[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

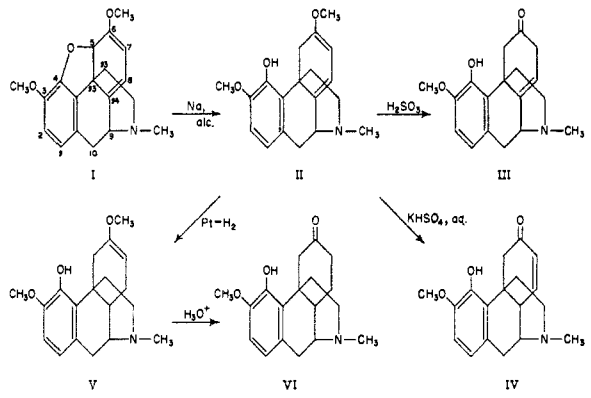
The Reduction of Thebaine

BY GILBERT STORK

The structures previously assigned to phenolic dihydrothebaine and β-dihydrothebaine are shown to be incorrect. The consequences of the recognition of the true structures of these substances are discussed.

The presence in thebaine (I) of a conjugated diene system as well as an allylic ether function leads one to expect that the reduction of that alkaloid by catalytic or chemical means would lead to a variety of substances. It is the purpose of this paper to re-examine the evidence on which are based the structures proposed for phenolic dihydrothebaine,[1,2,3] obtained by the reduction of thebaine with sodium and alcohol, and for β-dihydrothebaine which results from the reduction of the alkaloid with lithium aluminum hydride.[4]

The sodium and alcohol reduction of thebaine was first investigated by Freund and his associates, and the phenolic nature of the reduction product was recognized by Small and Browning who termed the substance phenolic dihydrothebaine and assigned to it structure II, compatible with the results of hydrolysis and hydrogenation experiments. Small and Browning's interpretation of these reactions is



Phenolic dihydrothebaine was shown to give, on hydrolysis with warm sulfurous acid, a substance, α-thebainone, which appeared to be the β,γ-unsaturated ketone III, while stronger acid conditions ($KHSO_4$ solution) led predominantly to β-thebainone (IV) an α,β-unsaturated ketone which must have the unnatural configuration at C_{14} since it is not identical with the well-known thebainone, also formed in small amounts together with α-thebainone in the hydrolysis. Catalytic hydrogenation of phenolic dihydrothebaine gives a substance which is hydrolyzed to dihydrothebainone (VI) and must then be an enol ether. Small and Browning formulated it as V, "$\Delta^{6,7}$-dihydrothebainone methyl enolate."

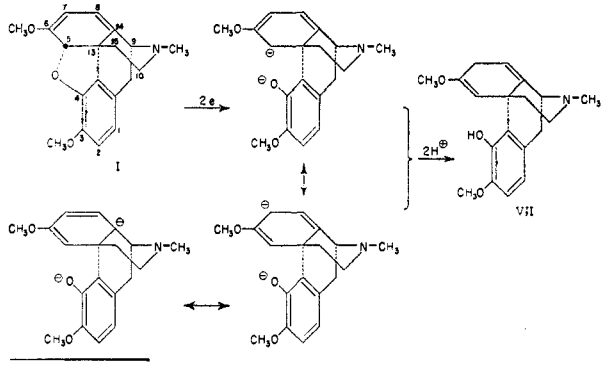
All the reactions just mentioned are compatible with the structure II proposed by Small and Browning for phenolic dihydrothebaine, although they do not establish it. In particular, the following facts are not reconcilable with the proposed structure: (1) The formation of a homoannular *conjugated* diene in good yield by a sodium and alcohol reduction in which a large excess of sodium is used is *a priori* unlikely.

(2) The ultraviolet absorption spectrum of phenolic dihydrothebaine has been measured and found to have a maximum at 282 mμ with log ε 3.3.[5] Now, although it is true that all the morphine alkaloids have a maximum at about 282–284 mμ due to the substituted catechol system, the presence or absence of a further absorbing system in that region is easily discernible if the *intensity* of the absorption is taken into account. For instance, those substances in which the light absorption is due solely to the aromatic system have a log ε at 284 mμ around 3.2, as expected,[6] while when the absorbing system of an alkoxy diene is superimposed on that due to the substituted benzene ring the intensity is much higher.[7]

The absence of a high intensity absorption in phenolic dihydrothebaine shows that a conjugated alkoxydiene system cannot be present in that molecule.

