being subject to alkaline decomposition,[3] and its known sequence and three-dimensional structure[33] is a particularly good single polypeptide chain for investigating lysine–cystine proximity in this manner. It is also possible that a lysine ε-amino group close to a cystine residue acts as a base catalyst for the elimination.

(33) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature*, **206**, 756 (1965).

Acknowledgments. Support of this investigation by Grant GB-2512 from the National Science Foundation and the assistance of David Ford and Mary Gallagher are gratefully acknowledged.

Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. I. Ketones Derived from 6,14-*endo*-Ethenotetrahydrothebaine[1]

K. W. Bentley and D. G. Hardy

Contribution from the Research Laboratories, Reckitt and Sons Ltd., Kingston-upon-Hull, England. *Received September 26, 1966*

Abstract: Several ketones II derived from 6,14-*endo*-ethenotetrahydrothebaine have been prepared by the Diels–Alder addition of certain α,β-unsaturated ketones to thebaine, by the action of cadmium alkyls on the corresponding acid chloride II (R = Cl), and, in some cases, by the action of Grignard reagents on the corresponding ester II (R = OEt) which is the adduct of thebaine and ethyl acrylate. Both 7α and 7β forms of the ketone II (R = Me), the ester II (R = OEt), and the nitrile III have been isolated. Attempts to convert the 7α ketone II (R = Me) into the 7β isomer have resulted only in the formation of a ketol X (R = H). Many of the bases prepared in this work are potent analgesics. The reaction product obtained from thebaine methiodide and *p*-benzoquinone has been shown to be a charge-transfer complex and not a true Diels–Alder adduct.

For many years determined efforts have been made to produce an analgesic markedly superior to morphine by minor and major modifications of the molecule of the alkaloid. The major modifications have all been in the direction of making simpler structures, representing what are believed to be the features of the molecule responsible for its analgesic action.[2] Structural simplifications of this type, however, have not so far resulted in any marked separation of the desirable and undesirable effects. It has been postulated that the action of such compounds is due to the fit of their molecules onto receptor surfaces, which triggers off their physiological effects.[3] Compounds of structure more simple than that of morphine, however, being more flexible, would be expected to fit at least as easily as the alkaloid to each of the similar receptor surfaces associated with the different effects, thus reproducing all of the physiological effects of the alkaloid. These considerations led us to examine bases more complex and, in particular, more rigid than morphine in the hope that the reduced flexibility and the differences in peripheral shape between such compounds and other known analgesics would result in the new bases being unacceptable at some of the receptor surfaces, and thus to a separation of the various effects.

Several series of such complex derivatives of codeine and thebainone, which are themselves derivatives of morphine, are accessible by the Diels–Alder addition of dienophiles to thebaine[4] and by chemical transformations of the resulting adducts,[5] and in these compounds the new two-carbon bridge across ring C renders the molecule rigid. Many of the compounds derived from thebaine in this way contain also a new reactive center, derived from the dienophile, at which further chemical reactions may be effected to yield bases of still greater peripheral complexity. Some of our early work along these lines has already been reported,[6] but the work was suspended owing to the difficulty experienced in securing adequate pharmacological appraisal of the compounds prepared. During the course of this work, however, it was found that the ketonic base I, obtained by the catalytic reduction of the adduct of thebaine and *p*-benzoquinone, is an analgesic with about one-seventh the potency of morphine, when tested in rats by the conventional techniques.

In further pursuit of this idea, the other known Diels–Alder adducts of thebaine, namely the aldehyde II (R = H), the ketones II (R = Me and Ph), the nitrile III, and the diester IV were prepared, together with a number of new analogous bases, and these were tested in animals for analgesic properties.

(1) (a) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1960). (b) Parts of this work are covered by British Patents 905,659 and 925,723.

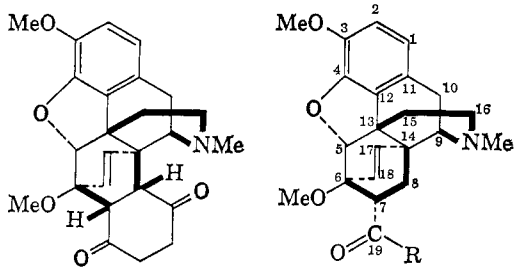
(2) F. Bergel and A. L. Morrison, *Quart. Rev.* (London), **2**, 349 (1948); E. S. Stern, *ibid.*, **5**, 405 (1951); A. H. Beckett, *J. Pharm. Pharmacol.*, **4**, 425 (1952); O. Braenden, N. B. Eddy, H. Halbach, and P. O. Wolff, *Bull. World Health Organ.*, **2**, 193 (1949); **10**, 1003 (1954); **13**, 937 (1955); **14**, 353, (1956); N. B. Eddy, *Chem. Ind.* (London), 1462 (1959); P. A. J. Janssen, "Synthetic Analgesics-Part I," Pergamon Press Ltd., London, 1960; P. A. J. Janssen, *Brit. J. Anaesthesia*, **34**, 260 (1962); P. A. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960); K. W. Bentley, *Endeavour*, **23**, 97 (1964); "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 123 1965: E. L. May and L. J. Sargent, p 123, and R. A. Hardy and G. M. Howell, p 179.

(3) A. H. Beckett, *Progr. Drug Res.*, **1**, 527 (1959).

(4) W. Sandermann, *Ber.*, **71**, 648 (1938); C. Schopf, K. von Gottberg, and W. Petri, *Ann.*, **536**, 216 (1938); S. I. Kanewskaya and S. F. Mitryagina, *J. Gen. Chem. USSR*, **17**, 1203 (1947).

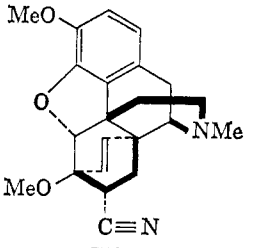
(5) (a) K. W. Bentley and J. Dominguez, *J. Org. Chem.*, **21**, 1348 (1956); (b) K. W. Bentley, J. Dominguez, and J. P. Ringe, *ibid.*, **22**, 409, 418, 422 (1957); (c) K. W. Bentley and J. P. Ringe, *ibid.*, **22**, 425, 599 (1957); (d) K. W. Bentley and J. C. Ball, *ibid.*, **23**, 1720, 1725 (1958); (e) K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *ibid.*, **23**, 941 (1958).

