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THE PHENYLDIHYDROTHEBAINES

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In a recent publication on the methyldihydrothebaines, Small and Fry (1) pointed out in detail the inexplicable peculiarities of phenyldihydrothebaine, and demonstrated that these remarkable properties are also shown by the four isomeric methyldihydrothebaines. These peculiarities are, briefly, resistance to hydrogenation, resistance of the enol ether group to hydrolysis, and retention of the vinyl group in the final step of exhaustive methylation. While their work did not result in a satisfactory structural formula for this type of thebaine derivative, it did establish the fact that the peculiarities mentioned are not the result of some specific influence (steric or "negative") of the phenyl group. The appearance of isomeric methyldihydrothebaines in the Grignard reaction led to the prediction (ref. 1, page 513, footnote) that the hitherto-known phenyldihydrothebaine (2, 3, 4) must be a mixture of isomers. With the object of settling this point, as well as to obtain additional structural evidence, the long-dormant phenyldihydrothebaine problem has been reopened.

THE ISOMERS

The reaction of thebaine (I) with phenylmagnesium bromide in ether, or preferably in benzene because of better solubility and more rapid reaction, gives a sirupy product which constitutes the so-called "phenyldihydrothebaine." This can be separated through the hydrochloride into two isomeric compounds of formula $C_{25}H_{27}NO_3$, differing empirically from thebaine, $C_{19}H_{21}NO_3$, by C_6H_6. The major product, obtained in a yield of 75–78% is named (+) α-phenyldihydrothebaine (II), in analogy with the methyl series. The minor product, yield 7–8% is (+) δ-phenyldihydrothebaine (III). Although the two compounds are identical in molecular formula, they have different physical properties, as do their salts and primary degradation products. They are phenolic (alkali solubility, diazosulfanilic acid reaction), and, as would be expected, show the same abnormalities as the mixture that had been studied by all previous investigators. Neither base can be hydrogenated in a normal manner like the parent thebaine (the reduction to phenyltetrahydrothebaimine described later is a degradative reduction), nor hydrolyzed at the 6-methoxyl (enol ether?) group by boiling concentrated hydrolchloric acid.

As in the methyldihydrothebaine series, (+) α-phenyldihydrothebaine can be caused to isomerize by very slow distillation in a high vacuum, or by heating in an evacuated sealed tube at 200° for 80 hours. About 75% of the α base is re-

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covered, together with 16% of a new phenyldihydrothebaine which is the optical opposite of the (+) δ-phenyldihydrothebaine described above, and will therefore be designated as (−) δ-phenyldihydrothebaine (IV). Its physical properties and those of its derivatives are identical with those of the corresponding (+) δ compounds except that optical rotations are equal and opposite in direction. The

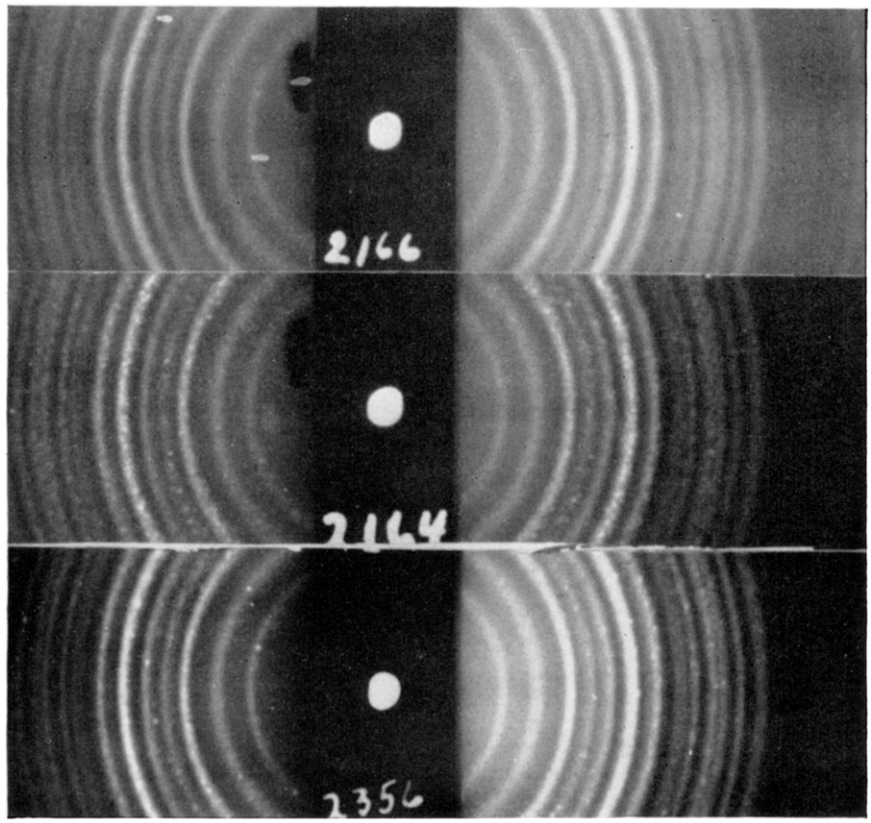


FIG. 1. X-RAY DIFFRACTION PATTERNS; 2166, (+) α-PHENYLDIHYDROTHEBAINE PERCHLORATE; 2164, (−) α-PHENYLDIHYDROTHEBAINE PERCHLORATE; 2356, (+) α-PHENYLDIHYDROTHEBAINE PERCHLORATE FROM REARRANGEMENT OF (−) δ-PHENYLDIHYDROTHEBAINE

new isomer corresponds to the "η-methyldihydrothebaine" of Small and Fry.[3] The transformation is probably an equilibrium reaction lying largely in the (+) α direction, for if pure (−) δ-phenyldihydrothebaine is subjected to the same treatment, 57% yield of (+) α-phenyldihydrothebaine is obtained and only traces of the starting material.

[3] The unfortunate nomenclature for the optical opposites was adopted at that time through over-caution in interpreting the transformation. Since assignment of the Greek letters is at best arbitrary, the δ title is retained to avoid further complicating a confused situation. This introduces the anomaly that some compounds designated as (+) are actually levorotatory, and vice versa.

When (+) δ-phenyldihydrothebaine (III) is treated in like manner, a fourth isomer, (−) α-phenyldihydrothebaine (V) results (corresponding to "ω-methyldihydrothebaine"). This is the optical antipode of (+) α-phenyldihydrothebaine. As indicated above, the equilibrium seems to be in favor of the α types, for this rearrangement gives 74% yield of (−) α and 24% recovery of (+) δ. Scarcity of material prevented demonstration of the reverse rearrangement of (−) α to (+) δ. In no instance did these rearrangements give rise to molecular

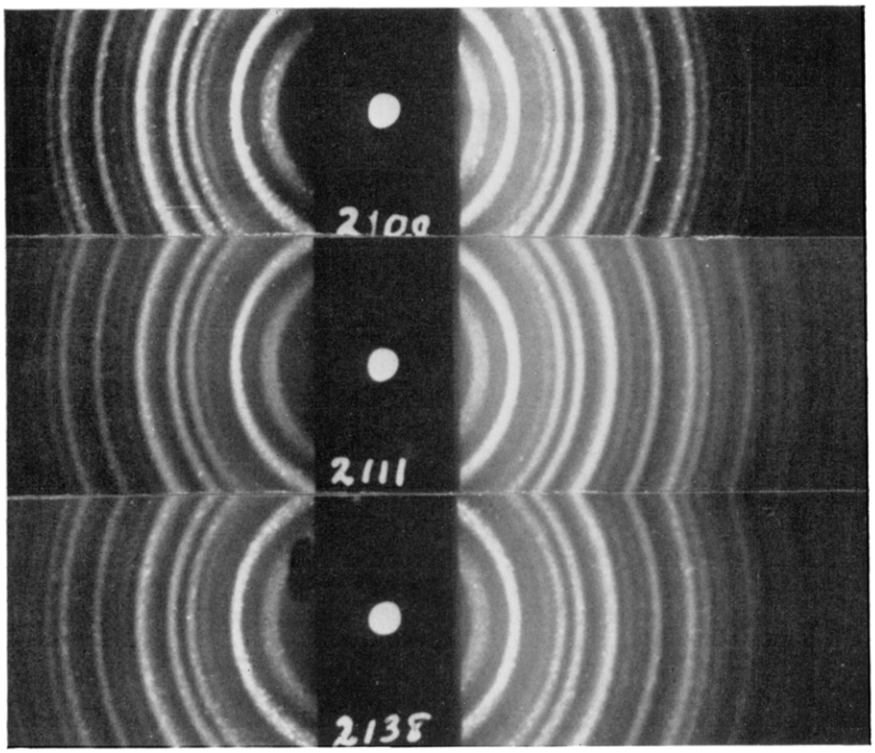


FIG. 2. X-RAY DIFFRACTION PATTERNS; 2100, + δ-PHENYLDIHYDROTHEBAINE; 2111, (−) δ-PHENYLDIHYDROTHEBAINE; 2138, (+) δ,(−) δ MIXED CRYSTAL

compounds of the type observed in the methyl series, nor did the pairs of antipodes give crystalline racemates, although some of their degradation products did.