(3) The infrared absorption spectrum of 1-alkoxy-1,3-dienes is characterized by a strong band at about 6.2 μ.[8] This band is present in thebaine (Fig. 3). In contrast to this, the highly characteristic spectrum of phenolic dihydrothebaine (Fig. 1) is remarkable for the complete absence of a band at 6.2 μ, indicating that the absorbing system is different from that present in thebaine.

The facts which have just been discussed make it clear that phenolic dihydrothebaine must be an *unconjugated* methoxy diene, for which only structure VII can be written.



(1) M. Freund and C. Holtoff, *Ber.*, **32**, 168 (1899).
(2) L. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).
(3) K. W. Bentley and R. Robinson, *Experientia*, **6**, 353 (1950).
(4) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **33**, 863 (1950).
(5) L. Small, L. J. Sargent and J. A. Bralley, *J. Org. Chem.*, **12**, 839 (1947).
(6) Codeine hydrochloride: λmax 284, log ε 3.1 (P. Steiner, *Bull. soc. chim. biol.*, **6**, 231 (1924)).
Dihydrothebainol-6-methyl ether: λ_{max}. 284, log ε 3.2 (H. Schmid and P. Karrer, ref. 4).
(7) Thebaine hydrochloride: λ_{max}. 283, log ε 3.8; P. Steiner, ref. 6. "β-Dihydrothebaine": λ_{max}. 284, log ε 4.05; H. Schmid and P. Karrer, ref. 4.
(8) Observations in this Laboratory.

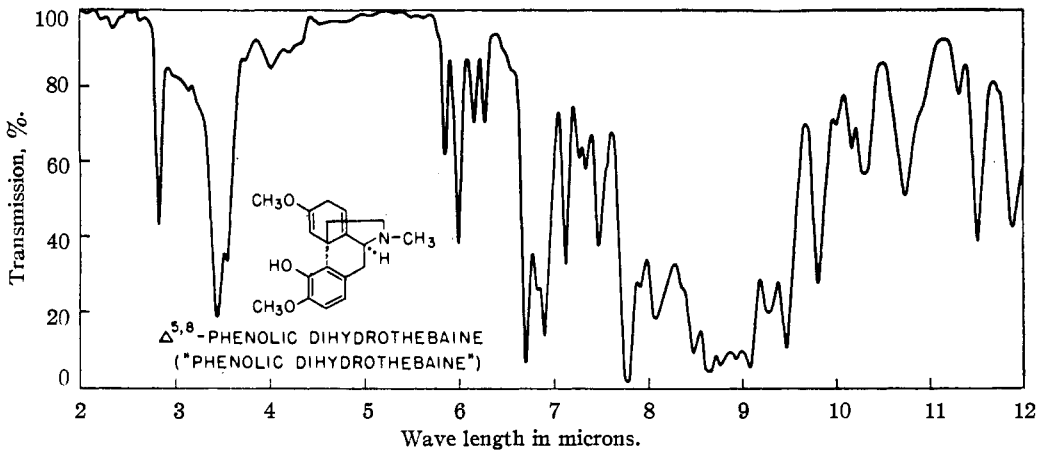
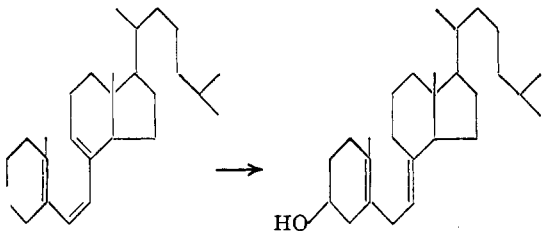


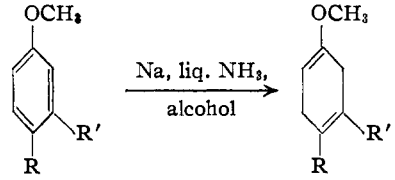
Fig. 1.