(6) K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1863 (1956).

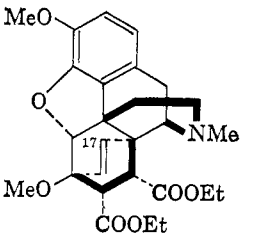


I

II



III

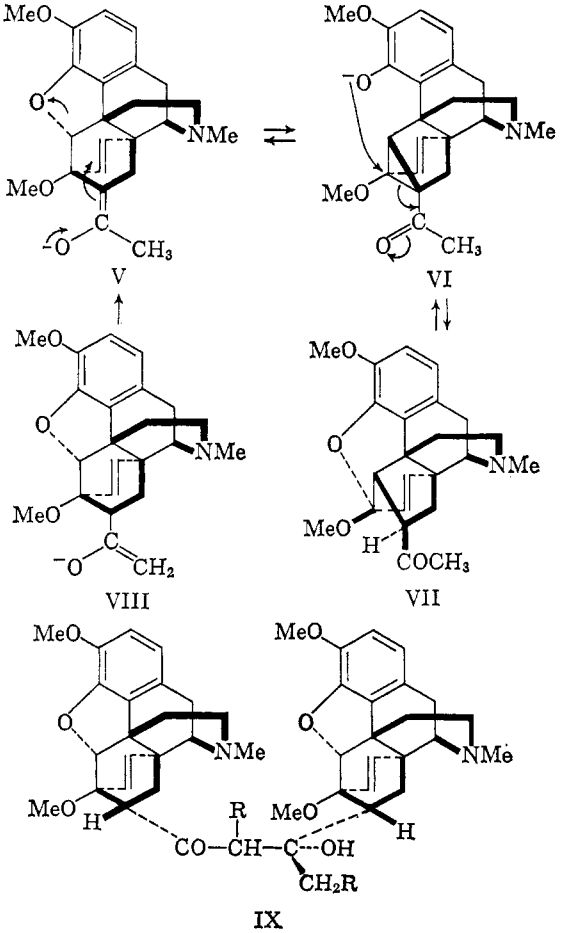


IV

The addition of dienophiles to thebaine can occur readily only on the exposed face of the diene system, and gives rise to derivatives of 6,14-*endo*-ethenotetrahydrothebaine, the atom numbering of which is shown in formula II. The prefix *endo* implies disposition of the 6,14-etheno bridge "inside" the tetrahydrothebaine skeleton, that is, on the opposite side of the molecule to that occupied by the hydrogen atoms at positions 6 and 14 in tetrahydrothebaine itself. Addition of the dienophile to the exposed face of the diene system in two ways, leading to isomeric adducts differing in stereochemistry at C-7, can also be envisaged, and the isomers obtained in this way can be differentiated by the symbols α and β, which have the same implications as when used in the steroid field. A careful examination of models of the 7α and 7β forms of the ketone II (R = Me), the aldehyde II (R = H), the ester II (R = OEt), and the nitrile III reveals that there is little difference in steric hindrance in the two forms, which might be expected, therefore, to be of comparable stability. The stereochemical factors generally governing the mode of addition in the Diels–Alder reaction would, however, be expected to give in this case mainly adducts having the 7α configuration, II and III. The addition of unsymmetrical dienophiles such as alkyl and aryl vinyl ketones, acrylic esters, and acrylonitrile to thebaine appears to take place under electronic control, giving rise exclusively to C-7-substituted tetrahydrothebaine derivatives, very careful examination of the products of addition of methyl vinyl ketone and ethyl acrylate to the alkaloid producing no evidence of the production of C-8-substituted compounds.

The primary adduct of thebaine and methyl vinyl ketone consists almost entirely of the 7α ketone II (R = Me), mp 122°, but from the mother liquors of the crystallization of this base the 7β ketone, mp 200–201°, has been isolated in 0.5% yield. That these two bases are indeed epimers at C-7, and not C-7 and C-8 ketones, was conclusively demonstrated by the base-catalyzed rearrangement of both isomers to the same product, which is the ketone VII (R = Me). This base-catalyzed rearrangement, which will be discussed in detail in a later paper in this series,[7] is analogous to the conversion of nepenthone (II, R = Ph) into isonepenthone (VII, R = Ph), and involves loss of the asymmetry at C-7 in the intermediate enolate ion V. A rational mechanism for this rearrangement, V → VI → VII,[5d] can only be devised if the $COCH_3$ group is situated at C-7. The assignment of the 7α configuration to the base, mp 122°, and the 7β configuration to the minor product, mp 200–201°, of the Diels–Alder reaction has been confirmed by detailed nmr spectroscopic studies.[8]

Attempts were made to convert the 7α ketone II (R = Me) into an equilibrium mixture with the 7β isomer by reversible enolization to the enolate ion V. The primary enolization of the ketone is, however, kinetically controlled, and leads to the enolate ion VIII, and this can react with unenolized ketone to give a ketol IX (R = H) (see below). The ketolization is reversible, however, and under reversible enolizing conditions the thermodynamically more stable ion V will eventually be formed and reversible discharge of this ion should give an equilibrium mixture of 7α and 7β ketones. In practice, however, the process is complicated by the ease with which the enolate ion V suffers rearrangement through the phenate ion VI to the ketone VII (R = Me), which appears to be more stable than either of the C-7 epimers of the adduct II (R = Me).



IX

Although these equilibration experiments provide no evidence as to which of the two C-7 epimers of the ketone II (R = Me) is the more stable, the formation of derivatives of the 7α-tertiary alcohol X (R = R′

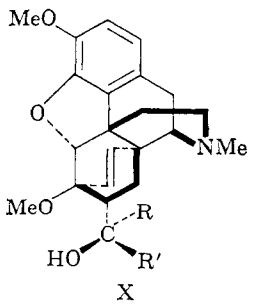
(7) K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Am. Chem. Soc.*, **89**, 3312 (1967).

(8) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. H. Howell, C. T. Nora, and R. A. Hardy, Jr., *ibid.*, **89**, 3322 (1967).

