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 $C_{25}H_{31}NO_3$: 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.

**Acknowledgments.** The authors wish to thank Dr. D. E. Webster of the University of Hull, England, for the determination of nmr spectra, Mr. A. C. Young for chromatographic separations, and the following for experimental assistance: Mr. J. Fulstow, Mr. T. J. Johnson, Mr. G. Mellows, Mr. T. M. Sutton, and the late Mr. S. R. Duff.

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

**K. W. Bentley,[2a] D. G. Hardy,[2a] C. F. Howell,[2b] W. Fulmor,[2b] J. E. Lancaster,[2c] J. J. Brown,[2b] G. O. Morton,[2b] and R. A. Hardy, Jr.[2b]**

*Contribution from the Research Laboratories, Reckitt and Sons Ltd., Kingston-upon-Hull, England, and The Organic Chemical Research Section, Lederle Laboratories, Division of American Cyanamid Co., Pearl River, New York.*
*Received September 26, 1966*

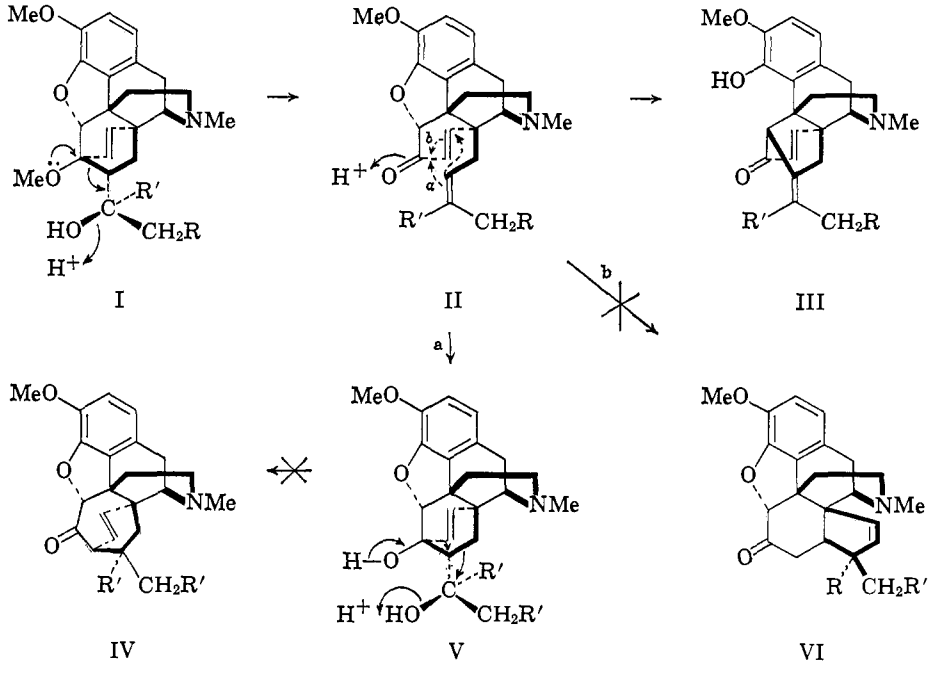
**Abstract:** The acid-catalyzed rearrangement of alcohols of the 6,14-*endo*-ethenotetrahydrothebaine series of general structure I has been shown to proceed in most cases *via* the 14-alkenylcodeinones (II) to 7,8-dihydrocyclohex-4′-eno- and -cyclohex-5′-eno[1′,2′:8,14]codeinones of general structures 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).

(2) (a) Reckitt and Sons Ltd., Kingston-upon-Hull, England. (b) Lederle Laboratories, Pearl River, N. Y. (c) Central Research Laboratories, American Cyanamid Co., Stamford, Conn.

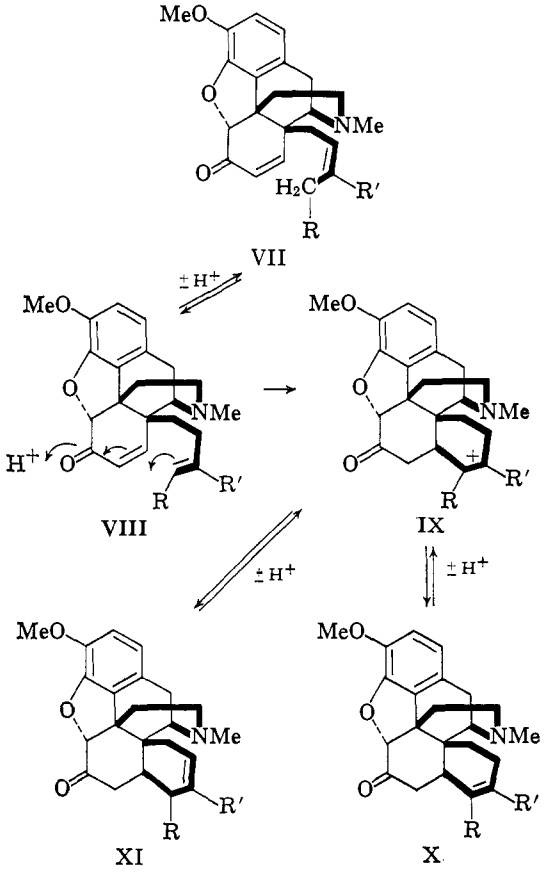



jugated ketone IV by the successive 1,2 shifts shown in formula V is also a plausible process, several variants of which can be envisaged.

The nmr spectra of three of these ketones, obtained by the acid-catalyzed rearrangement of the tertiary alcohols I (R = H, R′ = Ph; R′ = Me, R = Me; and R′ = Me, R = *i*-Bu), however, showed no evidence of the presence in these three bases of the system CH=CH, signals due to which are clearly observed in the spectra of the parent alcohols I and the alkenylcodeinone II (R = H, R′ = Ph). Indeed only in the spectrum of the first of these ketones (from the alcohol I, R = H, R′ = Ph) is the presence of even a single olefinic proton indicated. Further the spectrum of the first of these ketones shows no signal attributable to a C-methyl group, and the spectrum of the second ketone (from the alcohol I, R′ = Me, R = Me) shows C-methyl signals only at δ 1.53 and 1.61, which evidently arise from groups in the system $C{=}CCH_3$. The spectrum of the third ketone (from the alcohol I, R′ = Me, R = *i*-Bu) also shows a three-proton singlet at δ 1.62 ($C{=}CCH_3$) as well as a complex signal centered at δ 0.81, attributed to the system $CHMe_2$.

The spectra of all three ketones show signals attributable to two aromatic protons at C-1 and C-2, at about δ 6.68, and in addition the first of the three shows a five-proton complex signal at about δ 7.33 clearly due to the phenyl group. All three ketones show a one-proton singlet at δ 4.5–4.55, which is attributed to the proton at C-5 at the end of the cyclic ether bridge.

These spectra rule out of consideration the structures IV and VI for the three above-mentioned ketones, but do lead to the assignment of plausible structures to these and analogous compounds on the basis of a rational reaction mechanism for the acid-catalyzed rearrangements. The 14-alkenylcodeinone (II), which may be redrawn as VII, may very reasonably be expected to be in prototropic equilibrium in acid solution with the isomeric alkenylcodeinone VIII, which can then suffer protonation of the enone system and Markovnikov addition of the resulting carbonium ion to the double bond in the side chain to give the carbonium ion IX, which can lose a proton in either of two ways to give the ketones X and XI. The examination of models suggests that a similar cyclization of the codeinone VII to give IV, in addition to requiring anti-Markovnikov addition to the double bond, is inhibited by the impossibility of arranging the double bond in a position relative to the enone system suitable for cyclization. The examination of models of the isomeric system VIII, however, shows that in this the double bond in the side chain can readily be positioned over C-8 in precisely the geometry required for per-



pendicular attack of the enone system in the manner favored for Michael addition[3] and the conjugated addition of Grignard reagents.[4] Such a process would result in the formation from the alcohol I (R′ = Me, R = Me) of the ketone X (R = R′ = Me) which contains the system $CH_3C{=}CCH_3$ and no olefinic proton, and from the alcohol I (R′ = Me, R = *i*-Bu) of the ketone X (R′ = Me, R = *i*-Bu). In these cases hyperconjugation effects may be presumed to favor the formation of the olefin X rather than the isomeric olefin XI.