The course of the reduction process is illustrated in the scheme shown above. The addition of electrons at the oxygen atom of the oxide bridge results in the formation of a mesomeric anion, as shown. Addition of a proton at C_7 results in the formation of the thermodynamically unstable unconjugated substance. In contrast to the process encountered in the acidification of the salt of a nitroparaffin, in which the initially formed *aci*-nitro compound slowly changes to the more stable nitro form, the transformation of the unconjugated phenolic dihydrothebaine to the more stable conjugated substance is a process which requires considerable activation energy (removal of proton from carbon), and the product is determined in this case by rate rather than equilibrium considerations. It is apparent that sodium ethoxide is not a strong enough base to effect the isomerization of phenolic dihydrothebaine to the stable isomer.[9]

The stability of some unconjugated 1,4-dienes in the presence of hot alcoholic sodium ethoxide has been noticed previously. For instance, the reduction of tachysterol or vitamin D_2 with sodium and propyl alcohol leads to the formation of dihydro vitamin D_2.[10]



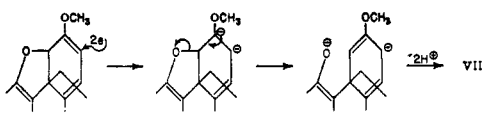
e structure now proposed for phenolic dihydrothebaine is similar to that of the compounds which result by Birch reduction[11] of various substituted benzene derivatives such as dialkyl anisoles, for example



Experience in this Laboratory has shown that such dihydroanisoles have uniquely characteristic infrared absorption spectra, with two narrow bands at 5.9 and 6.0 μ which differ from the carbonyl bands, which also occur in this region, by their lower intensity and their sharpness. The relative intensity of the two bands varies but their position is remarkably constant in various dihydroanisole derivatives. The infrared spectrum of a typical member of this class, 5-[2-dimethylaminoethyl]-1-methoxy-4-methyl-1,4-cyclohexadiene,[12] is reproduced in Fig. 2. The absorption bands at 5.9 μ and 6.0 μ in phenolic dihydrothebaine (Fig. 1) correspond exactly to those in the model dihydroanisole and establish the correctness of structure VII which is now proposed for phenolic dihydrothebaine.

The revision of the structure of phenolic dihydrothebaine necessitates the formulation of its previously mentioned catalytic hydrogenation product, which was shown by Small and Browning[2] to be an enol ether of dihydrothebainone, as Δ^5-dihydrothebainone enol methyl ether (VIII) instead of the Δ^6-structure which had been ascribed to it. This further renders incorrect the Δ^5-structure as-

(9) There is an alternate process by which one might envisage the formation of phenolic dihydrothebaine



This is however considered unlikely because S_N2' reactions should be difficult when they involve attack by highly concentrated negative charges, as in this case, a process rendered further unlikely by the electrical effect of the methoxyl group.

(10) F. V. Werder, *Z. physiol. Chem.*, **260**, 119 (1939); S. K. Reichel and M. Deppe, *ibid.*, **239**, 143 (1936).

(11) A. J. Birch, *J. Chem. Soc.*, 593 (1946). It is interesting that Bentley and Robinson have been able to prepare phenolic dihydrothebaine in excellent yield by the reduction of thebaine with sodium in liquid ammonia. Experiments by Dr. Weisenborn in this Laboratory have shown that this result can be obtained *only* in the presence of added ethanol. The methine base, m.p. 99°, from phenolic dihydrothebaine obtained by these workers may well be a $\Delta^{5,8}$ rather than a $\Delta^{6,8}$ substance. It may also be noted that, in the absence of further evidence, thebenone and β-thebenone have a six-membered ether ring as postulated by Small and Browning,[2] and as would be expected, rather than the five-membered structure used by Bentley and Robinson. This applies also to the substances they describe as 6-methoxythebentriene, tetradehydrothebenone, morphirane and β-morphirane.

(12) This substance was prepared in this Laboratory by Dr. S. S. Wagle.