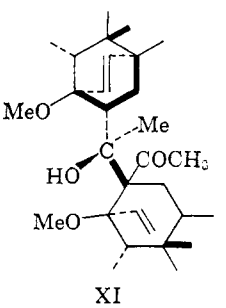
= Me) from bases in which the bicyclooctene system has been opened, described in part IV of this series,[9] suggests that in the alcohols the 7α form is the more stable.

Treatment of the adduct II (R = Me) with 1 equiv of methylmagnesium iodide or other Grignard reagent gives little or no tertiary alcohol, the product being a viscous gum very similar in infrared absorption to the original ketone. The same product is obtained by the action of anhydrous magnesium iodide on the adduct, and it is shown by thin layer chromatography to consist of a mixture of the ketone II (R = Me) (20%), a new base (75%), and the product VII (R = Me) of base-catalyzed rearrangement (5%). This mixture on treatment with 0.1 equiv of potassamide in liquid ammonia rapidly affords a good yield of the ketone II (R = Me), which is sparingly soluble in ammonia, and, when treated with an excess of methylmagnesium iodide, it gives an excellent yield of the tertiary carbinol X (R = R′ = Me), which is obtained directly from the ketone II (R = Me) and an excess of this Grignard reagent (see following paper).

Separation of the main component of the mixture was achieved on alumina plates, and it was obtained as prisms, mp 151–152°, and found to be isomeric with the original ketone II (R = Me). Its infrared spectrum shows carbonyl absorption at 1715 cm^{-1}, and hydrogen-bonded hydroxyl absorption at 3490 cm^{-1}. The intensities of these absorption bands relative to the adjacent C–H bands, at 1450 and 2950 cm^{-1}, respectively, was 0.52 and 0.19, whereas the intensities of the carbonyl and hydroxyl absorption bands relative to the same C–H bands in the ketone II (R = Me) and the tertiary alcohol X (R = Me, R′ = *i*-Am) are 1.07 and 0.42, respectively. The new base must, therefore, be a double molecule containing one hydroxyl and one carbonyl group between two ethenotetrahydrothebaine units, and, since it is convertible back into the ketone II (R = Me), can only be a ketol resulting from attack of the ketone by its own enolate ion. Enolization by Grignard reagents or anhydrous magnesium iodide would be irreversible and, hence, kinetically controlled and lead to the ion VIII, attack of which on the ketone would afford the ketol X (R = H). That this does correctly represent the structure of the ketol was confirmed by dehydration of the ketol to an α,β-unsaturated ketone by heating with 98–100% formic acid. Ketol formation from the ketone and the enolate ion V would lead to a product containing the part structure XI, dehydration of which to an α,β-unsaturated ketone would be impossible.



X



XI

The nmr spectrum of the ketol fully supports the assigned structure X (R = H). The spectrum, obtained on a 40-Mc/sec instrument, shows no signal attributable to $COCH_3$ but does show signals (in δ units) at 6.58 (four aromatic H), a complex signal pattern from 6.2 to 5.4 attributed to two *cis* CH=CH systems in slightly different environments, and signals at 4.95 (OH), 4.61 (2OCH<), 3.86 (two aromatic OCH_3), 3.80 (three protons in the hydrogen-bonded C-6 OCH_3 group in the alcoholic part of molecule), 3.67 (three protons in the unbonded C-6 OCH_3 group in the ketonic part), 2.41 ($2NCH_3$), and 1.17 (CCH_3). It may be noted that the C-6 methoxyl group in the alcohol X (R = R′ = Me) gives a signal at δ 3.75 and that in the ketone II (R = Me) gives a signal at δ 3.61.

Stereochemically, since enolization in this case does not involve C-7, both units in the ketol IX (R = H) belong to the 7α series, and the formation of the 7α ketone in good yield on deketolization of the base with potassamide in liquid ammonia is in agreement with this representation.

The addition of ethyl acrylate to thebaine is also highly stereospecific, giving about 94% of the 7α ester II (R = OEt) and 6% of the isomeric 7β compound. That the major product has the same stereochemistry at C-7 as the adduct of thebaine and methyl vinyl ketone II (R = Me) was demonstrated by the conversion of both adducts into the tertiary carbinol XI (R = R′ = Me) by methylmagnesium iodide. The nmr spectra of the esters show signals (in δ units) for the C-5 proton at 4.60 (7α) and 5.17 (7β) compared with 4.55 and 4.98 in the spectra of the 7α- and 7β-methyl ketones. The other features of the spectra are entirely in accord with the assigned structures.

The primary adduct of thebaine and acrylonitrile is a mixture of 7α and 7β isomers from which, after treatment with charcoal, approximately equal amounts of the two pure isomers can be obtained by chromatography. The 7α nitrile III is identical with the product of dehydration of the oxime of the aldehyde II (R = H) previously reported.[5d] The assignment of configuration at C-7 in these nitriles was made on the basis of detailed nmr studies.[8]

Although aryl vinyl ketones are readily prepared in the laboratory from aryl methyl ketones, alkyl vinyl ketones, other than the methyl and ethyl compounds which are commercially available, are not readily accessible, and attempts were made to prepare 7-acyl-6,14-*endo*-ethenotetrahydrothebaines from the ester II (R = OEt) and the nitrile III. Some ketones were obtained in poor yield as minor products from the reaction of the ester II (R = OEt) with Grignard reagents. With methylmagnesium iodide the sole product of this reaction is the tertiary carbinol XI (R = R′ = Me), but with other alkylmagnesium halides the product consisted of a mixture of tertiary carbinol X (R = R′ = Me), ketone II, and phenolic material resulting from rearrangement of the ester.[9] The amount of tertiary carbinol produced decreased and the amount of phenolic material obtained increased very rapidly as the length and/or branching of the alkyl chain in the Grignard reagent increased; the amount of ketone produced remained low in all cases. Steric factors are presumably operative in this reaction, since the ease of accommodation of two identical alkyl groups around the carbon atom of the tertiary alcohol, in the presence of the large thebaine unit, would be

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

expected to decrease sharply as the complexity of the alkyl group increases. The ease of abstraction of a proton by the Grignard reagent from the α carbon would be expected to be almost independent of the size of the reagent, and hence rearrangement would be expected to be favored relative to carbinol formation by an increase in size or complexity of the reagent.

