2′-phenylethylidene)thebainone (III, R = CH_2Ph, R′ = Me). This was prepared by the acid hydrolysis of the noncrystalline reaction product of the action of benzylmagnesium bromide on the ketone V (R′ = Me), and was obtained as white prisms, mp 142°, ν_{max} 1690 cm^{-1}, from 70% ethanol.

Anal. Calcd for $C_{30}H_{33}NO_3 \cdot H_2O$: C, 76.1; H, 7.4. Found: C, 76.3; H, 7.6.

5,14-Ethano-18-(1′-cyclohexylethylidene)-4-O-methylthebainone (III, R = cyclohexyl, R′ = Me). This was obtained by the acid hydrolysis of the noncrystalline product of the reaction between cyclohexylmagnesium chloride and the ketone V (R′ = Me), and was recovered as white prisms, mp 98°, ν_{max} 1690 cm^{-1}, from ethanol.

Anal. Calcd for $C_{29}H_{37}NO_3$: C, 77.8; H, 8.3. Found: C, 77.4; H, 8.0.

5,14-Ethano-18-isopropylidene-4-O-methylthebainone Methine (XXI). 5,14-Ethano-18-isopropylidene-4-O-methylthebainone (9 g) and methyl iodide (60 ml) were boiled together under reflux for 3 days with stirring. The solid matter (12 g) was collected, when the methiodide was obtained as almost colorless prisms, mp 236°, from ethanol.

Anal. Calcd for $C_{24}H_{29}NO_3 \cdot CH_3I$: C, 57.6; H, 6.2. Found: C, 57.4; H, 6.4.

The methiodide (12 g) in water (100 ml) was boiled with potassium hydroxide (15 g) for 10 min. The mixture was cooled and the solid was collected (8.7 g) and recrystallized from benzene–petroleum ether (bp 60–80°), when the methine base was obtained as elongated white prisms, mp 152°, ν_{max} 1690 cm^{-1}, λ_{max} 272 and 305 mμ, ϵ_{max} 12,600 and 47,200.

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.3; H, 7.9. Found: C, 76.8; H, 8.1.

The methine methiodide formed rapidly from the base and methyl iodide in benzene, and was obtained from methanol as white prisms, mp 180°.

Anal. Calcd for $C_{25}H_{31}NO_3 \cdot CH_3I$: C, 58.3; H, 6.4. Found: C, 58.4; H, 6.4.

This methiodide resisted Hofmann degradation in aqueous solution, and pyrolysis of the methohydroxide resulted in the loss of methanol and the production of the methine base in very high yield. Only a trace of uncharacterized neutral matter was obtained.

18-Acetyl-5,14-ethano-4-O-methylthebainone Methine (XXII). 18-Acetyl-5,14-ethano-4-O-methylthebainone methiodide (see above) (4.0 g) was boiled with water (100 ml) and potassium hydroxide (15 g) for 10 min. The precipitated oil was isolated by ether extraction, and the uncrystallizable product was converted into its hydrochloride, which was obtained as white prisms, mp 210°, from ethanol–ether; ν_{max} 1690 cm^{-1}; λ_{max} 272, 298, and 308 mμ; ϵ_{max} 10,000, 4800, and 4000.

Anal. Calcd for $C_{24}H_{29}NO_4 \cdot HCl \cdot H_2O$: C, 64.2; H, 7.2. Found: C, 64.2; H, 7.4.

The methine methiodide, prepared from the methine base in benzene, was obtained from ethanol as white prisms, mp 283°.

Anal. Calcd for $C_{24}H_{29}NO_4 \cdot CH_3I$: C, 55.9; H, 6.0. Found: C, 55.5; H, 6.0.

18-Acetyl-5,14-ethano-7,8,9,10-tetradehydrothebenone (XXIII). 18-Acetyl-5,14-ethano-4-O-methylthebainone methine methiodide (0.20 g) in water (10 ml) was boiled under reflux with potassium hydroxide (1.5 g) for 6 hr. The insoluble brown product (0.031 g) was dissolved in benzene, and the solution was passed through a short column of alumina, which removed a trace of a violet impurity. The almost colorless solid recovered from the eluate (one spot on thin layer chromatography) was recrystallized from petroleum ether (bp 60–80°), when the ketone XXIII was obtained as white prisms, mp 167–168°, ν_{max} 1690 cm^{-1}.

Anal. Calcd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 74.7; H, 6.3.