The application of this reaction mechanism to the rearrangement of the alcohol I (R = H, R′ = Ph) would lead through the codeinones VII (R = H, R′ = Ph) and VIII (R = H, R′ = Ph) to the ketones X (R = H, R′ = Ph) or XI (R = H, R′ = Ph) or both. Both of these ketones are formulated with styrenoid chromophores, and indeed the product of the rearrangement does show styrenoid ultraviolet absorption. This rearrangement product has been separated into two isomeric ketones, the infrared and ultraviolet spectra of which are closely similar, and these can be formulated as the two isomers X (R = H, R′ = Ph) and XI (R = H, R′ = Ph). The nmr spectra of both isomers showed complex patterns for one olefinic proton, which made a distinction between structures X and XI very difficult without additional information. The identification of one isomer was possible, however, using spin-decoupling techniques. The spectrum of one of these ketones (mp 161–163°) (Figure 1) showed an olefinic proton as a multiplet (1 H) at about δ 6.1. Irradiation at about δ 2.1 collapsed this δ 6.1 multiplet into a doublet ($J \cong 7$ cps), indicating further coupling with another proton. That this proton is one absorbing at about δ 3.8 was shown by irradiation at this point, when the olefinic proton signal then appeared as a broad single peak. The proton pattern at δ 3.8 is a quartet, which collapsed to a doublet ($J = 18$ cps) when the olefinic proton was irradiated. The proton absorbing at δ 3.8 was also coupled with the one absorbing at about δ 2.1 ($J = 18$ cps), as shown by irradiation at about δ 2.1. The $J = 18$ cps can only be a *gem*-coupling constant. The proton giving the quartet at δ 3.8 must, therefore, be one-half of a methylene group adjacent to an olefinic proton.

Since the double bond is presumably the one present in the styrenoid system this ketone evidently contains the system $CH_2CH{=}CPh$, which is that present in the base XI (R = H, R′ = Ph). The downfield shift of one of the methylene protons in this system to δ 3.8 is regarded as resulting from this proton being both allylic and near the unshared pair of electrons on the nitrogen atom[5,6] as it is in a model of the ketone XI (R = H, R′ = Ph). The other proton in this methylene group resonates at δ 2.17. Such large differences between halves of a methylene group are unusual, but not unprecedented.[7]

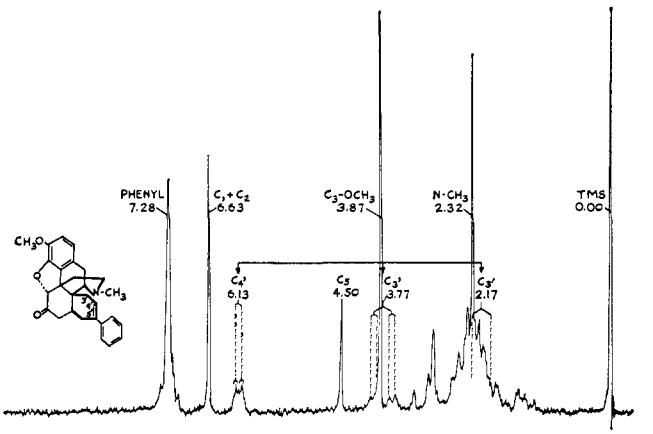
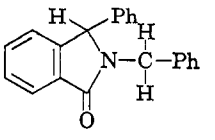



Figure 1. Nmr spectrum of 7,8-dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeinone (XI, R = H, R′ = Ph). Arrows show spin system established by decoupling experiments.

It is clear, therefore, that the nmr spectrum of this ketone (mp 161–163°) is entirely consistent with the structure XI (R = H, R′ = Ph). The isomeric ketone (mp 212–214°), which is the minor product of the acid-catalyzed rearrangement of the alcohol I (R = H, R′ = Ph), gave an nmr spectrum substantially similar to that of the ketone (mp 161–163°). In this case, however, the complex olefinic proton signal at about δ 6.0 collapsed and appeared as a single peak, still showing residual coupling, on irradiation at about δ 2.4, thus establishing that the olefinic proton is coupled to a proton or protons absorbing at the latter point. Owing to the coincidence of other resonances in the δ 2.4 region, however, it was not possible to observe clear-cut changes in the spin–spin decoupling studies. Since this ketone is styrenoid and isomeric with one whose spectrum is consistent with the structure XI (R = H, R′ = Ph) it may with confidence be assigned the structure X (R = H, R′ = Ph). If these structural assignments are correct the two ketones represent the products of alternative modes of the loss of a proton from the carbonium ion IX (R = H, R′ = Ph), through which they may be equilibrated in acid solution. This equilibration has been independently achieved, for each of the two pure ketones on treatment with *p*-toluenesulfonic acid in glacial acetic acid[8] is converted into a mixture of approximately 80% of the ketone XI (R = H, R′ = Ph) and 20% of the isomer X (R = H, R′ = Ph), which is the composition of the crude product obtained in the rearrangement of the alcohol I (R = H, R′ = Ph).

Although the spectra of the ketones discussed above are compatible with one or other of the structures X or XI for these bases, they do not provide any definitive information pertaining to the structure of the carbonyl-containing ring C, and, accordingly, chemical transformations have been carried out on two of these bases



i

(3) E. L. Eliel, N. A. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 314–317.

(4) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

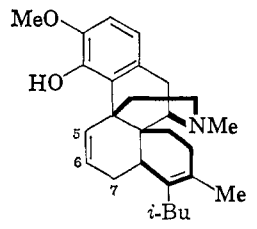
(5) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).

(6) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *ibid.*, **12**, 104 (1964).

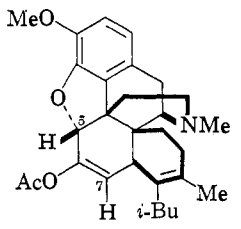
(7) For example, one of the benzylic methylene protons, shielded by the phenyl moiety in i, appears at δ 3.67 while the other methylene proton, deshielded by the carbonyl group, resonates at δ 5.42: A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Letters*, 1241 (1965).

(8) These conditions have been used for the equilibration of *cis*- and *trans*-2-phenyl-2-butene: D. J. Cram and M. V. R. Sahyun, *J. Am. Chem. Soc.*, **85**, 1257 (1963).

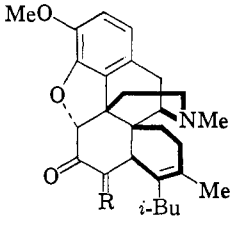
to characterise this portion of the molecule. That the ketones still contain the 4,5-oxygen bridge intact may be inferred from their nonphenolic nature, and from the presence in their nmr spectra of the sharp singlet at about $\delta$ 4.5 attributed to the C-5 proton. The presence of the oxygen bridge and the relationship of this to the carbonyl group in the ketones are demonstrated by the behavior of two of the ketones on Huang-Minlon reduction. The reduction of derivatives of dihydrocodeinone by this process occurs with great ease, and involves fission of the 4,5-oxygen bridge and the production of derivatives of the phenolic dihydrodeoxycodeines B and C.[9] The hydrazones of the ketones XI (R = H, R′ = Ph) and X (R = *i*-Bu, R′ = Me) lose nitrogen at about 120° in alkaline solution and give phenolic products, which give positive tests with Gibb's reagent (dichloroquinone chlorimine) and with diazotized sulfanilic acid. The major product of reduction of the base X (R = *i*-Bu, R′ = Me) shows nmr signals as doublets at $\delta$ 6.3 and 5.5 (CH=CH, $J_{A,B}$ = 9 cps) and a singlet at $\delta$ 5.87 shifted to $\delta$ 7.95 in dimethyl sulfoxide, attributed to the phenolic hydroxyl proton. On mechanistic grounds this major product of the reaction is assigned the formula XII and the minor product may be the analogous derivative of dihydrodeoxycodeine-C with a 6,7-double bond. This reaction can only be represented by a satisfactory mechanism if the carbonyl group in the ketones is located at C-6.