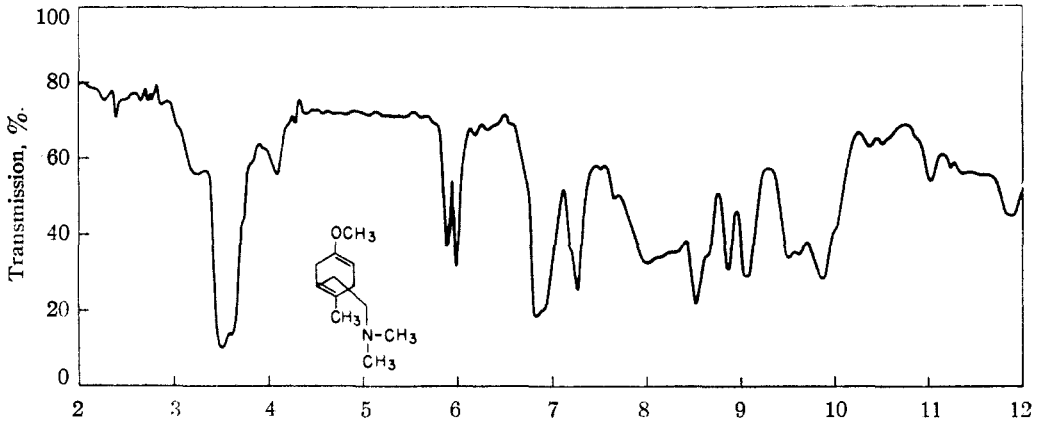
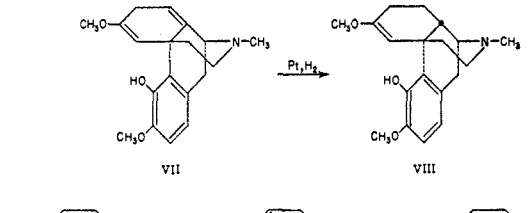
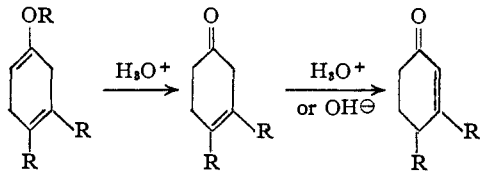


Fig. 2.

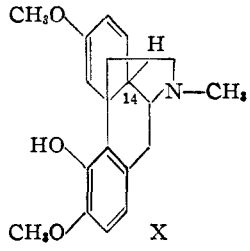
signed to the enol ether obtained by the neutral catalytic hydrogenation of thebaine or of $\Delta^{5,7}$-thebainone enol methyl ether (IX), as well as by the sodium and alcohol reduction of the latter substance. This second enol ether of dihydrothebainone must be correctly expressed by the Δ^{6}-dihydrothebainone enol methyl ether structure (V). The formulas previously assigned to the two dihydrothebainone enol methyl ethers must then be interchanged, and the reductions just discussed may be represented as



The previously mentioned formation of the β,γ-unsaturated ketone, α-thebainone, on mild acid hydrolysis of phenolic dihydrothebaine finds an exact parallel in the demonstration by Birch[11] that 2,5-dihydroanisoles can be hydrolyzed to the β,γ-unsaturated ketones. As in the case of phenolic dihydrothebaine and, as would be expected, stronger acid conditions result in the formation of the α,β-unsaturated isomer

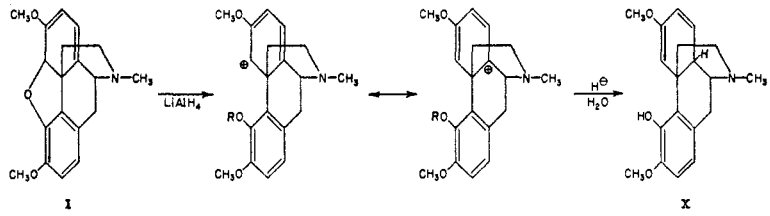


The reduction of thebaine with lithium aluminum hydride will now be considered.[4] Schmid and Karrer have shown that this results in the formation of a phenolic dihydro compound which can be hydrolyzed to β-thebainone (IV), and which they claimed to be correctly represented by formula X, the unnatural configuration at C_{14} being expressed by their description of the compound as "β-dihydrothebaine."[4]



The formation of β-dihydrothebaine was presumed to proceed by the path I → X (below).

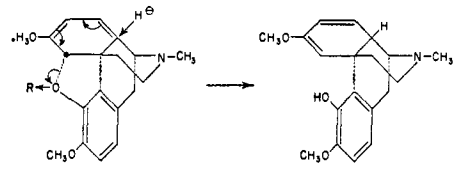
The production of a substance with the structure postulated by Schmid and Karrer,[4] and accepted by Bentley and Robinson,[3] attracted our attention because it is not compatible with the stereochemistry which can be considered established for



thebaine (I) and codeine.[13] The following two points can be made: (1) If the reaction took place by addition of a hydride ion (from AlH_4^-) at C_{14}, as in Schmid and Karrer's interpretation, the result would be the attachment of hydrogen on the *unhindered* side of the molecule, *trans* to the benzene ring, as shown below[14]

(13) See G. Stork, Stereochemistry and Reaction Mechanisms of the Morphine Alkaloids in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, New York, N. Y., 1952.