5,14-Ethano-6,18-(2′-oxoethano)thebainol (XXV). Potassium hydroxide (1 g) in water (10 ml) was added to a solution of 18-acetyl-5,14-ethanothebainone (VII, R′ = H) (5 g) in 2-ethoxyethanol (80

ml), and the solution was heated in the boiling water bath for 5 min. Water was then added (100 ml), and a pale yellow solution was obtained. The addition of saturated ammonium chloride solution (20 ml) discharged the yellow color. Almost immediately a crystalline solid began to separate, and the separation was complete after 10 min. The solid was collected, washed with water, and recrystallized from 2-ethoxyethanol, when the base XXV was obtained as white prisms, mp 275–276°, ν_{max} 1740 cm^{-1}.

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.9; H, 6.8. Found: C, 71.8; H, 6.8.

The same base was obtained on warming the diketone VII (R′ = H) in aqueous potassium hydroxide containing sufficient ethanol to prevent the separation of the potassium salt. Dilution of the solution with water and addition of ammonium chloride gave an immediate precipitate which, on collection and recrystallization from aqueous 2-ethoxyethanol, afforded the base XXV as prisms, mp 275–276°, ν_{max} 1740 cm^{-1}.

The methiodide, prepared from the base and methyl iodide in 2-ethoxyethanol solution under reflux for 5 hr, was obtained as elongated prisms, mp 268–270°, from water.

Anal. Calcd for $C_{22}H_{25}NO_4 \cdot CH_3I \cdot H_2O$: C, 52.3; H, 5.7. Found: C, 52.0; H, 5.9.

5,14-Ethano-6,18-(2′-oxoethano)thebainol Methine (XXIV). a. 18-Acetyl-5,14-ethanothebainone methiodide (4.5 g) was boiled with water (60 ml) and potassium hydroxide (15 g) for 30 min. The solution was cooled and the liquid decanted from the glassy solid, which was dissolved in water, and the solution was acidified with dilute hydrochloric acid. On basification of the solution with ammonia, no precipitate was obtained, and the base was isolated by extraction with chloroform, when it was obtained as a yellow solid. On recrystallization from methanol it was recovered as white prisms, mp 204°, ν_{max} 1740 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.4; H, 7.1. Found: C, 72.6; H, 7.4.

b. The same base was obtained in the same way from 5,14-ethano-6,18-(2′-oxoethano)thebainol methiodide.

5,7-Dehydro-6,14-*endo*-etheno-7-ethoxycarbonyl-6-O-methyldihydrothebainol (X, R = Et, R′ = H). 6,14-*endo*-Etheno-7α-ethoxycarbonyltetrahydrothebaine (I, CH_3 = OEt) (15 g) in dry *t*-butyl alcohol (100 ml) was added to a solution of potassium (6 g) in *t*-butyl alcohol (150 ml), and the mixture was boiled under reflux for 15 min. The resulting solution was cooled and poured into an excess of saturated aqueous ammonium chloride, and the organic layer was separated, concentrated under reduced pressure, and kept in the refrigerator overnight. The crystalline ester that separated was collected (14 g) and recrystallized from methanol, when it was obtained as white prisms, mp 186°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_5 \cdot H_2O$: C, 67.2; H, 7.2. Found: C, 67.1; H, 7.0.

The same base was obtained during the reaction of 6,14-*endo*-etheno-7α-ethoxycarbonyltetrahydrothebaine with Grignard reagents other than methylmagnesium iodide. Being phenolic it was readily separated by virtue of its solubility in aqueous alkalis from the tertiary carbinols resulting from normal Grignard attack of the ester. The phenolic material so obtained, however, contained some tertiary alcohol II (CH_3 = R), which was removed by acid-catalyzed hydrolysis in cold 2 *N* hydrochloric acid (in which the ester is stable) to the sparingly soluble hydrochloride of the related ketone III (CH_3 = R). In this way the ester X (R = Et, R′ = H) was obtained from the reaction of the ester I (CH_3 = OEt) and ethylmagnesium bromide and *n*-propylmagnesium chloride, together with the hydrochlorides of 5,14-ethano-18-pent-3′-ylidenethebainone (III, R′ = H, CH_3 = R = Et), mp 285–287°, ν_{max} 1690 cm^{-1} (*Anal.* Calcd for $C_{25}H_{31}NO_3 \cdot HCl$: C, 69.8; H, 7.4. Found: C, 70.0; H, 7.3) and 5,14-ethano-18-hept-4′-ylidenethebainone (III, R′ = H, CH_3 = R = *n*-Pr), mp 291°, ν_{max} 1690 cm^{-1} (*Anal.* Calcd for $C_{27}H_{35}NO_3 \cdot HCl$: C, 70.8; H, 7.9. Found: C, 70.6; H, 8.0).