XII




XIII




XIV

The ketones X (R = *i*-Bu, R′ = Me) and XI (R = H, R′ = Ph) are converted into enol acetates on heating with acetic anhydride and sodium acetate, and the enol esters are readily hydrolyzed to the parent ketones by hot hydrochloric acid. The examination of models shows that if the carbonyl group is contained in a five-, six-, or seven-membered ring enolization cannot involve the hydrogen atom at C-5 since the introduction of a 5,6 double bond would impose an unacceptable degree of strain on the oxygen-containing ring. Enolisation must, therefore, involve C-7, and the nmr spectrum of the enol acetate XIII supports the assigned structure, showing signals (in $\delta$ units) at 6.7 (two aromatic H), 5.38 doublet (C-7, $J_{7,5}$ = 2 cps), 4.91 doublet (C-5 H, $J_{5,7}$ = 2 cps), 3.88 (aromatic $OCH_3$), 2.33 ($NCH_3$), 2.16 ($COCH_3$), 1.62 ($C{=}CCH_3$), and a complex six-proton peak at 0.82 ($CHMe_2$). C-Methylation of the ketone X (R = *i*-Bu, R′ = Me) can be accomplished with potassium *t*-butoxide and methyl iodide, and the nmr spectrum of the product XIV (R = $Me_2$) is very similar to that of the starting material except in the region $\delta$ 0.6–1.2 in which signals are found integrating for a total of 12 protons, indicating that two new methyl groups have been introduced at C-7. The dimethylated ketone, which bears no enolizable hydrogen atom, is recovered unchanged after heating with sodium acetate and acetic anhydride. These reactions clearly show that the parent ketones contain the system $OCHCOCH_2$ as in formulas X and XI.

The presence of this system in the ketone X (R = *i*-Bu, R′ = Me) was confirmed by the conversion of the base into an $\alpha$-oximino ketone XIV (R = NOH) by the action of sodium ethoxide and amyl nitrite. The base obtained in this way was soluble in alkalis and was precipitated from the solution by ammonium chloride or carbon dioxide. It also gave an insoluble stable copper chelate with methanolic cupric acetate, which was soluble in dilute acids and reprecipitated unchanged by ammonia. The $\alpha$-oximino ketone was hydrolyzed by hot dilute sulfuric acid to a yellow $\alpha$-diketone XIV (R = O), which gave a dark brown cupric complex and with ferric chloride gave a deep wine red solution that became intensely blue-green on the addition of a trace of ammonia. From this it may be concluded that the diketone is enolizable, and hence must contain the system OCHCOCOCH, which means that the original ketone X (R = *i*-Bu, R′ = Me) must contain the system $OCHCOCH_2CH$. Further evidence for the presence of this system in the same ketone was obtained from the action on it of bromine and potassium carbonate in methanol, in an attempt to prepare the diketone XIV (R = O) by the method used in the dihydrocodeinone and sinomenine series.[10] The reaction afforded a mixture of products from which a small quantity of an $\alpha,\beta$-unsaturated ketone was isolated. Presumably this is formed from the $\alpha$-bromo ketone by the loss of hydrogen bromide.

The chemical evidence given above indicates the nature of most of ring C in the rearranged bases, and, if the reasonable assumption is made that the dihydrocodeinone ring system remains intact, the complete structures of these bases must be made up by the addition of a new ring, which can only be added at positions 8 and 14. This new ring can only be five or six membered and must contain a double bond to satisfy the compositions of the bases, and the nmr spectra of the bases examined are only compatible with the arrangement of this ring as shown in formulas X and XI. The complete structures based on these general formulas can, therefore, be confidently assigned to the rearranged bases.

The position of the double bond in the end products of the rearrangement is determined by the nature of the substituents in the unsaturated ring. The major product of the rearrangement of the alcohol I (R = H, R′ = Ph) is the ketone XI (R = H, R′ = Ph), though some of the isomeric ketone X (R = H, R′ = Ph) is also formed. The cyclohexenocodeinone obtained in the rearrangement of the alcohol I (R = H, R′ = Me) has also been identified as the $\Delta^{4'}$ ketone XI (R = H, R′ = Me) [nmr signals (in $\delta$ units) at 6.64

(9) T. D. Perrine and L. F. Small, *J. Org. Chem.*, 17, 1540 (1952).

(10) C. Schopf, T. Pfeiffer, and H. Hirsch, *Ann.*, 492, 213 (1932).

(C-1 and C-2 H), 5.38 (C-4′ H; multiplet, $J_{3,4}$ = *ca.* 5.5 cps, 1 H), 4.50 (C-5 H; singlet, 1 H), 3.88 (C-3 $OCH_3$), *ca.* 3.45 (C-3′ H; diffuse double doublet, $J_{3',3'}$ = *ca.* 16.5 cps, $J_{3',4'}$ = *ca.* 5.5 cps), 2.33 ($NCH_3$), 1.65 (C-5′ $CH_3$; singlet, 3 H)]. The base obtained by the rearrangement of the alcohol I (R = Me, R′ = Ph) also belongs to the $\Delta^{4'}$ series, having the structure XI (R = Me, R′ = Ph) and showing nmr signals (in $\delta$ units) at 7.35 (5 aromatic H), 6.72 (C-1 and C-2 H), 5.95 (diffuse multiplet, 1 olefinic H), 4.55 (C-5 H, singlet, 1 H), 3.95 (C-3 $OCH_3$), 2.41 ($NCH_3$), and 1.1 ($CHCH_3$; doublet, $J$ = *ca.* 10 cps, 3 H). By contrast, the rearranged bases bearing alkyl substituents at C-5′ and C-6′ give nmr spectra showing no signal for olefinic hydrogen, and must belong to the $\Delta^{5'}$ series X.

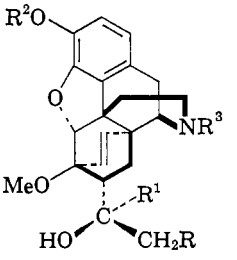
Hyperconjugation effects may be expected to favor the $\Delta^{5'}$ form over the $\Delta^{4'}$ form when alkyl groups are present at C-5′ and C-6′, and similar effects would be expected to favor the olefin VIII (R = R′ = alkyl) over VII (R = R′ = alkyl) at equilibrium in acid solution. Such effects would not, however, greatly favor the production of the olefin VIII (R = H, R′ = Me) from the codeinone VII (R = H, R′ = Me), and a considerable amount of the latter would be expected to be present at equilibrium in acid solution. As this latter base can rearrange irreversibly to the flavonepenthone analog III (R = H, R′ = Me), a considerable quantity of the phenol is obtained in the rearrangement, which gives almost equal amounts of the phenol III (R = H, R′ = Me) and the ketone XI (R = H, R′ = Me). Since some of the phenol III is obtained in all of the acid-catalyzed rearrangements, the processes II → III and VIII → IX may be assumed to have similar rates, the composition of the initial rearrangement product being determined by the position of the equilibrium VII ⇄ VIII. Clearly, bases such as II ($CH_2R$ = H, R′ = Ph and also $CH_2R$ = R′ = Ph) which cannot be isomerized to olefins of structure VIII give only bases belonging to series III on rearrangement.

Although the olefin VIII is a necessary intermediate in the rearrangement of the alkenylcodeinone VII to the cyclized bases X and XI, no such olefin has been isolated from solutions of the bases VII (R = H, R′ = Ph) and VII (R = H, R′ = Me) in hydrochloric acid, presumably owing to the speed with which cyclization to the carbonium ion IX occurs.

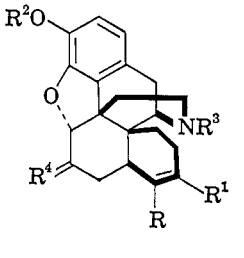
The cyclohexenodihydrocodeinones of general structures X and XI, being stable end products of acid-catalyzed reactions, are readily demethylated without further change on heating with 48% hydrobromic acid to give the corresponding derivatives of dihydromorphinone. These bases are also preparable by the rearrangement of the corresponding phenolic alcohols in the 6,14-*endo*-ethenotetrahydrooripavine series,[11] or by the combined rearrangement and demethylation of the alcohols in the 3-methoxy series I with 48% hydrobromic acid.