A better laboratory preparation of certain of the ketones of structure II was found to be the reaction between cadmium alkyls and the acid chloride II (R = Cl), prepared from the ester II (R = OEt) *via* the acid II (R = OH). The product of the reaction between the acid chloride and *n*-propylcadmium was resolved on alumina plates into the 7α-*n*-propyl ketone II (R = *n*-Pr) (80%), its 7β epimer (0.1%), the ketol X (R = Et) (20%), and a trace of phenolic base. The major product was identified as the 7α-*n*-propyl ketone II (R = *n*-Pr) by its infrared and its nmr spectra. The former showed carbonyl absorption at 1715 cm^{-1} and the latter showed a signal due to the C-5 proton as a finely split doublet at δ 4.55 (as in the spectrum of the 7α-methyl ketone) as well as signals (in δ units) at 6.6 (two aromatic H), 6.0 and 5.55 (doublets, CH=CH), 3.83 (C-3 OCH_3), 3.61 (C-6 OCH_3), 2.29 (NCH_3), and 0.95 (doublet, CHC_3). The 7β ketone was identified by its infrared spectrum, which was almost identical with that of the 7α isomer, and by its less polar behavior on thin layer chromatography.

The ketol IX (R = Et) showed carbonyl and hydrogen-bonded hydroxyl absorption in the infrared, and its nmr spectrum was similar to that of the ketol IX (R = H), showing signals (in δ units) at 6.59 (four aromatic H), 5.45–6.1 (complex, 2 CH=CH), 4.6 and 4.75 (two C-5 H), 3.82 (9 H, two C-3 OMe, C-3′ OMe, and C-6′ OMe), 3.64 (3 H, C-6 OMe), 2.31 and 2.36 (2NMe), and complex signals due to CCH_3 in the region 1.38–0.98 attributed to the ethyl and propyl groups.

The ethyl and *n*-propyl ketones prepared in this way were converted by the action of methylmagnesium iodide into tertiary alcohols X (R = Et, R′ = Me and R = *n*-Pr, R′ = Me) diastereoisomeric at C-19 with those (R = Me, R′ = Et and R = Me, R′ = *n*-Pr) obtained by the reaction of the 7α ketone II (R = Me) with ethyl- and *n*-propylmagnesium halides, respectively (see following paper).

The adduct of thebaine and acrylonitrile (mixture of 7α and 7β isomers) reacts readily with methyl and other alkylmagnesium halides, but the reaction involves only base-catalyzed rearrangement, the same product being obtained in all cases. This reaction is discussed in detail in a later paper in this series.[9] With phenylmagnesium bromide, however, the 7α ketone, nepenthone (II, R = Ph), was obtained in about 25% yield (about 50% based on the amount of 7α-nitrile present in the original adduct), and the *o*- and *p*-tolyl analogs were prepared in a similar manner. Differences in the behavior of nitriles with aliphatic and aromatic Grignard reagents have previously been reported.[10]

It was hoped that ketones II would be preparable by the oxidation of the related secondary alcohols X (R = H), many of which can be prepared by the action of Grignard reagents on the aldehyde II (R = H), but neither of the diastereoisomeric alcohols X (R = H, R′ = Me and R = Me, R′ = H) (see following paper) nor nepenthol (X, R = Ph, R′ = H)[5b] could be oxidized in this way.

Quaternization of the Diels–Alder adducts of thebaine is very difficult to accomplish, but good yields of the quaternary salts of the ketone II (R = Me) and the ester II (R = OEt) were obtained by heating the bases under reflux for 7 days with methyl iodide in acetone solution. Since the adducts of thebaine with acetylenic dienophiles can be quaternized with much greater ease, the sluggish reaction of the adducts II may be attributed to steric hindrance of attack of the nitrogen atom by the proximity of the C-8β hydrogen. It may be mentioned that other workers have found that this proximity and anisotropy of the tertiary nitrogen also appear to affect the resonance of the 8β hydrogen in the nmr spectra of bases in this series.[8] Models of the quaternary salts can be constructed without difficulty, and in these there is no appreciable hindrance between this hydrogen atom and the N-methyl group. The slow quaternization of the adduct II (R = Me) contrasts markedly with the rapid reaction between thebaine methiodide and benzoquinone[11] and α-naphthaquinone[6] previously reported. Since attempts to prepare quaternary salts of the adducts by the addition of acrolein, methyl vinyl ketone, phenyl vinyl ketone, ethyl acrylate, acrylonitrile, and maleic anhydride to thebaine methiodide were quite unsuccessful, the reaction between methiodide and *p*-benzoquinone has been reexamined.

The reaction in chloroform solution rapidly affords a very good yield of a red crystalline solid having the composition of a 1:1 adduct, which is recovered unchanged on rapid recrystallization from hot water.[11] The use of high-boiling solvents, such as cyclohexanol, for the recrystallization, however, results in the recovery of thebaine methiodide, which is also obtained when the solid is heated in open vessels at 140–150°. Reduction of a solution of the salt in aqueous ethanol with sodium borohydride or sulfurous acid proceeds with the production of a transient violet color, presumably due to quinhydrone, and the formation of hydroquinone and thebaine methiodide. The material is, therefore, clearly not a true adduct, but is a charge-transfer complex of thebaine methiodide with benzoquinone, representing the initial stage in the Diels–Alder reaction. The reaction is prevented from proceeding to completion by steric hindrance to a sufficiently close approach of the two molecules for bond formation, as a result of the presence of the additional methyl group on the nitrogen atom. The examination of models shows that such steric hindrance would be expected to be operative in preventing the addition of other dienophiles to thebaine methiodide, and in these cases the charge-transfer complexes are presumably insufficiently well stabilized for them to be isolated.

Neither methyl isopropenyl ketone nor crotonaldehyde gives adducts with thebaine at temperatures up to 140°, but the examination of models of the expected adducts shows that steric hindrance in the molecules is no greater than in the ketone II (R = Me), its 7β isomer, or its methiodide. The failure of the reaction in these cases must be attributed to steric hindrance to a sufficiently close approach of the reactants for the forma-

(10) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable and Co. Ltd., London, 1954, p 773.