In support of the evidence for optical isomerism given by melting points and rotatory values of these bases and their derivatives, we have examined x-ray diffraction patterns, which for optical opposites must of course be identical. Since the α bases are liquids, we show in Fig. 1 the patterns of (+) and (−) α-phenyldihydrothebaine perchlorates, and also the pattern of the (+) α-perchlorate obtained by rearrangement of (−) δ-phenyldihydrothebaine; apart from other physical properties recorded, the identity is obvious. Fig. 2 shows the patterns of the (+) and (−) δ bases, and of a recrystallized mixture of equal amounts of these, where racemate formation did not take place. The properties of the four isomers and some of their derivatives are summarized in Table I. We wish to

TABLE I

PHYSICAL PROPERTIES OF THE ISOMERIC PHENYLDIHYDROTHEBAINES AND SOME DERIVATIVES

NAME	BASE		PERCHLORATE		METHIODIDE	
	M.P., °C.	$(\alpha)_D$	M.P., °C.	$(\alpha)_D$	M.P., °C.	$(\alpha)_D$
(+) α-Phenyldihydrothebaine (II)	liq'd	+10.2	248 d.	+8.2[a] +35	216–218	+42.7
(−) α-Phenyldihydrothebaine (V)	liq'd	−10	248 d.	−8.0[a] −35	216	−43.6
(+) αPhenyldihydrothebaine isomethine (XXI)	101	−280	111–117[b]	−197		
(−) α-Phenyldihydrothebaine isomethine (XXXIII)	101	+281	111–116[b]	+197		
(+) δ-Phenyldihydrothebaine (III)	143.5	−131[a] −109	209–213	−44.5	206–208	−43
(−) δ-Phenyldihydrothebaine (IV)	143.5	+131[a] +110	209–213	+42.8	206–208	+44
(+) δ-Phenyldihydrothebaine isomethine (IX)	117–119	+153	114–116[b]	+89.6	202–203	+108
(−) δ-Phenyldihydrothebaine isomethine (XXX)	117–119	−154	114–116[b]	−90.0	202–203	−105
(+) Phenyltetrahydrothebaimine (VIII)	120–121	−35.0[a] −4.2			235[c]	−5.2
(−) Phenyltetrahydrothebaimine (XIII)	120–120.5	+35.5[a] +4.9			235[c]	+5.3
rac. Phenyltetrahydrothebaimine (XIV)	134	0.0				
(+) Hexahydrophenyltetrahydrothebaimine (XVI)	129–130.5	−9.0			231–232.5	−4.8
(−) Hexahydrophenyltetradrothebaimine (XXXI)	128–129.5	−10.0			231–232	+6.6
(+) Vinylphenyldihydrothebaol (XIX)	149	+47.1				
(−) Vinylphenyldihydrothebaol (XXIII)	147–148.5	−47.4				
rac. (?) Vinylphenyldihydrothebaol (XXIV)	146–147	0.0				

[a] Rotations in different solvents.
[b] Solvated.
[c] N-methomethiodide.

emphasize at this point that the designations (+) and (−) are based entirely on derivation, and relationship to the methyl series, and not on actual direction of rotation, since in many transformations the rotational direction is reversed. Furthermore, the structural formulas given are based on the arbitrary assumption of a 1,4-addition of the Grignard reagent, and are offered only as illustrative of the changes taking place in reactive portions of the molecule.

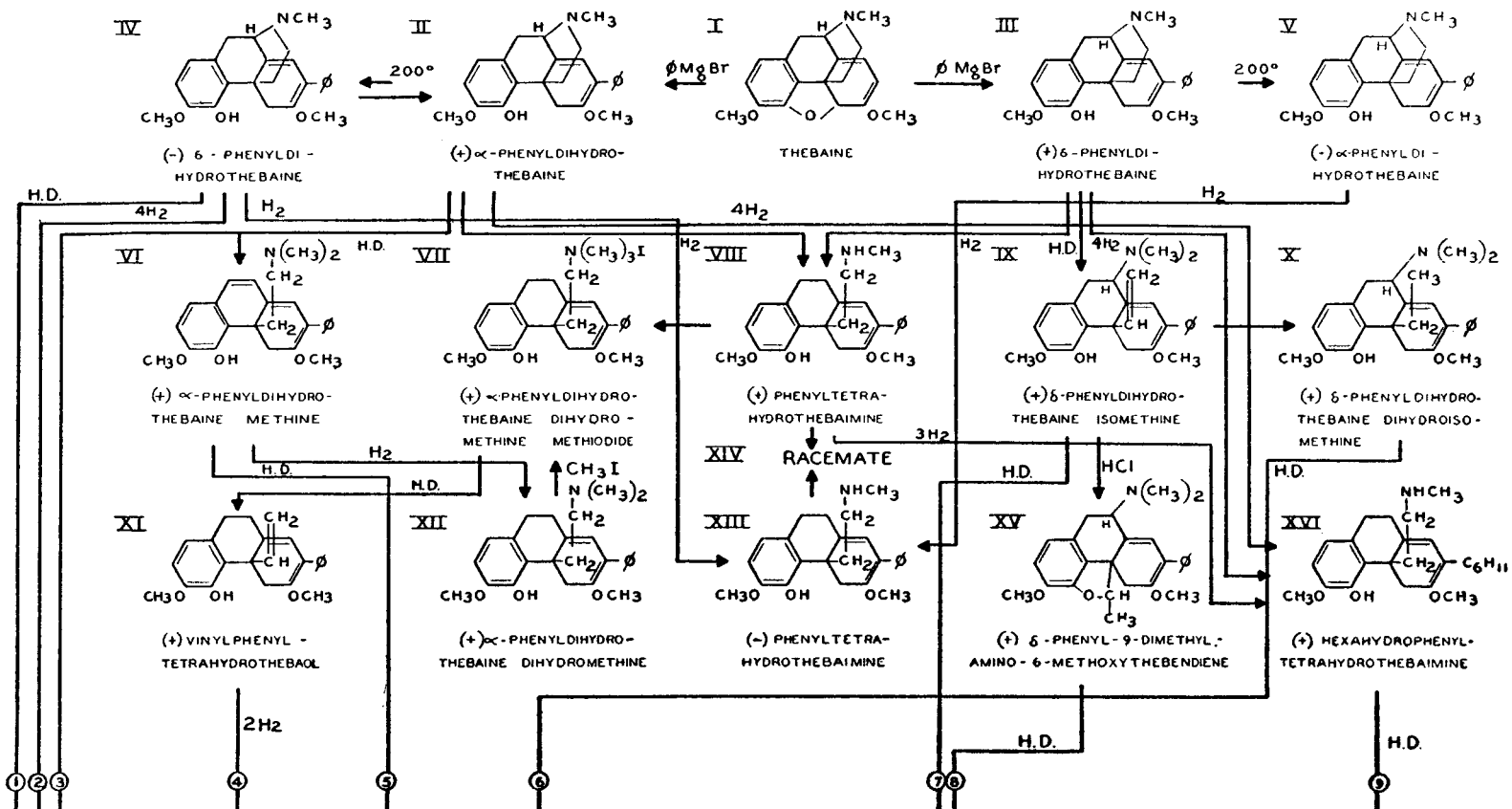
DEGRADATION OF THE PHENYLDIHYDROTHEBAINES

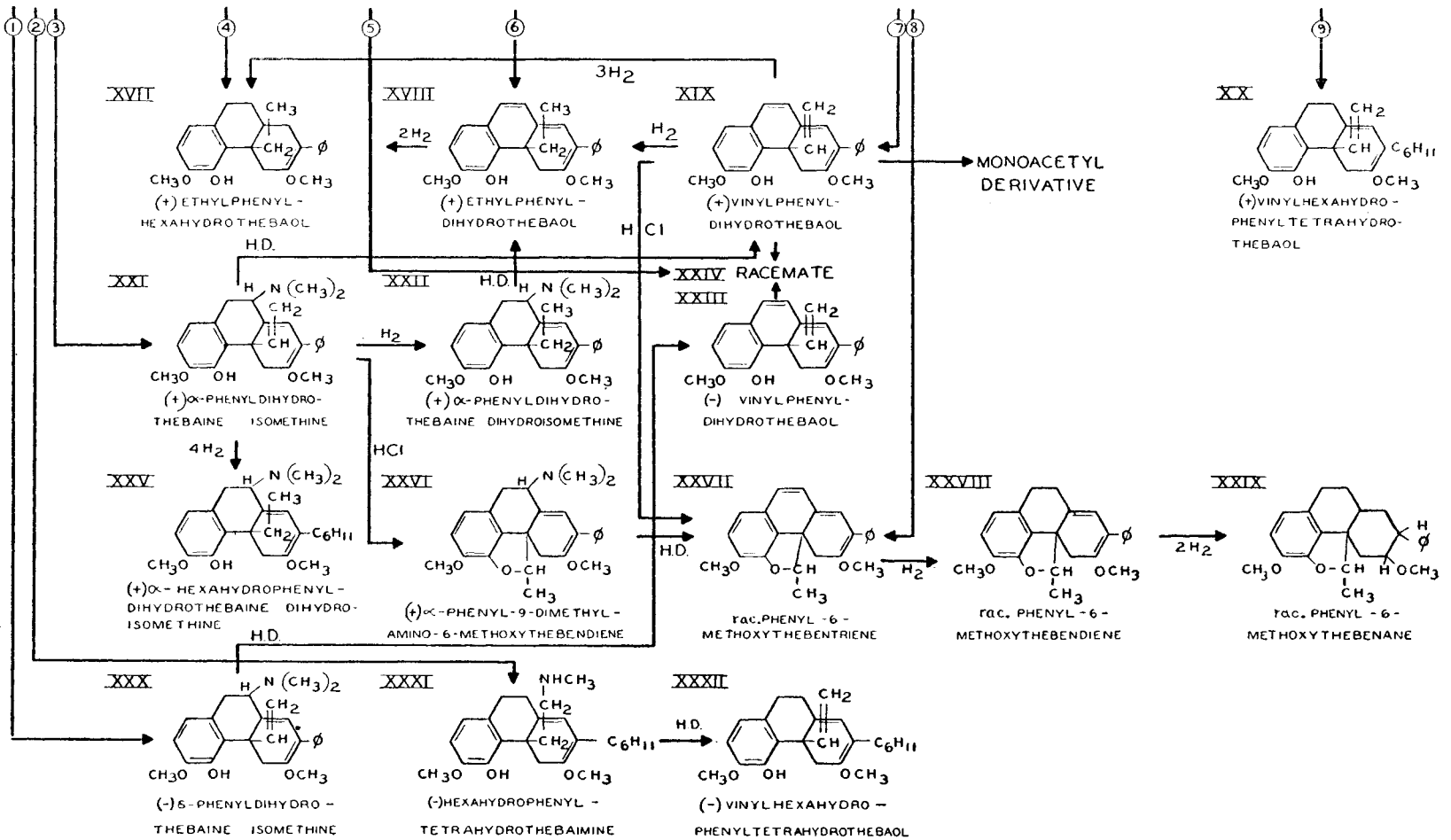
The degradation of the phenyldihydrothebaines proceeds parallel to that of the methyl analogs, and furnishes strong support for the interpretation of the results in that series. Although the phenyl types are more resistant to alkaline degradation, all except the rare (−) α isomer have been converted to the nitrogen-free end-products. Like the methyl analogs, the phenyldihydrothebaines undergo rupture of the nitrogen-containing ring chiefly in the abnormal manner to give isomethines, with nitrogen still attached to C-9, and carbons 15 and 16 in the form of a vinyl group. No other morphine derivatives containing the typical carbon-nitrogen morphine skeleton have ever been observed to break down in this way. This is an important consideration, which may indicate a fundamental structural change. On the other hand, in the majority of degradations recorded (see ref. 5, pp. 285, 286) the basic product in the final step was not identified, or recorded only as trimethylamine; only in those where β-hydroxyethyldimethylamine or a similar fragment was identified is it certain that the normal mechanism was involved. It should be pointed out here, that this initial abnormal course of the first step in the Hofmann degradation cannot be considered responsible for the anomalous retention of the vinyl group in the second step, for the normal methine type (a minor product from the first step) likewise breaks down (VI → XXIV) to a nitrogen-free product which still carries these two carbon atoms.