Bases in this series, bearing substituents other than a methyl group on the nitrogen atom, have been prepared by the rearrangement of the corresponding alcohols. In general, the acid-catalyzed rearrangement can be effected at any stage in the sequence of compounds represented by XV in which $R^3$ = Me, CN, H, or other substituent. The rearrangement of the N-cyano compounds XV ($R^3$ = CN) can be accomplished without hydrolysis of the NCN group in cold concentrated hydrochloric acid, the hydrolysis to the secondary base being subsequently accomplished in alkaline solution, since acid-catalyzed hydrolysis is generally slow and incomplete. Secondary bases in the cyclohexenodihydrocodeinone series are also preparable from the corresponding N-methyl compounds by treatment with methyl azodicarboxylate followed by acid hydrolysis, and by the combined hydrolysis and rearrangement of the N,N′-methylenebis alcohols (described in paper III of this series[11]) by heating with concentrated hydrochloric acid, though this last is not a preferred process.

Reduction of the C-6 carbonyl group in these derivatives of dihydrocodeinone and dihydromorphinone is readily effected with sodium borohydride. By one or other of the processes set out above, the bases of general structure XVI listed in Table I have been prepared. In all cases rearrangement of the alcohols of



XV

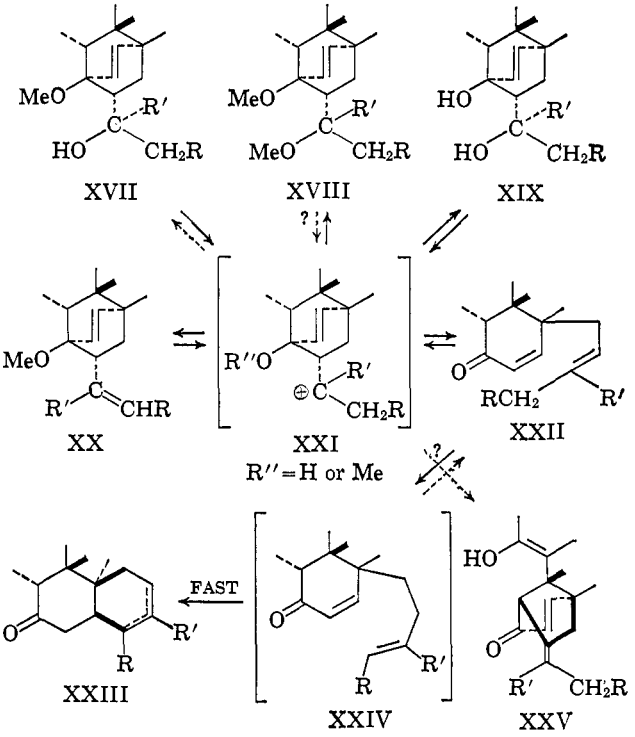


XVI

general structure XV results in a marked decrease in analgesic or morphine antagonizing potency. In general, however, the bases do still produce effects on the central nervous system, and the results of pharmacological appraisal will be published elsewhere.

The diversity of acid-catalyzed rearrangement products obtained from the *t*-carbinols I, as described in this series of papers, and their apparent interrelationships are summarized in Scheme I (partial structures).

**Scheme I**




(11) Part III: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, 89, 3281 (1967).

**Table I.** Bases of Structure XVI

| $R^2$ | $R^3$ | $R^1$ | R | $R^4$ | Mp, °C | Composition | Calcd, % C | Calcd, % H | Found, % C | Found, % H | Mp, °C, HCl |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Me[a] | Me | Me | H | =C | 112–114 | $C_{23}H_{27}NO_3$ | 75.6 | 7.45 | 76.0 | 7.4 | |
| Me[a] | Me | Ph | H | =O | 161–163 | $C_{28}H_{29}NO_3$ | 78.6 | 6.8 | 78.4 | 6.8 | |
| Me | Me | Ph | H | =O | 212–214 | $C_{28}H_{29}NO_3$ | 78.6 | 6.8 | 78.6 | 6.8 | |
| Me[a] | Me | Ph | H | <H, OH | 191 | $C_{28}H_{31}NO_3$ | 78.4 | 7.3 | 78.1 | 7.4 | |
| H[a] | Me | Ph | H | =O | 235 | $C_{27}H_{27}NO_3 \cdot H_2O$ | 75.3 | 6.7 | 75.5 | 6.8 | 276–278 |
| Me | Me | Me | Me | =O | 199 | $C_{24}H_{29}NO_3$ | 72.2 | 8.3 | 76.1 | 7.9 | 284 |
| Me | Me | Me | Me | <H, OH | 143 | $C_{24}H_{31}NO_3 \cdot H_2O$ | 72.2 | 8.3 | 72.0 | 8.4 | |
| Me | CN | Me | Me | =O | 265–272 | $C_{24}H_{26}N_2O_3$ | 73.8 | 6.7 | 73.4 | 6.7 | |
| Me | $CH_2$-*c*-$C_3H_5$ | Me | Me | =O | 137–140 | $C_{27}H_{33}NO_3$ | 77.3 | 8.0 | 77.7 | 8.0 | |
| Me | Me | Me | Et | =O | 229–230 | $C_{25}H_{31}NO_3$ | 76.4 | 8.0 | 76.3 | 8.0 | 282 |
| Me | Me | Me | Et | <H, OH | 166 | $C_{25}H_{33}NO_3$ | 76.1 | 8.4 | 75.7 | 8.4 | |
| Me | CN | Me | Et | =O | 277–279 | $C_{25}H_{28}N_2O_3$ | 74.2 | 7.0 | 74.8 | 7.0 | |
| Me | H | Me | Et | =O | 210–215 | $C_{24}H_{29}NO_3$ | 76.0 | 7.7 | 76.5 | 7.8 | |
| Me | $CH_2CH{=}CH_2$ | Me | Et | =O | 131–133 | $C_{27}H_{33}NO_3$ | 77.3 | 7.9 | 77.3 | 8.0 | |
| Me | $CH_2CH{=}CH_2$ | Me | Et | <H, OH | 45 | $C_{27}H_{35}NO_3$ | 76.9 | 8.4 | 76.5 | 8.4 | |
| Me | $CH_2CMe{=}CH_2$ | Me | Et | =O | 126–129 | $C_{28}H_{25}NO_3$ | 77.6 | 8.1 | 77.6 | 8.1 | |
| Me | $CH_2CH{=}CMe_2$ | Me | Et | =O | 109–113 | $C_{29}H_{37}NO_3$ | 77.8 | 8.3 | 77.7 | 8.4 | |
| Me | *n*-Bu | Me | Et | =O | 123–124 | $C_{28}H_{37}NO_3$ | 77.2 | 8.6 | 77.2 | 8.6 | |
| Me | *n*-Hexyl | Me | Et | =O | 129–131 | $C_{30}H_{41}NO_3$ | 77.7 | 8.9 | 77.5 | 9.0 | |
| Me | *n*-Octyl | Me | Et | =O | 103–104 | $C_{32}H_{45}NO_3$ | 78.2 | 9.2 | 78.3 | 9.3 | |
| Me | $CH_2$-*c*-$C_4H_7$ | Me | Et | =O | 146–147 | $C_{29}H_{37}NO_3$ | 77.8 | 8.3 | 77.5 | 8.1 | |
| H | Me | Me | Et | =O | 110–111 | $C_{24}H_{29}NO_3 \cdot H_2O$ | 72.6 | 8.3 | 73.0 | 8.0 | |
| H | Me | Me | Et | <H, OH | 78 | $C_{24}H_{31}NO_3$ | 75.5 | 8.2 | 74.8 | 8.3 | |
| H | $CH_2$-*c*-$C_3H_5$ | Me | Et | =O | | $C_{27}H_{33}NO_3 \cdot HCl \cdot H_2O$ | 68.4 | 7.6 | 68.4 | 7.4 | 185–187 |
| Me | Me | Me | *n*-Pr | =O | 144 | $C_{26}H_{33}NO_3$ | 76.8 | 8.5 | 76.5 | 8.2 | 260 |
| Me | CN | Me | *n*-Pr | =O | 218–219 | $C_{26}H_{30}N_2O_3$ | 74.6 | 7.2 | 73.9 | 7.1 | |
| Me | Et | Me | *n*-Pr | =O | 50 | $C_{27}H_{35}NO_3$ | 76.9 | 8.4 | 76.8 | 8.5 | 142–145 |
| Me | *n*-Pr | Me | *n*-Pr | =O | 50 | $C_{28}H_{37}NO_3$ | 77.2 | 8.6 | 77.3 | 8.6 | 140–144 |
| Me | $CH_2CH{=}CH_2$ | Me | *n*-Pr | =O | ... | $C_{29}H_{37}NO_3$ | 77.8 | 8.3 | 78.3 | 8.4 | 140–144 |
| H | Me | Me | *n*-Pr | =O | 114–115 | $C_{25}H_{31}NO_3 \cdot H_2O$ | 72.9 | 8.0 | 72.4 | 8.0 | 248–250 |
| Me | Me | Me | *i*-Pr | =O | 80 | $C_{26}H_{33}NO_3 \cdot HCl$ | 70.2 | 7.8 | 70.4 | 7.7 | 289 |
| Me | $CH_2CH{=}CH_2$ | Me | *i*-Pr | =O | ... | $C_{28}H_{35}NO_3 \cdot HCl$ | 71.5 | 7.7 | 71.4 | 7.5 | 260 |
| Me | Me | Me | *n*-Bu | =O | 68 | $C_{27}H_{35}NO_3 \cdot HCl$ | 70.7 | 7.9 | 70.5 | 7.7 | 306 |
| Me | CN | Me | *n*-Bu | =O | 202–205 | $C_{27}H_{32}N_2O_3$ | 75.0 | 7.5 | 74.9 | 7.4 | |
| Me | Me | Me | *i*-Bu | =O | 195 | $C_{27}H_{35}NO_3$ | 76.7 | 8.2 | 76.5 | 8.3 | 254 |
| Me | Me | Me | *i*-Bu | <H, OH | 184 | $C_{27}H_{37}NO_3$ | 76.3 | 8.7 | 76.5 | 8.9 | |
| Me | CN | Me | *i*-Bu | =O | 223–225 | $C_{27}H_{32}N_2O_3$ | 75.0 | 7.5 | 75.0 | 7.5 | |
| Me | Et | Me | *i*-Bu | =O | 65 | $C_{28}H_{37}NO_3$ | 77.2 | 8.5 | 76.6 | 8.6 | |
| Me | $CH_2CH{=}CH_2$ | Me | *i*-Bu | =O | | $C_{29}H_{37}NO_3$ | 77.8 | 8.3 | 78.3 | 8.4 | 140–144 |
| H | Me | Me | *i*-Bu | =O | 128–129 | $C_{26}H_{33}NO_3 \cdot H_2O$ | 73.5 | 8.2 | 73.3 | 8.4 | 265–267 |
| H | $CH_2$-*c*-$C_3H_5$ | Me | *i*-Bu | =O | 263–265 | $C_{29}H_{37}NO_3$ | 77.8 | 8.3 | 77.6 | 8.4 | 289–290 |
| Me | Me | Me | *n*-Am | =O | 104 | $C_{28}H_{37}NO_3$ | 77.2 | 8.5 | 76.7 | 8.5 | 248 |
| Me | Me | Me | $CH_2Ph$ | =O | 80 | $C_{30}H_{33}NO_3 \cdot HCl \cdot 2H_2O$ | 68.2 | 7.2 | 67.9 | 7.0 | 315 |
| Me[a] | Me | Ph | Me | =O | 224–226 | $C_{29}H_{31}NO_3$ | 78.8 | 7.0 | 78.6 | 6.9 | |
| Me | Me | Et | Me | =O | 198 | $C_{25}H_{31}NO_3$ | 76.4 | 8.0 | 76.2 | 8.1 | |