(11) K. W. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

tion of the new bonds to C-6 and C-14, and the study of models of the reactants supports this view. With crotonaldehyde, which has the CH_3 and CHO groups in the *trans* relationship, close approach to thebaine in such a way as to ensure maximum overlap of the unsaturated centers is severely hindered by carbon atoms 15 and 16 of the nitrogen-containing ring of the alkaloid. With methyl isopropenyl ketone, the hindrance is largely between the methyl group and the hydrogen atoms at C-5 and C-15 in the base. Maleic anhydride and *p*-benzoquinone, which have *cis*-1,2-disubstituted double bonds, can easily be brought into close proximity to the diene system of thebaine and form adducts with great ease.

Of the ketones of general structure II prepared in this work and listed in the Experimental Section, several were found to be more potent as analgesics than morphine, when tested in rats by the tail pressure method and administration by the subcutaneous route. By contrast, the ester II (R = OEt) showed no analgesic activity at doses up to 200 mg/kg.[12]

Experimental Section

Addition of Methyl Vinyl Ketone to Thebaine. Thebaine (1000 g) was boiled under reflux with methyl vinyl ketone (3 l.) for 1 hr. The excess of unsaturated ketone was removed by distillation under reduced pressure, and the viscous residue was dissolved in boiling methanol (1200 ml). The resulting solution was cooled in ice with vigorous stirring. The crystalline solid that separated was collected, washed with ice-cold methanol, and air dried, when 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me) (1140 g, 93%) was obtained as white prisms, mp 119–121°, sufficiently pure for all chemical pruposes, the melting point raised to 122° (lit.[5d] 122°) on recrystallization from methanol, 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 hydrochloride formed white prisms, mp 262°, from ethanol.

Anal. Calcd for $C_{23}H_{27}NO_4 \cdot HCl$: C, 66.1; H, 6.7. Found: C, 66.4; H, 6.8.

The hydrobromide formed white prisms, mp 270°, from 90% ethanol.

Anal. Calcd for $C_{23}H_{27}NO_4 \cdot HBr$: C, 59.7; H, 6.1. Found: C, 59.9; H, 6.1.

The methiodide formed slowly when the base was heated under reflux with methyl iodide in acetone for 7 days. On recrystallization from aqueous ethanol it was obtained as prisms, mp 172°.

Anal. Calcd for $C_{23}H_{27}NO_4 \cdot CH_3I \cdot H_2O$: C, 53.3; H, 6.0. Found: C, 53.4; H, 6.2.

The mother liquors from the separation of the 7β-acetyl compound were concentrated to 400 ml and kept at room temperature overnight, when crystalline material separated. This was collected, washed with ice-cold methanol, and dried (14 g). Thin layer chromatographic studies showed this base to comprise a mixture of about 40% of the 7α ketone II (R = Me) and 60% of a less polar base. The solid was boiled under reflux with methanol (50 ml) when the more soluble 7α ketone dissolved. The insoluble 7β-acetyl-6,13-*endo*-ethenotetrahydrothebaine (6 g) was collected and recrystallized from ethanol, when it was obtained as white rectangular plates, mp 200–202°, subliming slowly above 180°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.4; H, 7.1. Found: C, 72.4; H, 7.0.

The hydrochloride was obtained as white prisms, mp 266°, from ethanol–ether.

Anal. Calcd for $C_{23}H_{27}NO_4 \cdot HCl$: C, 66.1; H, 6.7. Found: C, 66.3; H, 6.8.

The hydrobromide was obtained as white prisms, mp 254°, from ethanol.

Anal. Calcd for $C_{23}H_{27}NO_4 \cdot HBr$: C, 59.7; H, 6.1. Found: C, 60.0; H, 6.3.

Concentration of the mother liquors from the separation of this base and from the isolation of the 7α–7β mixture gave a further 30 g of a mixture estimated by thin layer chromatography to contain about 70% of the 7α ketone and 30% of the 7β isomer, and this material was recovered unchanged in composition after boiling with, or recrystallization from, methanol. Allowing for material present in this mixture the Diels–Alder reaction affords a yield of at least 97.8% of adduct: 96.3% 7α and 1.5% 7β ketone.

Addition of Acrolein to Thebaine. On several occasions excellent yields (>85%) of the adduct were obtained by heating thebaine (25 g) with acrolein (75 ml) under reflux for 1 hr, removing the excess of acrolein by evaporation under reduced pressure, and crystallizing the residue from aqueous methanol. This process is, however, capricious and other reactions carried out under apparently identical conditions yielded only insoluble polymerized material from which neither adduct nor thebaine could be recovered. Neither careful purification of the reactants nor the addition of hydroquinone appeared to have any effect on the ease of polymerization. A more reliable process giving, however, a reduced yield of product was the following. A mixture of thebaine (25 g), benzene (250 ml), and acrolein (10 ml) was heated at 65–70° for 4 hr. The basic material was extracted from the benzene solution with aqueous 2 *N* acetic acid and then precipitated with ammonia. The crystalline material was collected, washed well with water, and recrystallized from aqueous methanol, when 6,14-*endo*-etheno-7α-formyltetrahydrothebaine (II, R = H) (17 g) was obtained as white prisms, 106° (lit.[5d] 104°), ν_{max} 1730 cm^{-1}.

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 72.0; H, 6.8. Found: C, 72.2; H, 6.9.

6,14-*endo*-Etheno-7α-propionyltetrahydrothebaine (II, R = Et). Thebaine (25 g) was heated with ethyl vinyl ketone (25 g) in the presence of a small amount of hydroquinone at ~100° for 4 hr. The excess of ethyl vinyl ketone was removed under reduced pressure, and the dark viscous residue was dissolved in warm glacial acetic acid (25 ml). This solution was diluted with water (300 ml) and extracted with ether. The aqueous phase was freed from ether by boiling and basified (100 ml, 20% w/v aqueous sodium hydroxide), and the precipitate was collected, washed with water, and dried to give the adduct, mp ~40° (80%).

The base was converted into its hydrochloride with ethereal hydrogen chloride; the salt was recrystallized from ethanol (twice) and then converted into the base, mp 40–45°, with aqueous sodium hydroxide.

Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.9; H, 7.4; N, 3.5. Found: C, 73.6; H, 7.6; N, 3.6.