The Hofmann degradation of (+) α-phenyldihydrothebaine methiodide results in 72% yield of the isomethine (XXI), 14% undegraded base (presumably by splitting off methanol, which is not uncommon), and 3% of the normal methine (VI). This is the only instance in which both methines were isolated. The isomeric methines can be differentiated by their behavior towards boiling concentrated hydrochloric acid; the normal methine is entirely unaffected, whereas the vinyl group of the isomethine undergoes cyclization with the 4-hydroxyl to give (+) α-phenyl-9-dimethylamino-6-methoxythebendiene (XXVI), which, in contrast to the isomethine, is no longer phenolic, and is indifferent towards catalytic hydrogenation. This reaction is similar to that observed in the methyldihydrothebaines, where Small and Fry demonstrated that the mechanism involved addition of the elements of water to the vinyl group, followed by cyclodehydration. In agreement with this concept, the hydrogenated (one mole) isomethine (XXII), which has an ethyl group in place of vinyl, is unchanged by the acid treatment.

Further degradation of the cyclized isomethine (XXVI) results in a non-phenolic, optically inactive, nitrogen-free product, *rac.* phenyl-6-methoxythebentriene (XXVII). The thebentriene takes up one mole of hydrogen in neutral medium (presumably at the 9,10 unsaturation), to give XXVIII, and two addi-

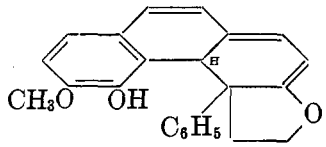
TRANSFORMATIONS OF THE PHENYLDIHYDROTHEBAINES




1 2 3
4
5
6
7 8
9
3H2
XVII
(+) ETHYLPHENYL - HEXAHYDROTHEBAOL
XVIII
(+) ETHYLPHENYL - DIHYDROTHEBAOL
XIX
(+) VINYLPHENYL - DIHYDROTHEBAOL
MONOACETYL DERIVATIVE
XX
(+) VINYLHEXAHYDRO - PHENYLTETRAHYDRO - THEBAOL
2H2
H2
HCl
H.D.
XXI
(+) α-PHENYLDIHYDRO - THEBAINE ISOMETHINE
XXII
(+) α-PHENYLDIHYDRO - THEBAINE DIHYDROISOMETHINE
XXIII
(-) VINYLPHENYL - DIHYDROTHEBAOL
XXIV RACEMATE
4H2
XXV
(+) α - HEXAHYDROPHENYL - DIHYDROTHEBAINE DIHYDRO - ISOMETHINE
XXVI
(+) α - PHENYL - 9 - DIMETHYL - AMINO - 6 - METHOXYTHEBENDIENE
XXVII
rac. PHENYL - 6 - METHOXYTHEBENTRIENE
XXVIII
rac. PHENYL - 6 - METHOXYTHEBENDIENE
XXIX
rac. PHENYL - 6 - METHOXYTHEBENANE
XXX
(-) 6 - PHENYLDIHYDRO - THEBAINE ISOMETHINE
XXXI
(-) HEXAHYDROPHENYL - TETRAHYDROTHEBAIMINE
XXXII
(-) VINYLHEXAHYDRO - PHENYLTETRAHYDROTHEBAOL

tional moles in acid medium, *rac.* phenyl-6-methoxythebenane (XXIX). A stepwise reduction of the external phenyl group seems excluded, so we are now faced with the question, why has it suddenly become possible to hydrogenate ring III, whereas the isomethine itself is so resistant at this point that forcing the hydrogenation (platinum oxide, hydrochloric acid) apparently even saturates the phenyl group (XXV) without affecting the alicyclic double bonds?

When uncyclized (+) α-phenyldihydrothebaine isomethine is degraded by the Hofmann method, a phenolic, dextrorotatory, nitrogen-free product, (+) vinylphenyldihydrothebaol (XIX) is obtained. This is identical in physical properties with a compound prepared by Freund (2) by the same method, and designated as phenyldihydrothebenol (XXXIV).



XXXIV. Phenyldihydrothebenol (Freund, 1905)

Probably because of the extremely low solubility of this substance in hydriodic acid (our first analysis, conducted as usual, showed more than one but less than two methoxyls), Freund found only one methoxyl group present, and sought to explain this by postulating hydrolysis of the 6-methoxyl, followed by cyclization with the vinyl group (at that time thought to be at C-5). Both combustion analysis and Zeisel (conducted with sufficient acetic anhydride to ensure solution) show the presence of two methoxyl groups, and phenyldihydrothebenol should therefore be deleted from the literature. The phenolic properties, and formation of a monoacetyl derivative show that the 4-hydroxyl group in the thebaol (XIX) has not been involved in a cyclization, and further proof that the vinyl group is unchanged, in contrast to Freund's claim, lies in the fact that boiling hydrochloric acid causes cyclization, and yields the above-described *rac.* phenyl-6-methoxythebentriene (XXVII). For unknown reasons, the acid treatment demethylates the nitrogen-free compound, and the strongly phenolic, optically active product must be remethylated and racemized with sodium ethoxide before XXVII is obtained.

In neutral solution XIX adds one mole of hydrogen at the vinyl group, as is shown by the fact that the same product, (+) ethylphenyldihydrothebaol (XVIII) is obtained when (+) α-phenyldihydrothebaine isomethine (XXI) is reduced at the vinyl group, (+) α-phenyldihydrothebaine dihydroisomethine (XXII), and subsequently degraded.

The reduction of (+) vinylphenyldihydrothebaol in acid solution is peculiar; two moles of hydrogen are taken up rapidly, presumably at the vinyl group and the 9,10-unsaturation, and a third mole is then added very slowly, and the hydrogenation stops, (+) ethylphenylhexahydrothebaol (XVII). Probably the ring double bond not involved in the enol ether group has been saturated. The same compound results from addition of two moles of hydrogen (one rapidly, one

slowly) to the above-described (+) ethylphenyldihydrothebaol (XVIII), which excludes the external phenyl group as the acceptor of hydrogen. This constitutes the second example of an apparent (partial) reduction of ring III in a nitrogen-free product.

(+) α-PHENYLDIHYDROTHEBAINE NORMAL METHINE (VI)

This minor product from the first step of the Hofmann degradation has the heterocyclic ring opened in the manner expected for the morphine series, and hence is referred to as the normal methine. Its methohydroxide breaks down with such difficulty that dry vacuum-distillation must be resorted to, so that it is not surprising that the product is optically inactive. *rac.* Vinylphenyldihydrothebaol (XXIV) contains a phenolic hydroxyl and two methoxyls, and is isomeric with the dextro compound from the degradation of the isomethine; it will be mentioned again in the discussion of (−) δ-phenyldihydrothebaine.

(+) α-Phenyldihydrothebaine normal methine adds one mole of hydrogen at the 9,10-unsaturation to give a dihydro derivative (XII), whose methiodide (VII) is identical with the N-methomethiodide of phenyltetrahydrothebaimine (VIII), a point of great importance for the structure of that compound.