[a] $\Delta^{4'}$ isomer.

Established reactions are indicated by solid arrows, and hypothetical reactions (which appear to be allowable by rational mechanistic considerations) are shown by dotted arrows.

The distribution of products formed depends on the reaction conditions (*i.e.*, the strength and concentration of acid and time of heating) and the substituents R and R′. For example, the transformations described in the upper two-thirds of Scheme I (XVII–XXII) are generally achieved with dilute hydrochloric acid at 25 to 50°, with 99% formic acid at 100°, or with perchloric acid in trimethyl orthoformate, methanol, and methylene chloride at 25°. Transformations of bases of structure XXII into those of structures XXIII and XXV, however, have required 6–12 *N* hydrochloric acid at 100°. The influence of substituents on the distribution of final products is illustrated by the conversion of the base XVII (R′ = Ph, R = H) into a mixture containing 95% of the base XXIII (R′ = Ph, R = H; as the isomeric olefins) and 5% of the phenol XXV (R′ = Ph, R = H), while treatment of the base XVII (R′ = Me, R = H) under similar conditions gave 35% of the phenol XXV (R′ = Me, R = H) and 36% of the ketone XXIII (isolated yields). Nepenthene (XII, R′ = Ph, $RCH_2$ = H) is, of course, incapable of isomerism to an olefin of structure XXIV and, therefore, yields flavonepenthone (XXV, R′ = Ph, $RCH_2$ = H). The observed recyclization reactions of the 14-alkenyl derivative XXII or XXIV (XXII → XXI → XIX, XXII → XXV, XXIV → XXIII) represent Markovnikov additions of an electrophilic center at C-5, C-6, or C-8 to the double bond, producing a five- or six-membered

ring. Products formed by anti-Markovnikov additions of these electrophilic centers or by Markovnikov additions to form four- or seven-membered rings have not been found. Similarly, products formed by 1,2 migration of the 7,8 or 6,7 bonds or by 1,3 migration of the 6,18 bond to the *t*-carbonium ion C-19 in XXI have not been observed.

## Experimental Section

**Rearrangement of 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (19-Phenylthevinol, I, R′ = Me, $CH_2R$ = Ph).** 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-phenyl-1-ethyl)tetrahydrothebaine (5 g) was heated with concentrated hydrochloric acid (100 ml) and ethanol (15 ml) on the steam bath for 30 min during which time a sparingly soluble salt separated. This was collected, washed with cold water, and dissolved in hot 50% aqueous ethanol. The resulting solution was basified with ammonia, and the precipitated solid was collected and recrystallized from ethanol, when it was obtained as almost colorless plates, mp 149–151°, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{28}H_{29}NO_3$: C, 78.6; H, 6.8. Found: C, 78.6; H, 7.8.

The same material was obtained when 6,14-*endo*-etheno-7α-(1-(*S*)-hydroxy-1-phenylethyl)tetrahydrothebaine or 14-(3-phenylbut-2-enyl)codeinone (II, R = Me, R′ = Ph) was rearranged in the same way with hot concentrated hydrochloric acid. Thin layer chromatographic studies showed this base to be a mixture of three components.

The base (0.363 g) was chromatographed on a column of Merck acid-washed alumina (60 g) and the chromatogram was developed with 200 ml of 1% ethyl acetate in benzene. Elution of the column with 2% (200 ml) and 5% (600 ml) ethyl acetate in benzene gave 29 20-ml fractions, each of which was examined by thin layer chromatography on alumina. Similar fractions were combined and concentrated. The first component eluted from the column (0.023 g) was 14-(3-phenylbut-2-enyl)codeinone (II, R = Me, R′ = Ph) identical in infrared absorption and behavior on thin layer plates with an authentic specimen. The second component (0.204 g) was 7,8-dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeinone (XI, R = H, R′ = Ph), mp 161–163° after two recrystallizations from methanol, $\nu_{max}$ 1730 $cm^{-1}$, $\lambda_{max}$ 241 mμ ($\lambda_{max}$ 248 mμ ($\epsilon_{max}$ 13,400) after subtraction of the benzenoid absorption of the base I, R = H, R′ = Me).