Addition of Ethyl Acrylate to Thebaine. Thebaine (500 g) was boiled under reflux with ethyl acrylate (850 ml) for 6 hr. The excess of ethyl acrylate was removed by evaporation under reduced pressure until separation of the solid matter began. The mixture was centrifuged, the solid obtained was washed well with cold methanol, when 6,14-*endo*-etheno-7α-ethoxycarbonyltetrahydrothebaine (500 g) was obtained as white prisms, mp 123–124°, raised to 124° by recrystallization from methanol, ν_{max} 1740 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.0; H, 7.1. Found: C, 70.0; H, 7.3.

The hydrochloride, prepared in and recrystallized from ethanol, was obtained as white prisms, mp 258°.

Anal. Calcd for $C_{24}H_{29}NO_5 \cdot HCl$: C, 64.4; H, 6.7. Found: C, 64.3; H, 6.7.

The methiodide formed slowly when the base was boiled under reflux in acetone with an excess of methyl iodide for 7 days and was obtained as white prisms, mp 240°, from ethanol.

Anal. Calcd for $C_{24}H_{29}NO_5CH_3I$: C, 54.3; H, 5.8. Found: C, 54.3; H, 5.8.

The mother liquors and methanol washings remaining after removal of the 7α ester were evaporated under reduced pressure and the residual gum was dissolved in methanol (150 ml) and cooled in ice. The solid matter (60 g), consisting of an approximately 1:2:1 mixture of the 7α and 7β esters and thebaine, was crystallized twice from methanol, when 6,14-*endo*-etheno-7β-ethoxycarbonyltetrahydrothebaine (9 g) was obtained as white prisms, mp 106–108°, ν_{max} 1740 cm^{-1}.

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.0; H, 7.1. Found: C, 69.6; H, 7.0.

The hydrochloride formed white prisms, mp 198–200°.

Anal. Calcd for $C_{24}H_{29}NO_5 \cdot HCl$: Cl, 7.9. Found: Cl, 7.8.

6,14-*endo*-Ethenotetrahydrothebaine-7α-carboxylic Acid (II, R = OH). 6,14-*endo*-Etheno-7α-ethoxycarbonyltetrahydrothebaine (50 g) was heated on the water bath with concentrated hydrochloric acid (250 ml) for 3 hr. The filtered hot solution was cooled in ice and the crystalline solid that separated was collected and washed

(12) R. E. Lister, *J. Pharm. Pharmacol.*, **16**, 364 (1964).

with ice–water, when the hydrochloride of the 7α-carboxylic acid (47 g) was obtained as white prisms, mp 246–247°.

Anal. Calcd for $C_{22}H_{25}NO_5 \cdot HCl \cdot H_2O$: C, 61.6; H, 6.3. Found: C, 61.2; H, 6.7.

The free acid was obtained by continuous ether extraction of an aqueous solution of the hydrochloride adjusted to pH 6.1. Evaporation of the ether extract afforded a solid which was recovered on recrystallization from ethanol as white prisms, mp 230°.

Anal. Calcd for $C_{22}H_{25}NO_5 \cdot 1.5H_2O$: C, 64.4; H, 6.9. Found: C, 64.6; H, 6.9.

7α-Chlorocarbonyl-6,14-*endo*-ethenotetrahydrothebaine Hydrochloride. 6,14-*endo*-Ethenotetrahydrothebaine-7-carboxylic acid hydrochloride (70 g), oxalyl chloride (25 ml), and dry benzene (250 ml) were heated together on the water bath for 2 hr. The volatile liquids were removed under reduced pressure, and the residue was heated again with oxalyl chloride (25 ml) and dry benzene (250 ml). Evaporation under reduced pressure afforded the acid chloride hydrochloride (70 g) as white prisms, mp 270° dec, sufficiently pure for further use.

Anal. Calcd for $C_{22}H_{24}NO_4Cl \cdot HCl$: Cl, 16.2. Found: Cl, 15.9, 16.5.

6,14-*endo*-Etheno-7α-methoxycarbonyltetrahydrothebaine (II, R = OMe). Thebaine (5 g) and methyl acrylate (25 ml) were boiled together under reflux for 6 hr. The excess of methyl acrylate was removed under reduced pressure, and the residue was crystallized and recrystallized from methanol, when the methyl ester II (R = OMe) was obtained as white prisms, mp 148°, ν_{max} 1740 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.5; H, 6.9. Found: C, 69.8; H, 7.0.

Diels–Alder Addition of Acrylonitrile to Thebaine. Thebaine (100 g) was boiled under reflux with acrylonitrile (350 ml) for 3 hr. The excess of acrylonitrile was removed by evaporation under reduced pressure, and the residue was crystallized from methanol, when the adduct (95 g) was obtained as white prisms, mp 146°, raised to 148° on recrystallization. Thin layer chromatographic studies showed the adduct to consist of two components. The adduct was boiled under reflux for 5 min in methanol solution with activated charcoal (15 g); the solution was filtered and cooled in ice. The solid separating (45 g) had mp 182–188° and consisted mainly of one compound. On recrystallization of this material, 7β-cyano-6,14-*endo*-ethenotetrahydrothebaine (35 g) was obtained as felted needles, mp 196–197°, ν_{max} 2230 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.4; H, 6.7; N, 7.5. Found: C, 72.4; H, 6.8; N, 7.4.

The filtrate remaining after removal of the 7β nitrile following charcoal treatment of the adduct was evaporated and the residue found to contain principally the 7α nitrile, which was obtained pure by partition chromatography on a Celite 545 column using heptane–methanol as the developing solvent.[13] Two components were eluted while monitoring the eluate at 230 mμ. The more polar compound was the second component to be eluted and was recovered from the eluate as plates, mp 183–184°, on recrystallization from ethanol, ν_{max} 2230 cm^{-1}. This 7α nitrile was identical in mixture melting point and R_f value with the product of dehydration of the oxime of the 7α aldehyde.[5d]

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.4; H, 6.7; N, 7.5. Found: C, 72.4; H, 6.9; N, 7.3.