(+) δ-PHENYLDIHYDROTHEBAINE (III)

The Hofmann degradation of (+) δ-phenyldihydrothebaine gives a crystalline isomethine (IX) in 58% yield; the normal methine, if present, could not be isolated in the small scale necessitated by the rarity of material. The isomethine, like the (+) α analog, undergoes cyclization with hydrochloric acid, giving (+) δ-phenyl-9-dimethylamino-6-methoxythebendiene (XV), a diastereoisomer of the cyclization product in the (+) α series. The second step of the degradation, elimination of the nitrogen atom, gives *rac.* phenyl-6-methoxythebentriene (XXVII). Similarly, when the uncyclized isomethine (IX) is further degraded, the product is (+) vinylphenyldihydrothebaol (XIX), identical in every respect with that obtained from the degradation of (+) α-phenyldihydrothebaine isomethine. Since the isomerism between the (+) α and the (+) δ series disappears with the elimination of the asymmetry at C-9, it follows that the (+) α and (+) δ compounds differ only in the configuration at this point. This is in agreement with the observations in the methyldihydrothebaine series. Furthermore, if the (+) δ-isomethine is reduced at the vinyl group (X), and then degraded, the product is the same (+) ethylphenyldihydrothebaol (XVIII) that is obtained from the parallel reaction in the (+) α series. Additional evidence on the isomerism of the (+) α and (+) δ compounds will be offered in the discussion of phenyltetrahydrothebaimine.

(−) α-PHENYLDIHYDROTHEBAINE (V)

This isomer, from rearrangement of the not-abundant (+) δ form, was not obtained in sufficient quantity for complete degradation. It was characterized as the perchlorate and methiodide. The latter undergoes degradation to a mixture of methine bases, from which the (−) α isomethine can be obtained pure,

but the very soluble normal methine cannot be separated. That the relationship of the (−) α-phenyldihydrothebaine to the (−) δ isomer is the same as has been demonstrated for the (+) series is amply shown by the transformation to the (−) phenyltetrahydrothebaimine discussed below.

(−) δ-PHENYLDIHYDROTHEBAINE (IV)

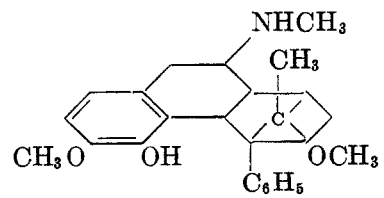
Degradation of (−) δ-phenyldihydrothebaine, as would be expected, since no asymmetric center is disturbed, yields an isomethine (XXX) that is the enantiomorph of (+) δ-phenyldihydrothebaine isomethine (IX), but a diastereoisomer of the (+) and (−) α-isomethines (XXI and XXXIII). This fact furnishes further confirmation of the mechanism of isomethine formation.

On completing the degradation, destroying the asymmetry at C-9, a (−) vinylphenyldihydrothebaol (XXIII) results that is the optical opposite of the degradation product from the (+) α- and (+) δ-isomethines, and combines with it to give the same racemic (?) vinylphenyldihydrothebaol (XXIV) that is obtained by dry distillation of (+) α-phenyldihydrothebaine normal methine methohydroxide. The (+) α and (+) δ pair evidently differ from the (−) α, (−) δ pair in having opposite configuration at the asymmetric center(s) remaining in the nitrogen-free degradation products.

THE PHENYLTETRAHYDROTHEBAIMINES

The conclusion reached above concerning the nature of the isomerism of the (+) α and (+) δ-phenyldihydrothebaines involves the tacit assumption that elimination of nitrogen takes place as usual in the morphine series, with creation of a double bond at C-9, C-10. It is however possible that the double bond might be formed between C-9 and C-14 (if C-14 is not already unsaturated or blocked), in which case either or both of these centers could be responsible for the isomerism. This possibility can now be excluded, both by spectral and chemical evidence.

Freund (3) first observed that reduction of phenyldihydrothebaine (mixture) in dilute acetic acid with colloidal palladium proceeds with absorption of one mole of hydrogen, involving reductive scission of the ethanamine chain. The product is a secondary amine, phenyltetrahydrothebaimine (VIII), and is one of the few pure substances that Freund had in his hands. From evidence involving his false concept of the structure of "phenyldihydrothebenol", Freund interpreted this degradative reduction as a rupture between the nitrogen and C-16 (XXXV).



XXXV. Phenyltetrahydrothebaimine (Freund, 1916)

We have proved it to be, instead, a break between nitrogen and C-9. The N-methomethiodide (VII) of phenyltetrahydrothebaimine is in every way iden-

tical with the methiodide of (+) α-phenyldihydrothebaine normal dihydromethine. Furthermore, we find that both (+) α- and (+) δ-phenyldihydrothebaine yield the *same* (+) phenyltetrahydrothebaimine. It is not possible that a break between C-16 and nitrogen could result in elimination of the isomerism; the destruction of the asymmetry at C-9 is in agreement with the proof already adduced from the Hofmann degradation, that the configuration at C-9 is solely responsible for the isomerism of this pair. In addition, (−) α- and (−) δ-phenyldihydrothebaines, reduced under the same conditions, yield a single (−) phenyltetrahydrothebaimine (XIII), the optical antipode of the one discussed above,

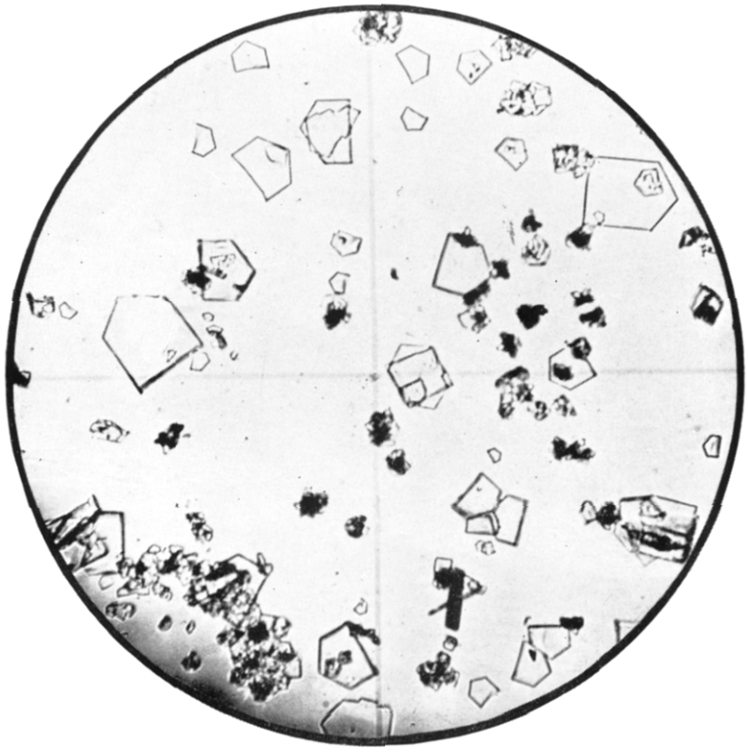


FIG. 3. (+) PHENYLTETRAHYDROTHEBAIMINE

with which it forms a racemate (XIV) of higher melting point, lower solubility, and zero rotation. Hence, the (−) α and (−) δ isomers also differ only in the configuration at C-9, and have the opposite configuration from the (+) α and (+) δ pair at the asymmetric center(s) other than C-9. Figures 3 and 4 demonstrate the identity of crystal form of the (+) and (−) phenyltetrahydrothebaimines, and Fig. 5 shows the entirely different crystal habit of the racemate. Optical crystallographic examination (Dr. Geo. L. Keenan) of the isomers gives identical data, and shows the racemate to have quite different properties (see Experimental Part). In Fig. 6 the identical x-ray diffraction patterns of the isomers are contrasted with that of the racemate.

(+) Phenyltetrahydrothebaimine N-methomethiodide (VII) undergoes alkaline degradation in a single step to (+) vinylphenyltetrahydrothebaol (XI), a compound isomeric with (+) ethylphenyldihydrothebaol (XVIII) obtained from (+) α-phenyldihydrothebaine dihydroisomethine (XXII). Had phenyltetrahydrothebaimine the Freund structure, these two must be identical. It is clear that they differ only by the position of one double bond (vinyl group and C-9,10) as required by our formulation of phenyltetrahydrothebaimine, for on hydrogenation (as the acetyl derivative), both give the same acetyl (+) ethylphenylhexahydrothebaol (acetyl-XVII). It may be remarked that Freund

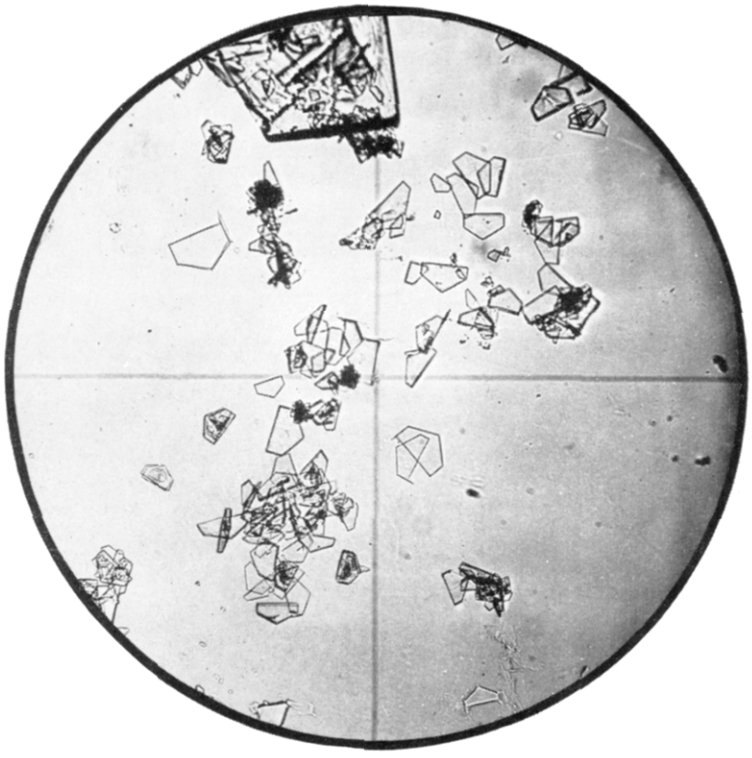


FIG. 4. (−) PHENYLTETRAHYDROTHEBAIMINE

degraded phenyltetrahydrothebaimine to a "phenyltetrahydrothebenol" (m.p. the same as that of XI), in which he found two methoxyl groups still present; he did not comment on the fact that the supposed cyclization with splitting of the 6-methoxyl failed to take place in this instance (probably because of the false structural concept shown in XXXV).