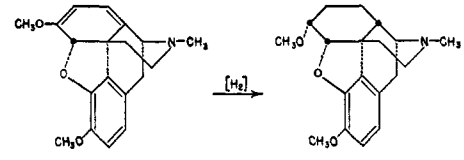
(14) Compare the formation of 14-hydroxycodeinone from thebaine and H_2O_2–acetic acid, as well as numerous hydrogenation experiments on $\Delta^{6,14}$ compounds, reference 13.



IX

This would result in the formation of a substance (IX) with the *same* configuration at C_{14} as codeine. Structure IX, however, represents thebainone enol methyl ether, a substance of unambiguous structure[2] which is clearly not the product obtained by Schmid and Karrer.

(2) The assumption by Schmid and Karrer that their compound is the C_{14} epimer of thebainone enol methyl ether is inconsistent with the fact that they obtained by catalytic hydrogenation of their so-called β-dihydrothebaine a substance obviously identical with the dihydrothebainol-6-methyl ether obtained by Small and Browning as one of the products of the neutral hydrogenation of thebaine. Dihydrothebainol-6-methyl ether is a compound with the natural configuration at C_{14} shown in XI since it results from the hydrogenation of an 8,14-double bond, a process which must lead to the introduction of hydrogen at C_{14} *trans* to the phenyl ring[14] (*cf. inter alia* the hydrogenation of thebaine to dihydrocodeine methyl ether (XII) shown below).

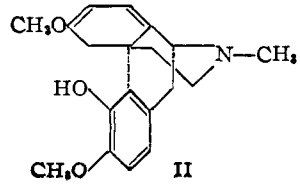


I XII

It would not be expected that a substance with the *unnatural* configuration at C_{14} postulated for β-dihydrothebaine would be reduced further to a product with the *natural* configuration at that center.

The ultraviolet absorption spectrum of Schmid and Karrer's product ($\lambda_{max.}$ 284, log ϵ 4.05) shows the presence of an alkoxy diene system superposed on the substituted guaiacol moiety, thus giving rise to the high intensity observed, in contrast to the intensity associated with the substituted guaiacol ring alone, as in dihydrothebainol-6-methyl ether (XI) for instance ($\lambda_{max.}$ 284, log ϵ 3.2).[1] There are only three possible structures which are phenolic dihydro derivatives of thebaine and which have the required absorbing system.

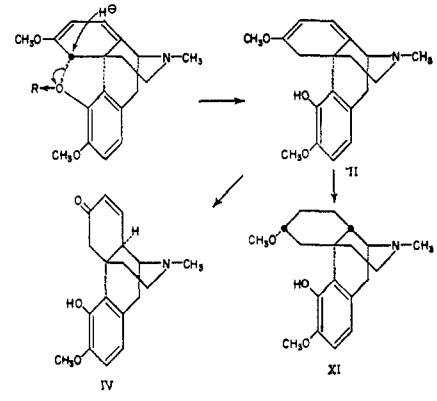
Two of these, IX and X, have already been mentioned and discarded as possible structures for the lithium aluminum hydride product. The third one, formula II, is a completely adequate representation of Schmid and Karrer's dihydro compound. In agreement with this structure, the



II

spectrum of II is closely similar in the 6–6.2 μ region to that of thebaine (Figs 3 and 4).

Structure II was considered by Schmid and Karrer who rejected it because the *different* compound formed by the sodium and alcohol reduction of thebaine, known as phenolic dihydrothebaine, had already been assigned that structure by Small and Browning. It has however, been shown earlier that the correct structure of phenolic dihydrothebaine is actually VII, and there is therefore no difficulty with the assignment to the lithium aluminum hydride reduction product of thebaine of structure II. The term "β-dihydrothebaine" cannot be applied to such a substance which might be described as $\Delta^{6,8}$-phenolic dihydrothebaine.[15b] The formation, hydrolysis, and further reduction of $\Delta^{6,8}$-phenolic dihydrothebaine I are illustrated



IV XI

The foregoing discussion makes it apparent that, contrary to the view of Schmid and Karrer, the mechanism of the formation of their dihydro compound is quite different from that involved in the formation of phenyldihydrothebaine[16] and cannot be said to throw light on it. The difference in the course of the reaction with phenylmagnesium bromide and lithium aluminum hydride serves to emphasize that the latter is a much weaker electron acceptor than magnesium bromide. A well-known illustration of this difference is found in the common occurrence of rearrangements when epoxides are treated with Grignard reagents (magnesium halides), while normal reduction results on treatment with lithium aluminum hydride.