*Anal.* Calcd for $C_{28}H_{29}NO_3$: C, 78.6; H, 6.8. Found: C, 78.3; H, 6.8.

The third component (0.020 g) was 7,8-dihydro-5′-phenylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = H, R′ = Ph), mp 208–210°, raised to 212–214° when separated from a small amount of the $\Delta^{4'}$ isomer on five 0.3-mm thick 20 × 20 cm alumina plates, $\nu_{max}$ 1730 $cm^{-1}$, $\lambda_{max}$ 241 mμ ($\lambda_{max}$ 252 mμ ($\epsilon_{max}$ 12,200) after subtraction of the benzenoid absorption of the base I, R = H, R′ = Me).

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

**Equilibration of the Isomeric Olefins X (R = H, R′ = Ph) and XI (R = H, R′ = Ph).** Solutions containing 2.5 mg each of 7,8-dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeinone (XI, R = H, R′ = Ph) and 7,8-dihydro-5′-phenylcyclohex-5′-eno[1′,2′:-8,14]codeinone (X, R = H, R′ = Ph) (the latter containing 16% of the $\Delta^{4'}$ isomer) in 0.10 ml of benzene were prepared. Each solution, after the withdrawal of 0.02 ml for standardization, was treated with 0.47 ml of 0.1 *M* *p*-toluenesulfonic acid in glacial acetic acid to make the solutions about 0.01 *M* in olefin and 0.09 *M* in toluenesulfonic acid. These solutions were heated at 95–100° and, after designated intervals, 0.14-ml aliquots were removed and added to a mixture of 0.2 ml of concentrated ammonium hydroxide and four drops of benzene. These mixtures were agitated and centrifuged, and the benzene layer was spotted along the bottom edge of a 5 × 20 cm silica gel G plate and developed with 2% triethylamine in benzene (occasionally redeveloped several times to obtain a satisfactory separation). The separated isomers were located with the aid of an ultraviolet lamp (250 mμ) and the respective zones were removed from the plates, extracted with methanol, and diluted to a known volume (5.0 to 25.0 ml, according to the size of the sample). The absorbances at 250 mμ were then measured for each solution, and the percentage composition of each aliquot removed from the reaction mixture was then calculated using the known $\epsilon_{250m\mu}^{MeOH}$ for the pure isomers. The results obtained are set out in Table II.

**Table II**

| Time, hr | % Composition of mixture A | | % Composition of mixture B | |
|---|---|---|---|---|
| | X | XI | X | XI |
| 0 | 0 | 100 | 84 | 16 |
| 1 | 8 | 92 | 63 | 37 |
| 2 | 12 | 88 | 42 | 58 |
| 20 | 18 | 82 | 19 | 81 |

**7,8-Dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeine (XI, R = H, R′ = Ph, CO = CHOH).** The mixture of isomers XI (R = H, R′ = Ph) and X (R = H, R′ = Ph) (5 g) obtained from the rearrangement of 6,14-*endo*-etheno-7α-(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (I, R′ = Me, $CH_2R$ = Ph) was reduced with sodium borohydride (0.5 g) in hot ethanol (200 ml). The resulting alcohol was precipitated from solution by the addition of water, collected (5 g), and recrystallized four times from ethanol, when it was obtained as white prisms, mp 191°, giving only one spot on thin layer chromatograms.

*Anal.* Calcd for $C_{28}H_{31}NO_3$: C, 78.4; H, 7.3. Found: C, 78.1; H, 7.4.

**7,8-Dihydro-6′-methyl-5′-phenylcyclohex-4′-eno[1′,2′:8,14]-codeinone (XI, R = Me, R′ = Ph).** 6,14-*endo*-Etheno-7α-(1-(*S*)-hydroxy-1-phenylpropyl)tetrahydrothebaine (I, R′ = Ph, R = Me) (2 g) was heated in the water bath for 1 hr with concentrated hydrochloric acid (50 ml). The mixture was diluted with water when a viscous hydrochloride separated. This was dissolved by the addition of ethanol, and the aqueous alcoholic solution was basified with ammonia. The precipitated noncrystalline base was collected, washed with water, and crystallized from 2-ethoxyethanol. On recrystallization from this solvent 7,8-dihydro-6′-methyl-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeinone was obtained as pale cream prisms, mp 224–226°, showing one spot only on thin layer chromatograms, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{29}H_{31}NO_3$: C, 78.8; H, 7.0. Found: C, 78.6; H, 6.9.

The same base was obtained by the rearrangement of 14-(3-phenylpent-2-enyl)codeinone (II, R = Me, R′ = Ph) in concentrated hydrochloric acid.

**7,8-Dihydro-5′-methylcyclohex-4′-eno[1,′2′:8,14]codeinone (XI, R = H, R′ = Me).** 6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (I, R = H, R′ = Me) (0.50 g) was heated in hydrochloric acid (2 ml, *d* 1.19) on the steam bath for 90 min, during which time crystals separated. Water (2 ml) was added, and the solid matter was collected, when 5,14-ethano-18-isopropylidenethebainone hydrochloride (III, R = H, R′ = Me) (0.175 g), mp 310–315°, was obtained (see part IV of this series).

The combined filtrate and washings from the collection of this hydrochloride were neutralized with aqueous sodium bicarbonate and the resulting base was isolated by extraction with methylene chloride. The glass remaining after removal of the solvent was dissolved in methylene chloride and chromatographed on alumina (Woelm, activity II, 20 g). Continued elution of the column with methylene chloride afforded material that was crystallized from *n*-hexane, when 7,8-dihydro-5-methylcyclohex-4′-eno[1′,2′:8,14]-codeinone (165 mg) was obtained as prisms, mp 112–114°, $\nu_{max}$ 1725 $cm^{-1}$.

*Anal.* Calcd for $C_{23}H_{27}NO_3$: C, 75.6; H, 7.45. Found: C, 76.0; H, 7.4.

**7,8-Dihydro-5,′6′-dimethylcyclohex-5′-eno[1,′2′:8,14]codeinone (X, R = R′ = Me).** 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-methylpropyl)tetrahydrothebaine (I, R′ = Me, R = Me) (5 g) was heated on the steam bath for 1 hr with concentrated hydrochloric acid (25 ml). The mixture was diluted with aqueous ethanol and made alkaline with ammonia. The resulting base was collected and recrystallized from ethanol, when it was obtained as white prisms, mp 199°, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.6. Found: C, 76.1; H, 7.9.

The same base was obtained by the rearrangement of 6,14-*endo*-etheno-7α-(1-(*S*)-hydroxy-1-methylpropyl)tetrahydrothebaine (I, R′ = Et, R = H) in the same way.

**7,8-Dihydro-5′-ethyl-6′-methylcyclohex-5′-eno[1,′2′:8,14]codeinone (X, R = Me, R′ = Et).** This base was obtained as above by heating 6,14-*endo*-etheno-7α-(1-hydroxy-1-ethylpropyl)tetrahydrothebaine (1 g) with concentrated hydrochloric acid (5 ml) on the steam bath for 1 hr. It formed prisms, mp 198°, from ethanol, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{25}H_{31}NO_3$: C, 76.4; H, 8.0. Found: C, 76.2; H, 8.1.

**7,8-Dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = Et, R′ = Me).** The diastereoisomeric alcohols I (R = H, R′ = *n*-Pr and also R = Et, R′ = Me), on heating on the steam bath with concentrated hydrochloric acid for 1 hr, yielded the same base obtained as prisms, mp 229–230°, from ethanol, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{25}H_{31}NO_3$: C, 76.4; H, 8.0. Found: C, 76.3; H, 8.0.

**7,8-Dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]morphinone (XVI, $R^2$ = H, $R^1$ = $R^3$ = Me, R = Et, $R^4$ = O). a.** 7,8-Dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = Et, R′ = Me) (5 g) was boiled under reflux for 1 hr with concentrated hydrobromic acid (48%) (100 ml). The mixture was cooled and diluted with aqueous ethanol, and the base was precipitated from the solution with ammonia. After collection and recrystallization from aqueous 2-ethoxyethanol the phenol (3.1 g) was obtained as cream plates, mp 110°, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{24}H_{29}NO_3 \cdot H_2O$: C, 72.6; H, 8.3. Found: C, 73.0; H, 8.0.