(+) Phenyltetrahydrothebaimine can be further reduced in acid solution with platinum oxide. Three moles of hydrogen are absorbed, presumably at the external phenyl group, since this is the only reducible system of three double bonds present (ring I of the morphine series has never been reduced; moreover, the product is still phenolic). (+) Hexahydrophenyltetrahydrothebaimine (XVI)

can also be made directly from either (+) α or (+) δ-phenyldihydrothebaine by addition of four moles of hydrogen. (−) δ-Phenyldihydrothebaine, as expected, reduces under these conditions to (−) hexahydrophenyltetrahydrothebaimine (XXXI), the optical opposite of the product from the (+) α and (+) δ isomers. The nitrogen-free products from degradation of these (+) and (−) hexahydrophenyltetrahydrothebaimines are also optical opposites, phenolic, with two methoxyl groups, and will be called (+) and (−) vinylhexahydrophenyltetrahydrothebaol, respectively, XX and XXXII. Attempts to verify reduction of the

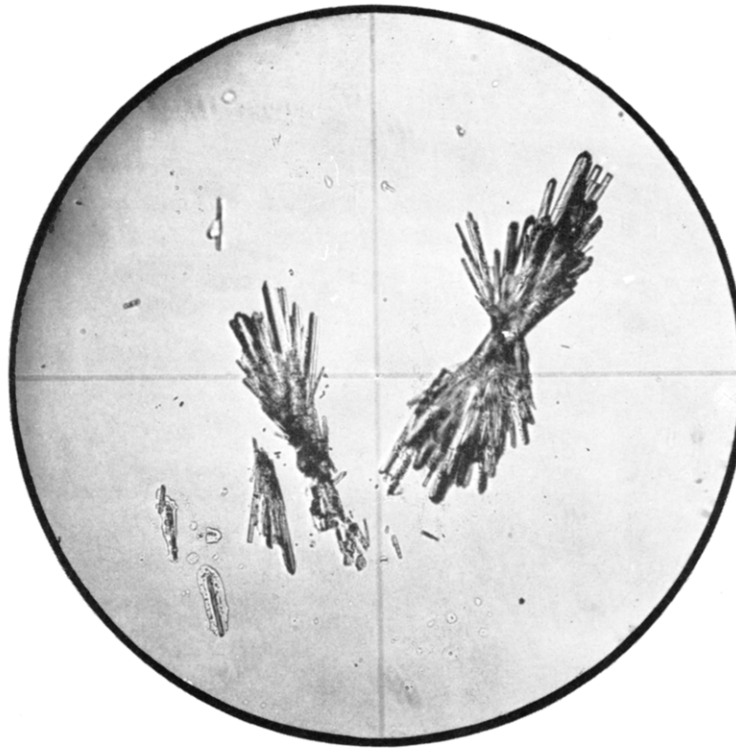


FIG. 5. *rac.* PHENYLTETRAHYDROTHEBAIMINE

external phenyl group by preparation of a cyclohexyldihydrothebaine were not successful. Although thebaine reacts with cyclohexylmagnesium bromide, the product is a sensitive (oxidation?), highly colored resin, from which no definite compound could be isolated.

The parallel hydrogenation of (+) α-phenyldihydrothebaine isomethine proceeds with absorption of four moles of hydrogen, one at the vinyl group, and three presumably at the phenyl group, to give an isomeric compound, (+) α-hexahydrophenyldihydrothebaine dihydroisomethine (XXV).

NORPHENYLDIHYDROTHEBAINE

In a brief investigation, not published beyond a dissertation, H. Hoek (6) observed that completely O-demethylated phenyldihydrothebaine behaves as

though it contains three phenolic hydroxyl groups. We have verified Hoek's work; demethylation with hydrobromic acid gives a well-characterized methoxyl-free base, which reacts with diazomethane to give a trimethyl ether which is identical with that resulting from the action of this reagent on phenyldihydrothebaine itself. This might be explained by assuming a keto-enol tautomerism at C-6, but like Hoek, we were unable to obtain an oxime from norphenyldihydrothebaine, which should be possible if such a tautomerism existed. This demethylation, which proceeds in 85% yield, offers another example of the extra-

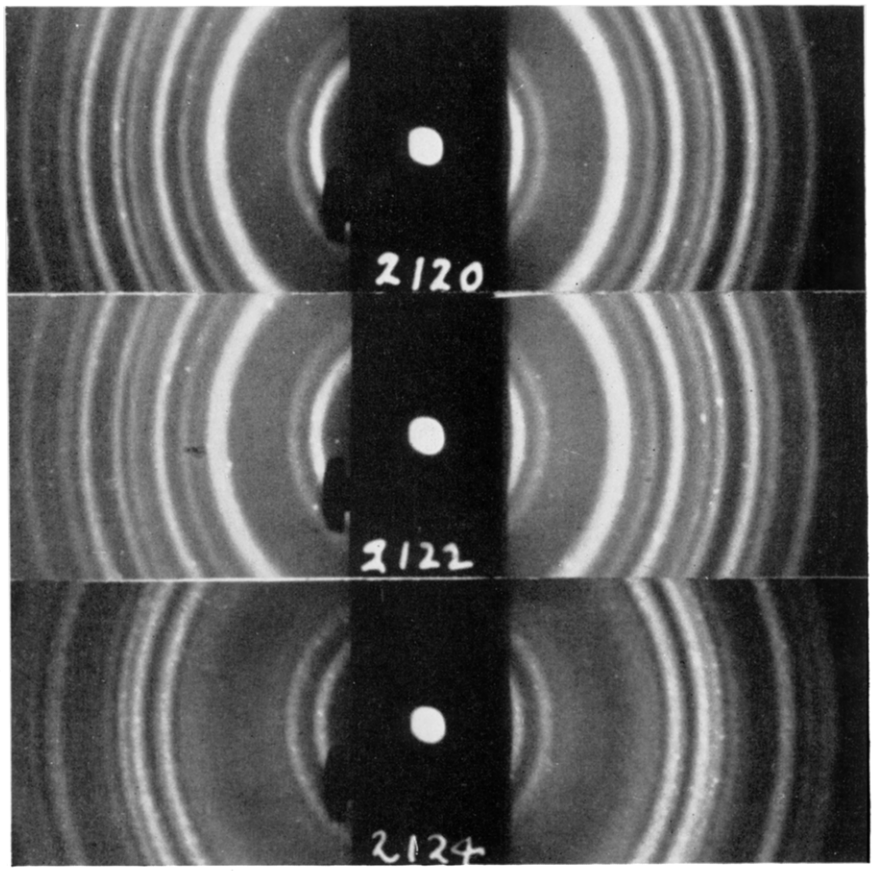


FIG. 6. X-RAY DIFFRACTION PATTERNS; 2120, (+) PHENYLTETRAHYDROTHEBAIMINE; 2122, (−) PHENYLTETRAHYDROTHEBAIMINE; 2124, *rac.* PHENYLTETRAHYDROTHEBAIMINE

ordinary stability of the ring system in phenyldihydrothebaine, in contrast to that of thebaine, which is destroyed almost completely by a few minutes boiling with normal sulfuric acid, or even potassium acid sulfate solution. Norphenyldihydrothebaine deserves further study.

DISCUSSION

In the foregoing description, we have demonstrated in four distinct ways that the (+) α, (+) δ pair and the (−) α, (−) δ pair of isomers owe their isomerism to a

configurational difference at C-9; namely, degradation of (+) α- and (+) δ-isomethines to the same (+) vinylphenyldihydrothebaol (XXI, IX, → XIX); degradation of (+) α- and (+) δ-dihydroisomethines to (+) ethylphenyldihydrothebaol (XXII, X, → XVIII); degradative hydrogenation of (+) α- and (+) δ-phenyldihydrothebaines to (+) phenyltetrahydrothebaimine (II, III, → VIII); and the parallel conversion of (−) α- and (−) δ-phenyldihydrothebaines to (−) phenyltetrahydrothebaimine (V, IV, → XIII). The last two examples also show that the (+) α, (+) δ pair differ from the (−) α, (−) δ pair in having the opposite configuration at the other asymmetric center(s). It is striking that all of the examples indicate that the interconversion of the isomers is through racemization of C-13 (?), never C-9.

On the other hand, the appearance of (+) δ-phenyldihydrothebaine along with (+) α-phenyldihydrothebaine in the Grignard reaction implies a racemization of C-9 *during* the reaction. How can phenylmagnesium bromide, obviously engaged in opening the ether ring, affect such a remote center? It is not an effect of the reagent in racemizing at this point in the α-compound after its formation, for pure α-phenyldihydrothebaine, on prolonged boiling in benzene with phenylmagnesium bromide, yields no trace of the isomer.