Preparation of Ketones from the Acid Chloride II (R = Cl). 7α-Butyryl-6,14-*endo*-ethenotetrahydrothebaine (II, R = *n*-Pr). Anhydrous cadmium chloride (1.8 g) was added to a solution of *n*-propylmagnesium bromide (from 0.54 g of magnesium and 3.2 g of *n*-propyl bromide) in ether (20 ml), and the mixture was boiled under reflux for 30 min, after which the ether was removed by distillation and replaced by methylene chloride (30 ml). 7α-Chlorocarbonyl-6,14-*endo*-ethenotetrahydrothebaine hydrochloride (5.0 g) in methylene chloride (20 ml) was added to the solution of dipropylcadmium, and the mixture was boiled under reflux for 1 hr, cooled, and then decomposed by the addition of cold 2 *N* hydrochloric acid (100 ml). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (50 ml). The combined methylene chloride solutions were dried and evaporated. The residue was suspended in dilute aqueous ammonia, and the suspension was extracted with ether and the extract evaporated. The residue was dissolved in benzene and the solution passed down an alumina column, with elution subsequently with benzene. The initial eluate containing the *n*-propyl ketone II (R = *n*-Pr) was evaporated to give a glass (3.5 g), ν_{max} 1715 cm^{-1}. A portion (400 mg) of this was chromatographed in ether on thick alumina plates. The least polar band on extraction with chloroform yielded 7β-butyryl-6,14-*endo*-ethenotetrahydrothebaine (4 mg), mp 128–130°, ν_{max} 1715 cm^{-1}. The immediately following band yielded 7α-butyryl-6,14-*endo*-ethenotetrahydrothebaine (II, R = *n*-Pr) (320 mg), prisms, mp 84°, ν_{max} 1715 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}NO_4 \cdot H_2O$: C, 70.3; H, 7.7. Found: C, 70.6; H, 7.4.

The most polar band afforded 7α,7′α-bis((2-ethyl-3-hydroxy-3-propyl-1-oxopropano)-6,14-*endo*-ethenotetrahydrothebaine) (IX, R = Et) (40 mg), ν_{max} 1715 and 3490 cm^{-1}, mp 130–133°.

Anal. Calcd for $C_{50}H_{62}N_2O_8$: C, 73.4; H, 7.6. Found: C, 73.1; H, 7.3.

By similar processes using the appropriate dialkylcadmium the following ketones were obtained: 6,14-*endo*-etheno-7α-valeryltetrahydrothebaine (II, R = *n*-Bu, mp 87–90°, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}NO_4$: C, 73.6; H, 7.8. Found: C, 73.7; H, 8.0); 6,14-*endo*-etheno-7α-isovaleryltetrahydrothebaine (II, R = *i*-Bu, mp 89–90°, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{26}H_{33}NO_4$: C, 73.6; H, 7.8. Found: C, 73.4; H, 8.0); 6,14-*endo*-etheno-7α-(4-methylpentanoyl)tetrahydrothebaine (II, R = *i*-Am, mp 98–100°, ν_{max} 1715 cm^{-1}. *Anal.* Calcd for $C_{27}H_{35}NO_4$: C, 74.2; H, 8.0. Found: C, 74.2; H, 8.3).

Preparation of Ketones from the Ester II (R = OEt). 6,14-*endo*-Etheno-7α-propionyltetrahydrothebaine (II, R = Et). 6,14-*endo*-Etheno-7α-ethoxycarbonyltetrahydrothebaine (10 g) was extracted from a Soxhlet extractor into a solution of ethylmagnesium bromide, prepared from magnesium (1.67 g), ethyl bromide (7.7 g), and ether (100 ml). The mixture was boiled under reflux for 2 hr and poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, when a viscous gum was obtained. This was triturated with cold methanol, and the solid so obtained was collected. (This was identified as a tertiary carbinol and is described in the following paper.) The methanol solution was acidified with dilute hydrochloric acid and poured into an excess of 2 *N* aqueous sodium hydroxide to give a yellow solution containing some insoluble matter. The insoluble matter (0.4 g) was collected and recrystallized from methanol, when the 7α-propionyl compound II (R = Et) was obtained as prisms, mp 42–45°, identical with the material obtained by the addition of ethyl vinyl ketone to thebaine (see above).

By similar processes, using the appropriate alkyl halide, the following ketones were prepared from the ester: 7α-butyryl-6,14-*endo*-ethenotetrahydrothebaine (mp 84°, identical with the base obtained from the acid chloride II (R = Cl) and propylcadmium); 6,14-*endo*-etheno-7α-oenanthyltetrahydrothebaine (II, R = C_6H_{13}, prisms, mp 210°, yield 6%, ν_{max} 1713 cm^{-1}. *Anal.* Calcd for $C_{28}H_{37}NO_4$: C, 74.4; H, 8.2. Found: C, 74.1; H, 8.4); 6,14-*endo*-etheno-7α-vinylacetyltetrahydrothebaine (II, R = $CH_2CH{=}CH_2$, prisms, mp 99°, from aqueous methanol, yield 5%, ν_{max} 1710 cm^{-1}. *Anal.* Calcd for $C_{25}H_{29}NO_4 \cdot 1.5H_2O$: C, 69.2; H, 7.4. Found: C, 69.2; H, 7.7); 6,14-*endo*-etheno-7α-tetrahydrofurylacetyltetrahydrothebaine (II, R = $CH_2C_4H_7O$, prisms, mp 125°, from aqueous ethanol, yield 6%, ν_{max} 1710 cm^{-1}. *Anal.* Calcd for $C_{27}H_{33}NO_5 \cdot H_2O$: C, 69.0; H, 7.4. Found: C, 68.7; H, 7.1); 6,14-*endo*-etheno-7α-(3-tetrahydrofurylbutyryl)tetrahydrothebaine (II, R = $CH_2CH_2CH_2C_4H_7O$, prisms, mp 98°, from aqueous methanol, yield 4%, ν_{max} 1710 cm^{-1}. *Anal.* Calcd for $C_{29}H_{37}NO_5 \cdot 2H_2O$: C, 67.6; H, 8.0. Found: C, 67.9; H, 8.2); 7α-cyclohexylcarbonyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = C_6H_{11}, prisms, mp 130°, from aqueous methanol, yield 7%, ν_{max} 1713 cm^{-1}. *Anal.* Calcd for $C_{28}H_{35}NO_4 \cdot 3H_2O$: C, 66.8; H, 8.1. Found: C, 66.9; H, 7.8).