It is of interest to consider here certain conclusions reached by Bentley and Robinson concerning the mechanism of the formation of "β-dihydrothebaine" and "phenolic dihydrothebaine". It is these authors' contention that the observed reductions show that . . . "whereas in the lithium aluminum hydride reduction of thebaine the initial cation isomerizes . . . before addition of H^-, in the sodium ammonia reduction, the anion adds a proton (from the ammonia) without isomerization." Such phenomena are not *isomerizations*, the lithium aluminum hydride reaction almost certainly involves no cation, and it is obvious from the foregoing discussion that the actual structures obtained

(15) NOTE ADDED IN PROOF:—In a paper just published Schmid and Karrer, *Helv. Chim. Acta.*, **34**, 1948 (1951), have accepted the structural conclusions which had been briefly outlined in a previous note on this subject (G. Stork, THIS JOURNAL, **73**, 504 (1951)).

(16) R. Robinson, *Nature*, **160**, 815 (1947).

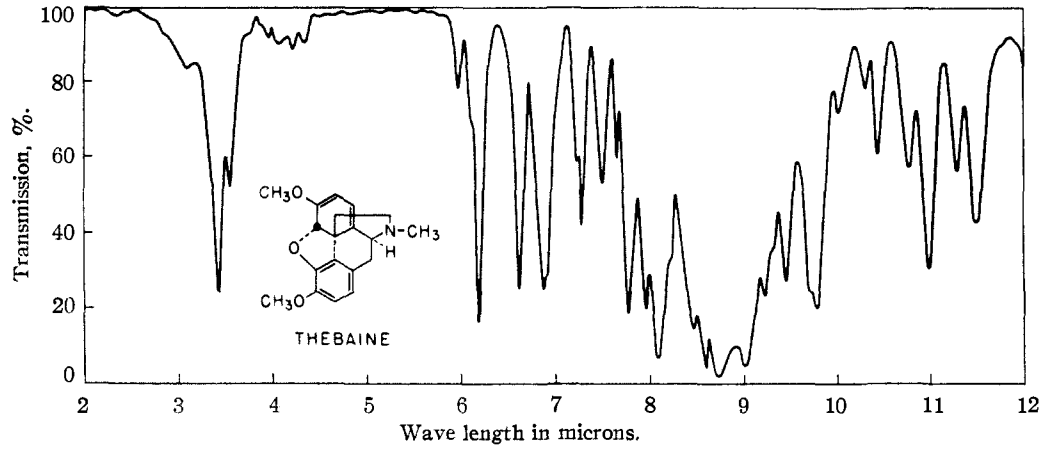


Fig. 3.

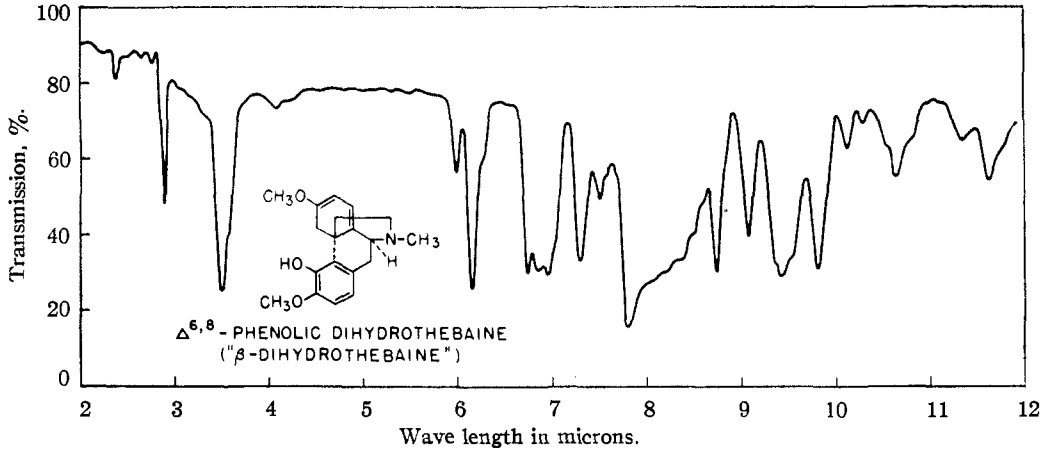
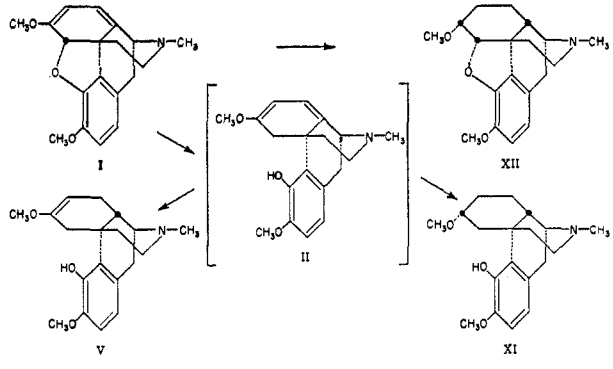