If one is willing to admit the possibility of a trans ring in such a structure as that of thebaine (or that the thebaine formula is fundamentally incorrect), there remains an explanation for the formation of the (+) δ isomer which must be considered, but which we suggest with reluctance; namely, that thebaine is not a single substance, and may already contain a certain amount of an isomer with inverted configuration at C-9. Tentative experiments on the separation of such an isomer from thebaine by physical and chemical methods have so far failed.

It will be noted that Small and co-workers (7, 8) observed some years ago that the reaction of methyl-, ethyl-, and phenyl-magnesium halides with dihydrothebaine resulted in the formation of isomeric nuclear-substituted dihydrothebainones, whereas the action of methylmagnesium iodide on dihydrocodeinone enol acetate (*ex* codeine) gave only one methyldihydrothebainone. This seemed at first to offer some support to the hypothesis advanced above, but further investigation shows that the isomerism in the methyldihydrothebainone series is not of the same type as that of the methyl- and phenyl-dihydrothebaines. Degradation of methyldihydrothebainone, and isomethyldihydrothebainone, gives in the first step different methine bases, and in the second step, where isomerism should disappear if it is due to C-9, entirely different, isomeric nitrogen-free end-products.

The extreme resistance of phenyldihydrothebaine to normal catalytic hydrogenation is not without parallel in the morphine series, and in every instance known to us, the recalcitrant compounds have arisen from the Grignard reaction. Small and Yuen (9) prepared a series of alkyl and aryl substituted derivatives from desoxycodeine-C, in which the ether ring was opened, and the organic residue of the reagent added. These could be hydrogenated (one mole) with difficulty in acid solution, which was assumed to be saturation of the double bond. Reinvestigation of one of these hydrogenation products still available, that from phenyldihydrodesoxycodeine, shows it to be a secondary amine, *i.e.*, the supposed

reduction of the double bond was actually a degradative reduction like that which results in the phenyltetrahydrothebaimines.

Small, Turnbull, and Fitch (8) observed that the phenolic product obtained from methylmagnesium iodide and pseudocodeine methyl ether resisted hydro-

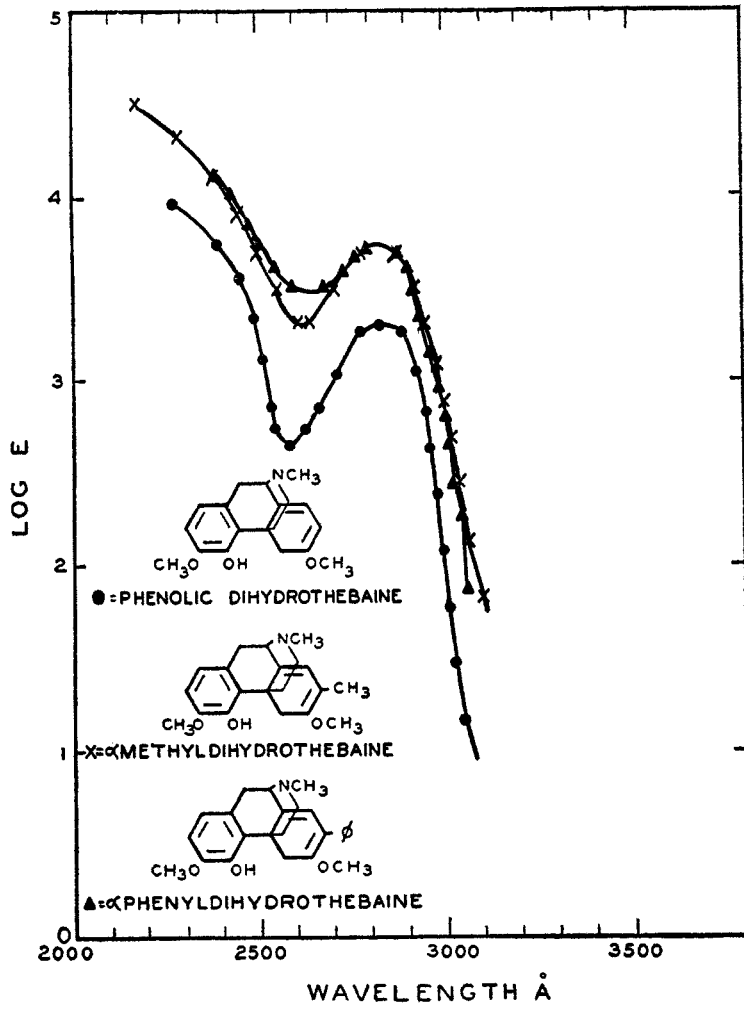


FIG. 7. ULTRAVIOLET ABSORPTION SPECTRA OF PHENOLIC DIHYDROTHEBAINE, α-METHYLDIHYDROTHEBAINE, AND (+) α-PHENYLDIHYDROTHEBAINE

genation under widely varied conditions. Similarly, the phenolic compound from methylmagnesium iodide and pseudocodeinone could not be hydrogenated, nor did it give any of the reactions for a carbonyl group (10).

The generally accepted morphine and thebaine formulas do not offer any rea-

sonable explanation of these facts, nor of the phenomena described in this communication. The unquestionable retention of the vinyl group in the degradation of the phenyldihydrothebaines is particularly disturbing, since the characteristic tendency of (ring) unhydrogenated morphine derivatives to revert to aromatic

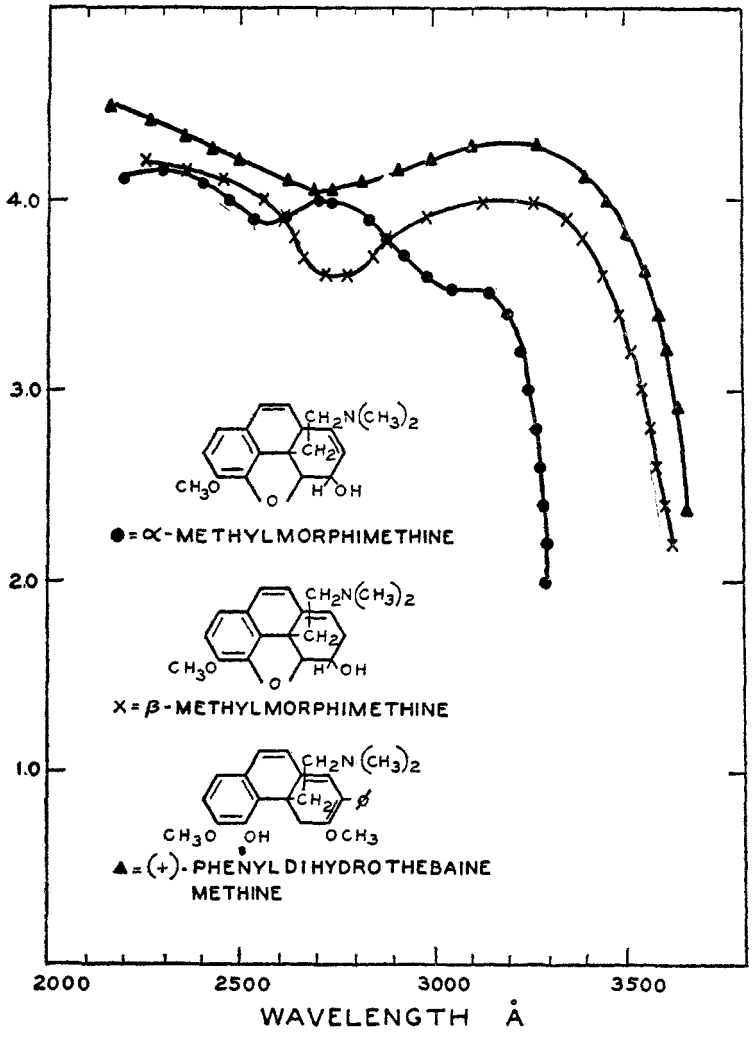


FIG. 8. ULTRAVIOLET ABSORPTION SPECTRA OF (+) α-PHENYLDIHYDROTHEBAINE NORMAL METHINE, β-METHYLMORPHIMETHINE, AND α-METHYLMORPHIMETHINE

(phenanthrene) systems through extrusion of this group constitutes one of the chief arguments for the Gulland and Robinson morphine formula.