5,7-Dehydro-6,14-*endo*-etheno-7-ethoxycarbonyl-4,6-O-dimethyldihydrothebainol (X, R = Et, R′ = Me). 6,14-*endo*-Etheno-7α-ethoxycarbonyltetrahydrothebaine (I, CH_3 = OEt) (10 g) was heated with a solution of potassium (4 g) in dry *t*-butyl alcohol (150 ml) under reflux for 15 min, and methyl iodide (8 ml) in *t*-butyl alcohol (20 ml) was then added slowly with vigorous stirring. The mixture was filtered from precipitated potassium iodide and evaporated, leaving a semisolid residue, which was extracted thoroughly with ether. Evaporation of the ether extract afforded a viscous gum, which was crystallized with difficulty from aqueous methanol, when the ester X (R = Et, R′ = Me) was obtained as white prisms, mp 100°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3. Found: C, 70.2; H, 7.1.

5,7-Dehydro-6,14-*endo*-etheno-7-isopropoxycarbonyl-6-O-methyldihydrothebainol (X, R = *i*-Pr, R′ = H). A solution of 6,14-*endo*-etheno-7α-ethoxycarbonyltetrahydrothebaine (10 g) in dry benzene was added to one of sodium (1 g) in 2-propanol (10 ml). The resulting mixture was boiled under reflux for 3 hr, with a Whitmore-Lux variable take-off head so adjusted that one drop in 12 of the refluxing liquid was removed. The resulting mixture was poured into an excess of ice-cold 2 *N* hydrochloric acid; the aqueous layer was removed and made alkaline with ammonia. The base precipitated in this way was collected and recrystallized from aqueous 2-ethoxyethanol, when the isopropyl ester was obtained as white prisms, mp 177–178°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3. Found: C, 70.5; H, 7.3.

The ester was soluble in alkalis and the solution coupled readily with diazotized sulfanilic acid to give a blood red solution.

The following esters were prepared by base-catalyzed rearrangement of the ester I (CH_3 = OEt), with simultaneous base-catalyzed ester exchange: 5,7-dehydro-6,14-*endo*-etheno-6-O-methyl-7-propoxycarbonyl dihydrothebainol (X, R = *n*-Pr, R′ = H, white prisms, mp 137°, from methanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3. Found: C, 70.5; H, 7.3), 5,7-dehydro-6,14-*endo*-etheno-7-isobutoxycarbonyl-6-O-methyldihydrothebainol (X, R = *i*-Bu, R′ = H, white prisms, mp 84°, from aqueous methanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}NO_5 \cdot 0.5H_2O$: C, 69.6; H, 7.6. Found: C, 69.2; H, 7.8); 7-butoxycarbonyl-5,7-dehydro-6,14-*endo*-etheno-6-O-methyldihydrothebainol (X, R = *n*-Bu, R′ = H, white prisms, mp 138°, from aqueous methanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}NO_5$: C, 71.0; H, 7.5. Found: C, 70.5; H, 7.3); 5,7-dehydro-6,14-*endo*-etheno-6-O-methyl-7-pentyloxycarbonyldihydrothebainol (X, R = *n*-Am, R′ = H, white prisms, mp 146°, from methanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{27}H_{35}NO_5$: C, 71.5; H, 7.7. Found: C, 71.0; H, 7.9); 5,7-dehydro-6,14-*endo*-etheno-7-furfuryloxycarbonyl-6-O-methyldihydrothebainol (X, R = furfuryl, R′ = H, white prisms, mp 211°, from ethanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{27}H_{29}NO_6$: C, 70.0; H, 6.3. Found: C, 69.6; H, 6.2); 5,7-dehydro-6,14-*endo*-etheno-6-O-methyl-7-tetrahydrofurfuryloxycarbonyldihydrothebainol (X, R = tetrahydrofurfuryl, R′ = H, noncrystalline, hydrochloride white prisms, mp 236°, from ethanol. *Anal.* Calcd for $C_{27}H_{33}NO_6 \cdot HCl$: C, 64.1; H, 6.8. Found: C, 63.6; H, 7.1); 7-cyclohexyloxycarbonyl-5,7-dehydro-6,14-*endo*-6-O-methyldihydrothebainol (X, R = cyclohexyl, R′ = H, white prisms, mp 200°, from ethanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{28}H_{35}NO_5$: C, 72.3; H, 7.5. Found: C, 72.6; H, 7.3); 5,7-dehydro-7-(2′-diethylaminoethoxycarbonyl)-6,14-*endo*-etheno-6-O-methyldihydrothebainol (X, R = $CH_2CH_2NEt_2$, R′ = H, noncrystalline, dihydrochloride, mp 238°, from ethanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{28}H_{38}N_2O_5 \cdot 2HCl \cdot H_2O$: C, 58.6; H, 7.3. Found: C, 58.8; H, 7.3). 5,7-Dehydro-6,14-*endo*-etheno-6-O-methyl-7-(2′-morpholinoethoxycarbonyl)dihydrothebainol (X, R = morpholinoethyl, R′ = H, noncrystalline, dihydrochloride, white prisms, mp 221°, from ethanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{28}H_{36}N_2O_6 \cdot 2HCl \cdot 4H_2O$: C, 52.3; H, 7.1. Found: C, 52.0; H, 6.8); and 5,7-dehydro-6,14-*endo*-etheno-7-(2′-ethoxyethoxycarbonyl)-6-O-methyldihydrothebainol (X, R = CH_2CH_2OEt, R′ = H, noncrystalline, hydrochloride white prisms, mp 270°, from ethanol, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}NO_6 \cdot HCl$: C, 63.5; H, 7.0. Found: C, 63.6; H, 7.3).