**b.** 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)tetrahydrothebaine (I, R′ = Me, R = Et) (1 g) was boiled under reflux for 1 hr with concentrated (48%) hydrobromic acid (10 ml). The base was isolated as in a and was obtained as plates, mp 110°, identical in infrared absorption with material prepared by that process.

**c.** 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)tetrahydrooripavine (XV, $R^2$ = H, $R^1$ = $R^3$ = Me, R = Et) (1 g) was heated on the steam bath with concentrated hydrochloric acid (8 ml) for 1 hr. The dihydromorphinone was isolated as in a and was obtained as plates, mp 110°, identical in infrared absorption with material prepared as in a and b above.

**N-Cyano-7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (XVI, $R^1$ = $R^2$ = Me, $R^3$ = CN, R = Et, $R^4$ = O).** N-Cyano-6,14-*endo*-etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)tetrahydronorthebaine (I, R′ = Me, R = Et, NMe = NCN) (12.2 g) was dissolved in concentrated hydrochloric acid (85 ml) and the solution kept at the room temperature for 18 hr. The product was precipitated by the addition of water, collected, and washed with hot ethanol, when N-cyano-7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (10.5 g) was obtained as white prisms, mp 277–279°.

*Anal.* Calcd for $C_{25}H_{28}N_2O_3$: C, 74.2; H, 7.0; N, 6.9. Found: C, 74.7; H, 7.0; N, 7.0.

**7,8-Dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (XVI, $R^1$ = $R^2$ = Me, $R^3$ = H, R = Et, $R^4$ = O). a.** N-Cyano-7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (37.5 g), water (1400 ml), 2-ethoxyethanol (600 ml), and potassium hydroxide (144 g) were boiled under reflux for 18 hr with vigorous stirring. The mixture was cooled and the solid matter (23.5 g) collected and recrystallized from aqueous ethanol, when the secondary base was obtained as white prisms, mp 210–212°, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.7; N, 3.7. Found: C, 76.5; H, 7.8; N, 3.7.

**b.** 6,14-*endo*-Etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)tetrahydronorthebaine (I, R′ = Me, R = Et, NMe = NH) (5 g) was heated at 100° with concentrated hydrochloric acid (50 ml) for 2 hr. The mixture was diluted with 40% aqueous ethanol (200 ml) and basified with aqueous ammonia. The precipitated base was collected, washed, and recrystallized from aqueous ethanol, when 7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (3.6 g) was obtained as white prisms, mp 210–212°, alone or mixed with a specimen prepared as in a.

*Anal.* Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.7. Found: C, 75.8; H, 7.9.

**N-Allyl-7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (XVI, $R^1$ = $R^2$ = Me, $R^3$ = $CH_2CH{=}CH_2$, R = Et, $R^4$ = O). a.** 7,8-Dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (XVI, $R^1$ = $R^2$ = Me, $R^3$ = H, R = Et, $R^4$ = 0) (8 g), allyl bromide (4.8 g), anhydrous potassium carbonate (16 g), and acetone (250 ml) were heated together under reflux with stirring for 18 hr. The mixture was filtered, the filtrate evaporated to dryness, and the residue treated with ethereal hydrogen chloride. The solid hydrochloride was collected and converted into the base with aqueous ethanolic ammonia. The product was recrystallized from aqueous ethanol, when N-allyl-7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone (4.9 g) was obtained as white prisms, mp 131–133°, $\nu_{max}$ 1730 $cm^{-1}$.

*Anal.* Calcd for $C_{27}H_{33}NO_3$: C, 77.3; H, 7.9; N, 3.3. Found: C, 77.3; H, 8.0; N, 3.3.

**b.** N-Allyl-6,14-*endo*-etheno-7α-(1-(*R*)-hydroxy-1-methylbutyl)-tetrahydronorthebaine (I, R′ = Me, R′ = Et, NMe = $NCH_2$-$CH{=}CH_2$) (3 g) was heated with concentrated hydrochloric acid (15 ml) at 100° for 2 hr. The mixture was diluted with 40% aqueous ethanol and basified with ammonia. The precipitated base was collected and recrystallized from aqueous ethanol, when N-allyl-7,8-dihydro-6′-ethyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]norcodeinone was obtained as prisms, mp 131–133°.

**7,8-Dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]-norcodeinone (XVI, $R^1$ = $R^2$ = Me, R = *i*-Bu, $R^3$ = H, $R^4$ = O). a.** 7,8-Dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]-codeinone (X, R = *i*-Bu, R′ = Me) (2.5 g) and methyl azodicarboxylate (0.87 g) were heated together under reflux in acetone (50 ml) for 45 min. The acetone was evaporated, and the residue was heated on the steam bath for 1 hr with aqueous ethanolic hydrochloric acid (5 *N*). The mixture was cooled and extracted three times with ether. The base was precipitated with ammonia and isolated by ether extraction, when it was obtained as a glass, $\nu_{max}$ 1730 $cm^{-1}$ (2.2 g).

*Anal.* Calcd for $C_{26}H_{35}NO_3$: C, 76.8; H, 8.5. Found: C, 76.2; H, 8.4.

**b.** N,N′-Methylenbis-6,14-*endo*-etheno-7α-(1-(*R*)-hydroxy-1,4-dimethylpentyl)tetrahydronorthebaine[11] (2.5 g) was heated on the steam bath with concentrated hydrochloric acid (12 ml) for 3 hr. The mixture was diluted with aqueous ethanol and basified with ammonia, and the precipitated base was isolated by ether extraction. The product was a mixture showing carbonyl absorption at 1730 and 1690 $cm^{-1}$ and gave a red color in alkaline suspension when treated with diazotized sulfanilic acid. The phenolic material (belonging to the general series III) was removed on passage of an ether solution through a column of alumina (60 g). The eluate was examined by thin layer chromatography and the first compound to be eluted (1.8 g) was the required nonphenolic secondary base identical in infrared absorption with material prepared as in a above.

The secondary base prepared by both processes on heating under reflux with methyl iodide, ethanol, and anhydrous sodium carbonate for 6 hr gave a good yield of 7,8-dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone, mp 195° (X, R = *i*-Bu, R′ = Me) identical with an authentic specimen in melting point, mixture melting point, and infrared absorption.

**Δ⁵-Dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]deoxycodeine.** 7,8-Dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]codeinone (XI, R = H, R′ = Ph) containing some of the Δ⁵′ isomer (X, R = H, R′ = Ph), mp 149–151° (1 g), and hydrazine hydrate (1 ml) were heated in diethylene glycol (25 ml) at 130° for 1 hr. The temperature was reduced to 75° and potassium hydroxide (1.5 g) was added, after which the temperature was slowly raised. Nitrogen evolution began at 85° and proceeded rapidly at 100°. When the temperature reached 140° it was maintained there until nitrogen evolution had almost stopped, and the mixture was then cooled and poured with stirring into 100 ml of water. The base was precipitated by the addition of aqueous ammonium chloride and isolated by ether extraction. On evaporation of the ether an uncrystallizable gum was obtained which was converted into the hydrochloride with ethanolic hydrogen chloride. The salt, which was very sparingly soluble in all solvents, was recrystallized with difficulty from 80% acetic acid, when Δ⁵-dihydro-5′-phenylcyclohex-4′-eno[1′,2′:8,14]deoxycodeine hydrochloride was obtained as colorless prisms, mp 266–270° dec.

*Anal.* Calcd for $C_{25}H_{31}NO_2 \cdot HCl$: C, 74.5; H, 7.1. Found: C, 74.0; H, 7.4.

Thin layer chromatography showed that this salt contained only a trace of impurity, presumably the Δ⁵,⁵′ isomer. The base, which could not be crystallized, in ethanolic alkali coupled readily with diazotized sulfanilic acid to give a blood red dye.