There remains, of course, the possibility that the Grignard reaction has caused deeper-seated changes in the thebaine molecule than we have assumed. We have

sought evidence on this point by comparison of the ultraviolet absorption spectra of methyldihydrothebaine and phenyldihydrothebaine with that of the most closely related thebaine derivative in which it is certain that there has been no fundamental structural change, namely, the phenolic dihydrothebaine[4] of Small and Browning (11). As shown in Fig. 7, the three compounds show maxima and

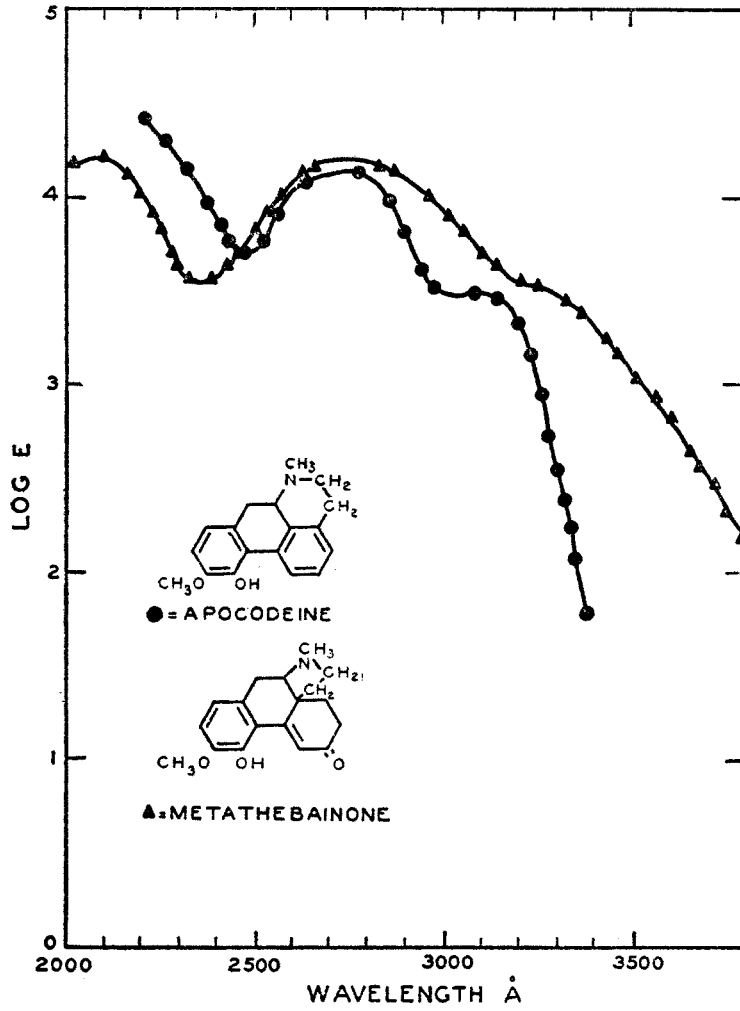


FIG. 9. ULTRAVIOLET ABSORPTION SPECTRA OF REARRANGEMENT TYPES, APOCODEINE AND METATHEBAINONE

minima at almost identical wavelengths. Furthermore, the absorption curves for β-methylmorphimethine and phenyldihydrothebaine normal methine (Fig. 8) are closely similar, whereas that for α-methylmorphimethine, with the unsatu-

[4] This compound can be converted by unequivocal methods to the well-known dihydrothebainone, which is further related through dihydrocodeinone to codeine.

ration of ring III out of conjugation, differs widely. Fig. 9 represents the spectra of two morphine types in which drastic rearrangement has taken place, apocodeine and metathebainone. We believe that the data of Fig. 8 strongly support the presence of the conjugated system of ring III, linked through the 9,10-double bond to the aromatic ring.

A further attempt to answer the question of structural change was made by the biological method; if the products in question showed morphine- or thebaine-like action, this might be considered evidence of unchanged fundamental structure. The hydrochlorides of α-methyldihydrothebaine, (+) α-phenyldihydrothebaine, and norphenyldihydrothebaine, on subcutaneous injection into mice in the normal morphine dosage, showed practically no action, not even the Straub reaction. The evidence is thus negative, for we have found a number of morphine derivatives with the ether ring opened to be similarly inactive.

The structural question will be resumed in the methyldihydrothebaine series, where degradation to a known methylphenanthrene may be possible.

ACKNOWLEDGMENTS

We are indebted to Merck & Co., Rahway, for the large amount of thebaine used in this work; to the National Research Council (L.J.S.) and the Mallinckrodt Chemical Works (J.A.B.) for fellowship aid. Absorption spectra are by Peter Cole and Dorothy Peterson, x-ray diffraction patterns by William C. White and Dorothy Hastings, of the Laboratory of Physical Biology of this Institute. Biological tests are by Nathan B. Eddy. Microanalyses are from the Institute analytical service laboratory under the direction of C. A. Kinser. Optical crystallographic data for the phenyltetrahydrothebaimines are by George L. Keenan.

EXPERIMENTAL

(+) *α-Phenyldihydrothebaine* (II). As much ether as possible was distilled from 330 ml. of 2-molar phenylmagnesium bromide on the steam-bath, and 200 ml. of anhydrous benzene added. Under reflux, with mechanical stirring, 100 g. (0.5 molar equivalent) of thebaine in 1900 ml. of warm benzene was added during 2 hours. Refluxing and stirring was continued for 6 hours, and the solution was poured into excess saturated ammonium chloride solution. The aqueous layer was extracted several times with benzene, and the combined benzene extracts were shaken out with 2 *N* hydrochloric acid. The base was liberated with ammonia and brought into ether in the presence of a little sodium dithionite. The purple syrup left on removal of the ether was taken up in 150 ml. of absolute alcohol, and treated with alcoholic perchloric acid (55 g. of 60% aqueous perchloric acid in 120 g. of ice-cold absolute alcohol) to litmus acidity. The mixture of crystalline perchlorates was triturated with two 75-ml. portions of alcohol, which removed practically all color. Eight such runs gave 1102 g. of crude perchlorate (89%). Recovery from the mother liquors, passing through the base, not over 1%.

The crude perchlorate was converted (ether extraction) to the syrupy base, and this treated with alcoholic hydrogen chloride. After 12 hours at 0°, the colorless crystals of (+) α-phenyldihydrothebaine hydrochloride were washed with cold methanol. The mother liquors were concentrated, converted to base, and again to hydrochloride, thus removing practically all of the (+) α isomer; yield 75–78% (based on thebaine). The mother liquors contain the (+) δ isomer.

(+) α-Phenyldihydrothebaine is a glass-like solid; from cold alcoholic solution it slowly

crystallizes solvated as colorless prisms, m.p. 40–70°, $(\alpha)_D^{20}$ +10.2° (alcohol, *c*, 1.98); satisfactory analyses on the solvated form could not be obtained.

Anal. Calc'd for $C_{25}H_{27}NO_3+C_2H_5OH$: C, 74.4; H, 7.60; C_2H_5OH, 10.6.
Found: C, 72.2; H, 7.30; loss at 100°, 10.8.

The base distills at 150°/0.1 mm. as a colorless glass, which necessarily contains some of the (−) δ isomer; $(\alpha)_D^{20}$ +25.3° (alcohol, *c*, 0.75).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.1; H, 6.98.
Found: C, 77.1; H, 6.88.

The base is soluble in dilute alkali, precipitated by CO_2 or NH_4Cl; ferric chloride test negative, diazosulfanilic acid intense red; indifferent to catalytic hydrogenation in neutral solution.

(+) *α-Phenyldihydrothebaine perchlorate*, crystallized from alcohol, melts at 248° (vac., decomp.) and has $(\alpha)_D^{26}$ +35° (alcohol, *c*, 0.21); one gram dissolves in 65 ml. of boiling alcohol. It is more soluble in acetone, in which it has $(\alpha)_D^{20}$ +8.2° (*c*, 0.98).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.3; H, 6.03.

(+) *α-Phenyldihydrothebaine methiodide*, from methanol, melts at 216.5–218°; $(\alpha)_D^{26}$ +42.7° (alcohol, *c*, 0.36).

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.69.
Found: C, 58.9; H, 6.04.

Degradation of (+) *α-phenyldihydrothebaine.* A suspension of 307 g. of the methiodide in one liter of 30% aqueous KOH was boiled vigorously for 5 minutes. After cooling, the alkali was poured from the glassy solid (potassium salts of the degradation products), which was shaken with water and ether; hydrolysis was practically complete, but the aqueous layer was saturated with ammonium chloride and extracted again. At 3° overnight, the ether yielded 99 g. of (+) *α-phenyldihydrothebaine isomethine*; recovery from the filtrate brought the yield to 123 g. (52.8%).

The final liquor was concentrated to a syrup, dissolved in 150 ml. of alcohol, and treated with 270 ml. of 1 part alcohol in 1 part 10% aqueous perchloric acid. The first crop of fine white crystals separating immediately was the perchlorate of undegraded phenyldihydrothebaine, 41.3 g. (14%), $(\alpha)_D$ +4°, m.p. 223–230°; it was removed quickly to avoid contamination of the small crop of *phenyldihydrothebaine normal methine perchlorate* which crystallized soon after; 8.7 g. (3%), m.p. 93–122°, $(\alpha)_D$ −34°. The mother liquors, in ice, gave 24.4 g. (19%) of the more soluble isomethine perchlorate, m.p. 105–115°, $(\alpha)_D$ −127°; total yield of basic material, 89%.

(+) *α-Phenyldihydrothebaine isomethine* (XXI) was best purified as the perchlorate, from alcohol to constant rotation. The base liberated with ammonia was brought into ether and the resulting oil dissolved in warm 75% alcohol; crystallized at 0° twelve hours, and recrystallized from 75% alcohol, m.p. 101°, $(\alpha)_D^{20}$ −280° (alcohol, *c*, 2.73); alkali-soluble, ferric chloride negative, red dye with diazosulfanilic acid. Analyses showed it to be partially hydrated. It was distilled at 120°/0.1 mm.; $(\alpha)_D^{20}$ −280°.

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.2; H, 7.16.

The *perchlorate*, prepared in warm alcohol with 60% perchloric acid, crystallized in balls of needles, m.p. 111–117° (gas), $(\alpha)_D^{25}$ −197° (alcohol, *c*, 0.58; ethyl acetate, *c*, 1.21).

Anal. Calc'd for $C_{26}H_{30}ClNO_7 + C_2H_5OH$: C, 61.1; H, 6.60; C_2H_5OH, 8.4.
Found: C, 61.0; H, 6.99; loss at 100°, 7.3.