5,14-Ethano-18-ethoxycarbonylthebainone (XI, R = COOEt, R′ = H). 5,7-Dehydro-6,14-*endo*-etheno-7-ethoxycarbonyl-6-O-methyldihydrothebainol (X, R = Et, R′ = H) (2 g) was heated with 2 *N* hydrochloric acid (20 ml) at 100° for 5 min. The solution was basified with ammonia, and the precipitated base was isolated by ether extraction and crystallized from methanol, when the ester XI (R = COOEt, R′ = H) (1.7 g) was obtained as white prisms, mp 168°, ν_{max} 1735 and 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.5; H, 6.8. Found: C, 69.6; H, 6.7.

5,14-Ethano-18-ethoxycarbonyl-4-O-methylthebainone (XI, R = COOEt, R′ = Me). Hydrolysis of the ester X (R = Et, R′ = H) with 2 *N* hydrochloric acid at 100° for 5 min, followed by basification of the solution with ammonia, afforded the ester XI (R = COOEt, R′ = Me), which was isolated by ether extraction and obtained from aqueous methanol with difficulty as white prisms, mp 78°, ν_{max} 1735 and 1690 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.0; H, 7.1. Found: C, 69.5; H, 7.0.

5,14-Ethano-18-(2′-ethoxyethoxycarbonyl)thebainone (XI, R = $COOCH_2CH_2OEt$, R′ = H) was obtained as above by the hydrolysis of the ester X (R = CH_2CH_2OEt, R′ = H) with 2 *N* hydrochloric acid at 100° for 5 min. The base could not be crystallized, but the hydrochloride was obtained from ethanol–ether as white prisms, mp 254–256°, ν_{max} 1735 and 1690 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}NO_6 \cdot HCl$: C; 62.7; H, 6.9. Found: C, 62.6; H, 6.8.

7-Cyano-5,7-dehydro-6,14-*endo*-etheno-6-O-methyldihydrothebainol (XII, R′ = H). 7-Cyano-6,14-*endo*-ethenotetrahydrothebaine (10 g, mixture of 7α and 7β isomers obtained directly from the Diels–Alder addition of acrylonitrile to thebaine[3]) in ether (200 ml) was added to a boiling solution of methylmagnesium iodide (from 2.52 g of magnesium and 15.4 g of methyl iodide) in ether (100 ml), and the mixture was heated and stirred under reflux for 4 hr, and then poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, and the crystalline residue (9.3 g) was recrystallized from methanol, when the nitrile XII (R′ = H) was obtained as almost white prisms, mp 234°, ν_{max} 2250 cm^{-1}, readily soluble in aqueous potassium hydroxide and coupling in solution with diazotized sulfanilic acid to give a red dye.

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.5; H, 6.7. Found: C, 72.8; H, 6.8.

The same base was obtained when 7-cyano-6,14-*endo*-etheno-tetrahydrothebaine (10 g) was added to a solution of potassium (5 g) in *t*-butyl alcohol (200 ml), the solution being maintained at 65° for 15 min after which it was poured into saturated aqueous ammonium chloride, and the product was isolated by ether extraction. It was obtained also by either process starting from the pure 7α and 7β nitriles.

7-Cyano-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (XII, R′ = Me). 7-Cyano-6,14-*endo*-ethenotetrahydrothebaine (6 g, mixture of 7α and 7β forms) was added to a solution of potassium (2.4 g) in *t*-butyl alcohol (40 ml) and methyl iodide (6 ml) was added to the resulting red solution. The mixture was stirred at *ca.* 65° for 1 hr and poured into aqueous ammonium chloride, and the organic layer was separated. The aqueous layer was extracted once with ether, and the combined organic solutions were evaporated to dryness. The residue (6 g) was recrystallized from methanol, when the O-methyl ether XII (R′ = Me) (5 g) was obtained as prisms, mp 187°, ν_{max} 2250 cm^{-1}.

Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 73.0; H, 6.9. Found: C, 72.6; H, 6.9.

7-Cyano-5,7-dehydro-6,14-*endo*-etheno-4-O-ethyl-6-O-methyldihydrothebainol (XII, R = Et). 7-Cyano-6,14-*endo*-ethenotetrahydrothebaine (3 g) in a solution of potassium (1.2 g) in *t*-butyl alcohol (20 ml) at 60° was ethylated by the addition of ethyl bromide (3 ml). Isolation of the product in the manner described above gave the 4-O-ethyl ether XII (R′ = Et) as white needles, mp 120°, from aqueous methanol.

Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.5; H, 7.15. Found: C, 73.0; H, 7.3.

4-O-Acetyl-7-cyano-5,7-dehydro-6,14-*endo*-etheno-6-O-methyldihydrothebainol (XII, R^1 = $COCH_3$). Acetyl chloride (3 ml) was added to a solution of 7-cyano-6,14-*endo*-ethenotetrahydrothebaine (3 g) in one of potassium (1.2 g) in *t*-butyl alcohol (30 ml). After 15 min at room temperature the mixture was poured into ammonium chloride solution containing ammonia. The product was isolated by ether extraction and recrystallized from methanol, when the acetylated nitrile XII (R′ = $COCH_3$) was obtained as elongated plates, mp 217°, ν_{max} 2250 and 1720 cm^{-1}.

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.9; H, 6.4. Found: C, 70.9; H, 6.4.

18-Cyano-5,14-ethanothebainone (XI, R = CN, R′ = H). 7-Cyano-5,7-dehydro-6,14-*endo*-etheno-6-O-methyldihydrothebainol (XII, R′ = H) (5 g) was heated for 5 min at 100° with 2 *N* hydrochloric acid (20 ml). The ketone was precipitated with ammonia and recrystallized from methanol, when it was obtained as white prisms, mp 200°, ν_{max} 2250 and 1690 cm^{-1}.

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.3. Found: C, 72.1; H, 6.2.

18-Cyano-5,14-ethano-4-O-methylthebainone (XI, R = CN, R′ = Me). Prepared as above by the hydrolysis of the methylated nitrile XII (R′ = Me), this ketone was obtained as prisms, mp 284°, ν_{max} 2250 and 1690 cm^{-1}, from ethanol.

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.5; H, 6.7. Found: C, 72.1; H, 6.3.

18-Cyano-5,14-ethano-4-O-ethyl-6-O-methylthebainone (XI, R′ = Et) was obtained by the hydrolysis of the nitrile XII (R′ = Et) with 2 *N* hydrochloric acid at 100° as above, and was recovered from aqueous methanol as prisms, mp 200°, ν_{max} 2250 and 1690 cm^{-1}.

Anal. Calcd for $C_{23}H_{26}N_2O_3 \cdot H_2O$: C, 69.7; H, 7.1. Found: C, 69.9; H, 6.7.

Reaction of the Nitrile XII (R′ = Me) with Methylmagnesium Iodide. 7-Cyano-5,7-dehydro-6,14-*endo*-etheno-4,6-O-dimethyldihydrothebainol (XII, R′ = Me) (6.1 g) in tetrahydrofuran (200 ml) was added to a boiling stirred solution of methylmagnesium iodide (from 2 g of magnesium and 4.6 ml of methyl iodide) in tetrahydrofuran (100 ml). The resulting mixture was stirred and heated under reflux for 5 hr, and poured into saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted once with ether. Evaporation of the combined organic solutions afforded a viscous material, which was warmed on the water bath for 30 min with 2 *N* hydrochloric acid (25 ml). Basification of the solution with ammonia and isolation of the product by ether extraction afforded a solid (4 g). On crystallization from ethanol this gave 18-acetyl-5,14-ethano-4-O-methylthebainone (VII, R′ = Me), mp 186°, identical in melting point, mixture melting point, and infrared absorption with the base obtained by the methylation of the phenol VII (R^1 = H).

Action of Boron Tribromide on the Ketone I. 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (5 g) in methylene chloride (30 ml) was treated with boron tribromide (3.2 g) at 5° for 1 hr. Aqueous ammonium chloride containing ammonia was added to the solution, and the organic layer was separated, dried, and evaporated, when 18-acetyl-5,14-ethanothebainone, mp 199–200°, alone or mixed with an authentic specimen was obtained.

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