Fig. 4.

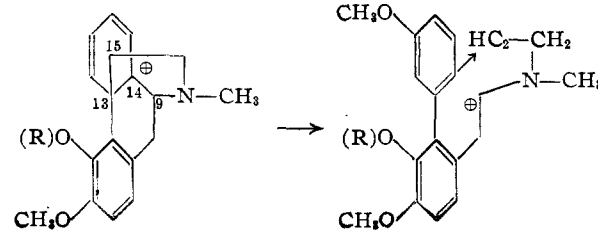
are not in agreement with Bentley and Robinson's formal commentary.

The structural conclusions reached on the structure of "β-dihydrothebaine" and of "phenolic dihydrothebaine" now allow the formulation of the catalytic hydrogenation of thebaine in neutral solution (the Wieland–Kotake reduction)[17] as follows



The intermediacy of $\Delta^{6,8}$-phenolic dihydrothebaine (II) in the reduction to dihydrothebainol-6-methyl ether (XI) and dihydrothebainone Δ^{6}-enol methyl ether (V) (called Δ^{5} by Small and Browning) had been ruled out since "phenolic dihydrothebaine," which was thought to be II, is not reduced to those compounds; the difficulty however is now removed with the assignment to "phenolic dihydrothebaine" of structure VII while the $\Delta^{6,8}$-phenolic dihydrothebaine formula (II) correctly belongs to the so-called β-dihydrothebaine, which Schmid and Karrer have shown to be reducible to dihydrothebainol-6-methyl ether.

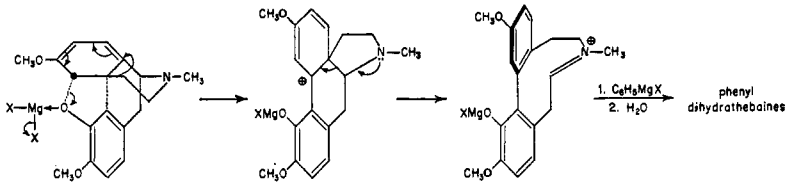
Some comment on Schmid and Karrer's discussion of the mechanism of formation of phenyl dihydrothebaine is pertinent at this point. These authors state that the change can only be represented in the following way. "The methylethylamine side chain separates as a cation, the electron pair remaining on C_{13} combines with C_{14}^{+} with the formation of a double bond thereby forming an aromatic ring.... The rearrangement takes place, however, with the simultaneous heterolysis of the C_{14}–C_{9} bond resulting in a C_{14} anion and a C_{1} cation. The C_{14}–C_{15} bond is then formed by the reaction of the $C_{14}^{\ominus}$ and the $C_{15}^{\oplus}$." The transformation was pictured as



(17) H. Wieland and M. Kotake, *Ber.*, **58**, 2009 (1925). This was reinvestigated by Small and Browning (ref. 2) who were unable to formulate the process satisfactorily.