**Δ⁵-Dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]-deoxycodeine (XII).** A solution of 7,8-dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = *i*-Bu, R′ = Me) (1.5 g) and hydrazine hydrate (3 ml) in diethylene glycol (25 ml) was heated at 140–150° for 1 hr. The mixture was cooled to 100° and potassium hydroxide (4 g) was added. The temperature was slowly raised, and evolution of nitrogen began at about 120°, became very rapid at 160–165°, and was complete after 20 min at the latter temperature. The mixture was then poured into aqueous ammonium chloride, and the precipitated solid (1.2 g) was collected, washed thoroughly with water, and recrystallized

from methanol, when the phenolic base XII was obtained (0.55 g) as white felted needles, mp 127–129°.

*Anal.* Calcd for $C_{27}H_{37}NO_2$: C, 79.5; H, 9.1. Found: C, 79.1; H, 9.3.

The infrared spectrum showed no carbonyl absorption, and the nmr spectrum showed signals (in $\delta$ units) at 6.61 (two aromatic H), 6.3 and 5.5 (doublets, $J_{AB}$ = 9 cps, CH=CH), 5.85 (OH), 3.85 ($OCH_3$), 2.3 ($NCH_3$), 1.58 ($C{=}CCH_3$), and 0.80 (complex, $CHMe_2$). The signal due to the hydroxyl proton was moved to $\delta$ 7.93 in dimethyl sulfoxide.

The base was not readily soluble in aqueous alkalis but in ethanolic potassium hydroxide it coupled readily with diazotized sulfanilic acid to give a blood red solution.

The picrate was obtained as canary yellow needles, mp 186° from ethanol.

*Anal.* Calcd for $C_{27}H_{37}NO_2 \cdot C_6H_3N_3O_7$: C, 62.2; H, 6.3; N, 8.8. Found: C, 61.9; H, 6.5; N, 9.2.

The methanolic mother liquors from the recrystallization of the original reaction product on evaporation afforded a gum from which a second picrate (0.200 g) was obtained as dark yellow prisms, mp 190°.

*Anal.* Calcd for $C_{27}H_{37}NO_2 \cdot C_6H_3N_3O_7$: C, 62.2; H, 6.3; N, 8.8. Found: C, 61.9; H, 6.5; N, 9.1.

This is believed to be the picrate of the $\Delta^6$ isomer of the base XII since the base recovered from the salt still gave a blood red color with diazotized sulfanilic acid in alcoholic potassium hydroxide solution.

**6-Acetoxy-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]-deoxycodeine-C (XIII).** 7,8-Dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = *i*-Bu, R′ = Me) (1.5 g), acetic anhydride (7.5 ml), and anhydrous sodium acetate (0.25 g) were boiled together under reflux for 1.75 hr. The mixture was poured into water and the base was liberated with sodium carbonate and extracted with ether. The extracts yielded an orange gum that crystallized on standing. Recrystallization from methanol afforded the enol acetate (1.0 g) as white needles, mp 132°, $\nu_{max}$ 1750 $cm^{-1}$.

*Anal.* Calcd for $C_{28}H_{37}NO_4$: C, 75.2; H, 8.0. Found: C, 75.5; H, 8.2.

This enol acetate was heated with aqueous ethanolic hydrochloric acid on the water bath for 30 min, and the mixture was neutralized with ammonia to give 7,8-dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = *i*-Bu, R′ = Me), mp 196° alone or mixed with an authentic specimen, $\nu_{max}$ 1730 $cm^{-1}$.

**7,8-Dihydro-6′-isobutyl-8,8,5′-trimethylcyclohex-5′-eno[1′,2′:8,14]codeinone (XIV, R = Me).** A suspension of 7,8-dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (X, R = *i*-Bu, R′ = Me) (1 g) in dry *t*-butyl alcohol (10 ml) was added to a solution of potassium (0.5 g) in dry *t*-butyl alcohol (75 ml) and the mixture stirred for 10 min at 30°. Excess of methyl iodide (2 ml) was then added, and the mixture was stirred for 1 hr after which it was poured into water. The product was isolated by ether extraction and recrystallized from methanol when 7,8-dihydro-6′-isobutyl-8,8,5′-trimethylcyclohex-5′-eno[1′,2′:8,14]codeinone (0.4 g) was obtained as white plates, mp 169–170°, $\nu_{max}$ 1710 $cm^{-1}$.

*Anal.* Calcd for $C_{29}H_{39}NO_3$: C, 77.5; H, 8.75. Found: C, 77.2; H, 8.8.

The nmr spectrum was identical with that of the starting material except in the region $\delta$ 0.6–1.2 in which region signals integrate for 12 protons instead of 6. The base was recovered unchanged after heating under reflux for 2 hr with acetic anhydride and anhydrous sodium acetate.

**7,8-Dihydro-7-hydroxyimino-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]codeinone (XIV, R = NOH).** A solution of sodium (0.25 g) in ethanol (10 ml) was added to a suspension of 7,8-dihydro-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:8,14]-codeinone (X, R = *i*-Bu, R = Me) (1 g) in ethanol (20 ml) and the mixture heated on the water bath for 5 min, then cooled to 60°. Isoamyl nitrite (0.4 g) in ethanol (1.5 ml) was then added and the resulting mixture, which rapidly became dark brown, set aside until a test portion gave only a slightly turbid solution when poured into excess of aqueous sodium hydroxide (about 15 min). The mixture was then poured into aqueous 2 *N* sodium hydroxide solution (50 ml) and insoluble matter was removed by ether extraction. The base was precipitated from the aqueous layer by the addition of ammonium chloride solution, collected, washed with water, and recrystallized from methanol, when the isonitroso ketone (0.8 g) was obtained as white prisms, mp 238–240°, $\nu_{max}$ 1700 $cm^{-1}$.

*Anal.* Calcd for $C_{28}H_{34}N_2O_4$: C, 72.0; H, 7.55. Found: C, 71.7; H, 7.5.

The base gave an immediate green-brown precipitate on treatment in methanol solution with methanolic cupric acetate. The precipitate dissolved readily to give an almost colorless solution in acids but was recovered unchanged on the addition of ammonia, no cupric tetraammine salt being obtained.

**7,8-Dihydro-6′-isobutyl-5′-methyl-7-oxocyclohex-5′-eno[1′,2′:8,14]codeinone (XIV, R = O).** A solution of 7,8-dihydro-7-hydroxyimino-6′-isobutyl-5′-methylcyclohex-5′-eno[1′,2′:-8,14]codeinone (XIV, R = NOH) (0.5 g) in 2 *N* sulfuric acid (10 ml) was heated at 100° for 30 min, then basified with ammonia. The precipitated base was isolated by ether extraction and dissolved in hot petroleum ether (bp 60–80°). On cooling the solution deposited a green amorphous solid, which in petroleum ether suspension slowly became crystalline. The crystalline solid was collected, washed free of amorphous material with cold benzene, and recrystallized from benzene, when the $\alpha$-diketone XIV (R = O) (0.28 g) was obtained as canary yellow prisms, mp 198–200°.

*Anal.* Calcd for $C_{27}H_{33}NO_4$: C, 74.5; H, 7.6. Found: C, 74.6; H, 7.8.

The base gave a deep wine red color with ethanolic ferric chloride, which became an intense blue green on the addition of a trace of ammonia.

The hydrochloride, prepared in ethanol and recrystallized from 2-ethoxyethanol containing 10% water, was obtained as light yellow prisms, mp 215–217°.

*Anal.* Calcd for $C_{27}H_{33}NO_4 \cdot HCl \cdot 1.5H_2O$: C, 64.8; H, 7.4. Found: C, 64.8; H, 7.6.

**Acknowledgments.** The authors wish to thank Dr. D. E. Webster of the University of Hull, England, and Dr. S. F. Dyke of the College of Science and Technology, Bristol, England, for the determination of some preliminary nmr spectra, and the following for experimental assistance: Dr. A. C. B. Smith, Mr. H. Fitton, Mr. J. Fulstow, Mr. M. J. Readhead, Mr. J. K. Saville, Mr. T. M. Sutton, Mrs. E. M. Walker, and the late Mr. S. R. Duff.