Preparation of Ketones from the Nitrile III. Nepenthone (II, R = Ph). The Diels–Alder adduct of thebaine and acrylonitrile (mixture of 7α and 7β forms) (10 g) in dry ether (400 ml) was slowly added to a boiling stirred solution of phenylmagnesium bromide, prepared from magnesium (1.67 g) and bromobenzene (11 g) in ether (250 ml). The mixture was boiled under reflux with stirring for 5 hr, and then poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, leaving a solid residue, which was heated on the water bath for 30 min with 2 *N* hydrochloric acid (150 ml). The acid solution was poured into an excess of aqueous sodium hydroxide, and the precipitated base was isolated by ether extraction. Evaporation of the extract afforded a viscous residue, which crystallized in part on trituration with methanol. The solid was collected and recrystallized, when nepenthone (1.1 g) was obtained as prisms, mp 155°, alone or mixed with an authentic specimen.

(13) We are indebted to Dr. J. J. Brown, Miss C. T. Nora, and Mr. C. Piddacks for details of this separation of the pure 7α and 7β isomers.

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 75.8; H, 6.6. Found: C, 75.6; H, 6.5.

In a similar manner, the following ketones were prepared in poor yield from *o*- and *p*-tolylmagnesium bromide: 6,14-*endo*-etheno-7α-(2-methylbenzoyl)tetrahydrothebaine (prisms, mp 223°, ν_{max} 1690 cm^{-1}. *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8. Found: C, 75.7; H, 7.1); 6,14-*endo*-etheno-7α-(4-methylbenzoyl)tetrahydrothebaine (prisms, mp 196°, ν_{max} 1690 cm^{-1}. *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8. Found: C, 75.8; H, 6.7).

7α,7′α-Bis(1-hydroxy-1-methyl-3-oxopropano)-6,14-*endo*-ethenotetrahydrothebaine (IX, R = H). 7α-Acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me) (5 g) in anhydrous benzene (20 ml) was added with vigorous stirring to a solution of anhydrous magnesium iodide (3.6 g) in ether (50 ml) and benzene (20 ml) at room temperature. A white precipitate formed almost immediately. After 15 min the mixture was decomposed by the addition of aqueous ammonium chloride. The ether–benzene layer was separated, dried, and evaporated, when a viscous gum was obtained. Chromatographic separation of this product on silica plates using a system of a 7:4:1 mixture of ethyl acetate, 2-propanol, and water showed it to contain three components in the ratio of approximately 3:6:1. Preparative plate chromatography using the same system afforded specimens of the two major components. The component with greatest R_f value (30%) was identified as 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me). The 60% component (intermediate R_f value) was obtained as off-white prisms, mp 150–151°, from methanol, ν_{max} 1715 and 3490 cm^{-1}, and was identified as 7α,7′α-bis(1-hydroxy-1-methyl-3-oxopropano)-6,14-*endo*-ethenotetrahydrothebaine (IX, R = H).

Anal. Calcd for $C_{46}H_{54}N_2O_8$: C, 72.4; H, 7.1. Found: C, 72.3; H, 7.0.

Separation of this ketol was also achieved on alumina plates using ether as solvent, and from these plates the minor component (10%) was also isolated. This has been identified as a product of rearrangement of the ketone II (R = Me) and is described in detail in another publication.[7]

7α,7′α-Bis(1-methyl-3-oxoprop-1-eno)-6,14-*endo*-ethenotetrahydrothebaine. Repeated chromatographic purification of the ketol XVI on alumina plates in ether solution led to the isolation also of a small quantity of a new base, mp 234°, ν_{max} 1690 cm^{-1}. This was also obtained by heating the ketol (70 mg) with 98–100% formic acid (1 ml) at 100° for 10 min. The solution was diluted with water, basified with ammonia, and extracted with ether, when the unsaturated ketone (50 mg) was obtained as white prisms, mp 234°, from methanol.

Anal. Calcd for $C_{46}H_{52}N_2O_7$: C, 74.2; H, 7.0. Found: C, 74.0; H, 7.1.

Charge-Transfer Complex, Thebaine Methiodide–Benzoquinone. Thebaine methiodide (5 g) and benzoquinone (1.5 g) were heated on the water bath in chloroform (25 ml) until separation of an orange crystalline solid began. The mixture was cooled, and the orange complex was collected (5.0 g), mp 205–206°, on rapid heating (lit.[11] mp 205°).

Reduction of Complex. A solution of sodium borohydride (0.1 g) in water (2 ml) was added to a warm stirred solution of the complex (1 g) in ethanol (15 ml). A transient violet color developed, and the solution rapidly became almost colorless. On cooling the solution, thebaine methiodide (0.6 g), mp 224°, was recovered, and on filtration and dilution of the solution with dilute ammonium chloride hydroquinone (0.12 g), mp 170°, was obtained.

Similar results were obtained when the complex in aqueous ethanol was reduced with sulfur dioxide.

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Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. II.[1] Alcohols Derived from 6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine

K. W. Bentley, D. G. Hardy, and B. Meek

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Abstract: A series of secondary and tertiary alcohols have been prepared by the reduction and reaction with Grignard reagents of the aldehyde I (R = H), the ketones I (R = Me, Et, *n*-Pr, and Ph), and their 6,14-ethano analogs. The stereospecificity of the reactions is explained. In this way analgesics of very high potency, up to 500 times that of morphine, have been obtained.

The high analgesic activity of the ketone I (R = Me) and its C-7 epimer, reported in the preceding paper, contrasts with the inactivity of the related esters I (R = OMe or OEt). The effects on the activity of further modifications of the keto group, involving removal of the electron deficiency at the carbon atom, were accordingly studied. Reduction of the ketone I (R = Me) with aluminum isopropoxide affords a product consisting of 95% of one isomer of the secondary alcohol II (R = H, R′ = Me), whereas reduction with sodium borohydride yields an approximately 1:1 mixture of this and the diastereoisomeric alcohol II (R = Me, R′ = H), which was resolved into its components by preparative thin layer chromatography. Since there is more or less free rotation about the bond linking the carbonyl group to C-7, both sides of this group are almost equally accessible to attack by a hydride ion, but in the Meerwein–Pondorff reduction, which proceeds through hydrogen transfer in a cyclic transition state,[2] steric hindrance in the transition state results in the preferential transfer of hydrogen to one

(1) (a) Part I: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967). (b) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963). (c) This work is covered by British Patent 925,723.

(2) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 2641 (1949).