It seems, however, that the process thus described and illustrated is equivalent to the statement that as C_{15} becomes attached to C_{14}, the dihydroanisole ring becomes aromatic and the C_9–C_{14} bond is broken. The more detailed description of Schmid and Karrer has little heuristic value. Further, the detachment of the ethanamine chain as a *cation* is observed only in those morphine derivatives in which the C_9–N bond has previously been broken, thus allowing the stabilization of the incipient C_{15} cation by the spacially proximate basic nitrogen.[18] This situation cannot occur when the C_9–N bond is present and the loss of C_{15} as a cation becomes equivalent to the formation of an unstabilized primary carbonium ion. This applies even more strongly to Schmid and Karrer's representation where the presence of a positive charge on C_9 would make still more difficult the stabilization of a C_{15} cation by the nitrogen electrons.[19]

The change thebaine → phenyldihydrothebaine seems to be most simply represented as



The first step is a simple Wagner–Meerwein rearrangement which is here shown as a concerted process, although this is not an essential feature of the scheme, while the second step is merely the establishment of the aromatic ring with transfer of the positive charge to the nitrogen atom. The resulting asymmetric intermediate now reacts with a phenyl anion with the formation of optically active phenyldihydrothebaines.

(18) The rearrangements of the morphine alkaloids in which the side chain is *not* lost (*e.g.*, apomorphine, morphothebaine, metathebainone, etc.) although sometimes said to be the result of a "cationoid" tendency of the ethanamine chain, obviously never involve C_{15} as a detached cation, since in the migration from C_{13} to C_{14}, C_{15} is always bonded to one or both of these atoms.

(19) The separation of C_{15} as a "cation" is observed only in the special circumstance noted above, *e.g.*, in the change from α-methyl morphimethine to methylmorphol under the influence of HCl.

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[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

4-Arylcyclohexanones[1]

BY E. C. HORNING,[2] M. G. HORNING, M. S. FISH[3] AND M. W. RUTENBERG[4]

A new method of synthesis of 4-arylcyclohexanones from the corresponding arylacetonitriles is described.

An apparently general method for the synthesis of 4-arylcyclohexanones, from the corresponding arylacetonitriles, is outlined in Fig. 1. We have applied this new sequence of established reactions to the preparation of 4-(3',4'-dimethoxyphenyl)-cyclohexanone, and have confirmed the validity of the method through the preparation of known 4-phenylcyclohexanone. The trinitrile II, obtained by the Bruson cyanoethylation of I, was converted to the dimethyl ester with hydrogen chloride in methanol. The ester was cyclized through the use of sodium–potassium alloy, without affecting the tertiary nitrile group, to the ester IV. Hydrolysis–decarboxylation of IV in hydrochloric–acetic acid gave V, which was converted to the ketal VI with ethylene glycol. This method of protection of the ketone function was employed by Schinz and Schäppi,[5] in connection with a sodium–alcohol reduction; we have used it here to protect the ketonic group during removal of the tertiary cyano group by the procedure of McElvain.[6] The McElvain method, using sodium and ethanol in toluene, gave excellent results in this application. Hydrolysis of the ketal VII by a method involving steam distillation to remove ethylene glycol proved satisfactory.

4-Phenylcyclohexanone may be obtained from 4-phenylphenol, by reduction to 4-phenylcyclohexanol, followed by oxidation. This method is not sufficiently general to permit its use for the preparation of certain methoxyphenylcyclohexanones, and the procedure described here was therefore developed for this purpose.

Experimental

All melting points are corrected.

γ-Cyano-γ-(3',4'-dimethoxyphenyl)-pimelonitrile (IIA).—To a solution of 159 g. (0.9 mole) of 3,4-dimethoxyphenylacetonitrile in 300 ml. of *t*-butyl alcohol there was added with stirring 5 ml. of acrylonitrile (freshly distilled) and a solution of 5 g. of potassium hydroxide in 10 ml. of methanol. Acrylonitrile (95 g., 1.8 mole) was added at such a rate that the temperature remained at 30–40°. Stirring was continued for two hours after addition was complete. In order to recrystallize the product, 100 ml. of ethanol (95%) was added, and the mixture was heated until a solution resulted. While cooling and stirring, 200 ml. of water was added, the crystallized product was removed by filtration, washed with 50% ethanol and air-dried. There was obtained 222 g. (86%) of light tan crystals, m.p. 112–114°. Recrystallization from methanol gave a colorless sample, m.p. 112–113°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3$: C, 67.82; H, 6.05. Found: C, 67.95; H, 5.89.

Dimethyl γ-Cyano-γ-(3',4'-dimethoxyphenyl)-pimelate (IIIA).—A stirred solution of 215 g. of crude γ-cyano-γ-

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(5) Schinz and Schäppi, *Helv. Chim. Acta*, **30**, 1483 (1947).

(6) Walter and McElvain, THIS JOURNAL, **56**, 1614 (1934).