The *methiodide* crystallized hydrated from 25% alcohol as colorless, felted needles, m.p. 100–110°, $(\alpha)_D^{25}$ −207° (alcohol, *c*, 1.62).

Anal. Calc'd for $C_{27}H_{32}INO_3 + 2H_2O$: H_2O, 6.2 Found: loss at 80°, 6.1.

The anhydrous salt melted at 159–160°, and appeared to become hydrated on short standing.

Anal. Calc'd for $C_{27}H_{32}INO_3 + 1.5H_2O$: C, 56.4; H, 6.49; H_2O, 4.7.
Found: C, 56.3; H, 6.64; loss, 5.5.

Cyclization. (+) *α-Phenyl-9-dimethylamino-6-methoxythebendiene* (XXI → XXVI). (+) α-Phenyldihydrothebaine isomethine was boiled for one minute with concentrated hydrochloric acid. The resulting oily product was insoluble in alkali, diazosulfanilic acid test negative. With 5% aqueous-alcoholic perchloric acid it gave a crystalline *perchlorate*, purified from alcohol, m.p. 168°; $(\alpha)_D^{23}$ +26.5° (alcohol, *c*, 0.11).

Anal. Calc'd for $C_{26}H_{30}ClNO_7$: C, 61.9; H, 6.00.
Found: C, 61.6; H, 6.36.

The *methiodide* formed long, square-ended prisms, m.p. 212–213°, $(\alpha)_D^{20}$ +0.6° (alcohol, *c*, 1.58).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.4; H, 5.91.
Found: C, 59.1; H, 6.21.

rac. Phenyl-6-methoxythebentriene (XXVII). The methiodide of the cyclized isomethine was degraded by boiling 3 minutes in 6% sodium ethoxide solution; dilution with water gave an amorphous solid, crystallized from ethyl acetate; m.p. 162.5–163°, $(\alpha)_D^{20}$ 0.0° (acetone, *c*, 0.48).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19; $2OCH_3$, 17.3.
Found: C, 80.4; H, 6.16; OCH_3, 16.6.

XXVII was indifferent to acetylation, diazobenzene reaction negative; in ethyl acetate, blue-violet fluorescence.

rac. Phenyl-6-methoxythebendiene (XXVIII). In ethyl acetate with platinum oxide, XXVII absorbed one mole of hydrogen. The product crystallized from methanol in lustrous leaflets, m.p. 119–120.5, $(\alpha)_D^{20}$ 0.0° (ethyl acetate, *c*, 0.32).

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71.
Found: C, 79.8; H, 6.85.

rac. Phenyl-6-methoxythebenane (XXIX). The reduction of XXVII as above but with the addition of a little glacial acetic acid proceeded with the absorption of three moles of hydrogen; from acetone, long colorless prisms, m.p. 80–83.5°, $(\alpha)_D^{20}$ 0.0° (ethyl acetate, *c*, 0.37).

Anal. Calc'd for $C_{24}H_{28}O_3$: C, 79.1; H, 7.74.
Found: C, 79.0; H, 8.19.

DEGRADATION OF (+) α-PHENYLDIHYDROTHEBAINE ISOMETHINE

(+) *Vinylphenyldihydrothebaol* (XIX). (+) α-Phenyldihydrothebaine isomethine methiodide was refluxed with 6% sodium ethoxide solution for one hour. Dilution with water precipitated a granular product, which was suspended in ether and washed with dilute HCl. The residue from ether was crystallized from alcohol, 78% yield; m.p. 149°, $(\alpha)_D^{25}$ +47.1° (ethyl acetate, *c*, 0.51).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19; 2 OCH_3, 17.3.
Found: C, 80.5; H, 6.43; OCH_3, 17.3.

XIX couples with diazotized aniline in alcoholic alkali to give an orange-red dye.

Degradation with 30% aqueous KOH gave only 33% yield, and apparently caused some racemization, $(\alpha)_D^{20}$ +21.4°. XIX also shows lowered rotation after heating with KOH.

(+) *Acetylvinylphenyldihydrothebaol.* In pyridine with acetic anhydride for 50 hours, XIX gave an acetyl derivative, colorless quadratic plates from alcohol, m.p. 145.5–147°; $(\alpha)_D^{23}$ +24.7° (ethyl acetate, *c*, 0.32).

Anal. Calc'd for $C_{26}H_{24}O_4$: C, 78.0; H, 6.04.
Found: C, 77.7; H, 5.91.

(+) *Ethylphenyldihydrothebaol* (XVIII). Three grams of XIX in neutral ethyl acetate with 100 mg. of platinum oxide absorbed 246 ml. of hydrogen (for 1 mole, 210 ml.). The crystalline product from evaporation was purified from alcohol, 2.6 g., m.p. 118°, $(\alpha)_D^{25}$ −74.4° (ethyl acetate, *c*, 0.31); mixed m.p. with product from degradation of XXII, 118°.

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71.
Found: C, 79.6; H, 6.76.

Its *acetyl derivative* crystallized from ethanol in rectangular plates, m.p. 122.5–123°, $(\alpha)_D^{25}$ −77.0° (ethyl acetate, *c*, 0.31); mixed m.p. with acetyl degraded XXII, 122.5–123°.

Anal. Calc'd for $C_{26}H_{26}O_4$: C, 77.6; H, 6.51.
Found: C, 77.6; H, 6.63.

(+) *Ethylphenylhexahydrothebaol* (XVII). When the hydrogenation of XIX was carried out as above but with addition of a little gl. acetic acid, two moles of hydrogen were taken up in 15 minutes, and a third in 36 hours. The product was an oil, whose acetyl derivative crystallized from 70% alcohol, m.p. 82.5–83° $(\alpha)_D^{20}$ −23.4° (ethyl acetate, *c*, 0.26).

Anal. Calc'd for $C_{26}H_{30}O_4$: C, 76.8; H, 7.44.
Found: C, 76.4, 77.3; H, 7.10, 7.21.

Cyclization of (+) *vinylphenyldihydrothebaol to rac. phenyl-6-methoxythebentriene* (XIX → XXVII). (+) Vinylphenyldihydrothebaol was boiled for 10 minutes in conc'd HCl and dioxane (10:1). Dilution with water precipitated a strongly phenolic resin, which after distillation in a high vacuum showed $(\alpha)_D^{20}$ −115° (acetone, *c*, 1.09). This was methylated in alkali with dimethyl sulfate, giving an amorphous, non-phenolic product having $(\alpha)_D^{20}$ −111° (acetone, *c*, 0.48). This was racemized by boiling with sodium ethoxide solution for ten minutes, and crystallized from ethyl acetate; m.p. 161–163°, no depression in mixture with *rac.* phenyl-6-methoxythebentriene (XXVII) from degradation of XXVI; $(\alpha)_D^{26}$ 0.0° (acetone, *c*, 0.96).

(+) *α-Phenyldihydrothebaine dihydroisomethine* (XXII). A solution of 11.5 g. of the isomethine in 300 ml. of alcohol with 50 mg. of platinum oxide absorbed one mole of hydrogen in 30 min. The colorless solution rapidly took on a yellow-green fluorescence in contact with air. Alcohol was removed to 75 ml., and 60% $HClO_4$ added until the fluorescence disappeared (Congo acidity). On addition of 50 ml. of ether, 13.2 g. of fine white needles separated. The base was liberated with ammonia, brought into ether, and the residue from the ether was purified from 70% alcohol, m.p. 70–72°, $(\alpha)_D^{20}$ −175° (alcohol, *c*, 1.06).

Anal. Calc'd for $C_{26}H_{31}NO_3$: C, 77.0; H, 7.71.
Found: C, 76.7; H, 7.97.

The *perchlorate* crystallized solvated from 25% alcohol, m.p. 85–87° (foaming) and showed in alcohol $(\alpha)_D^{25}$ −104° (*c*, 1.08). It lost 8.7% in a vacuum at 57° and then had the m.p. 111–117°; calc'd for $3H_2O$: 9.6, for C_2H_5OH: 8.2. When brought to analysis it again melted at 85° and appeared to be the dihydrate.

Anal. Calc'd for $C_{26}H_{32}ClNO_7 + 2H_2O$: C, 57.6; H, 6.64; H_2O, 6.6.
Found: C, 57.7, 57.6; H, 7.05, 6.79; loss at 110°, 6.5.

The *methiodide* was prepared in ethyl acetate, purified from dilute methanol; m.p. 212–213°, $(\alpha)_D^{25}$ −121° (alcohol, *c*, 2.86).

Anal. Calc'd for $C_{27}H_{34}INO_3 + 1.5\ H_2O$: C, 56.4; H, 6.49, I, 22.1; H_2O, 4.7.
Found: C, 56.8, 56.3; H, 6.49, 6.64; I, 22.1; loss at 110°, 5.9.

Degradation of this methiodide by boiling for 90 min. with 6% sodium ethoxide solution gave ethylphenyldihydrothebaol (XVIII) of m.p. 118°, $(\alpha)_D^{20}$ −76.7° (ethyl acetate, *c*, 0.36); mixed m.p. with product from hydrogenation of XIX, 118°.

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71; 2 OCH_3, 17.2.
Found: C, 80.0; H, 6.77; OCH_3, 17.3.

Acetylation in pyridine gave sparkling rectangular plates (from alcohol) of m.p. 122.5–123°, mixed m.p. with acetyldihydro-XIX, 122.5–123°, $(\alpha)_D^{20}$ −77.8° (ethyl acetate, *c*, 0.32).

Anal. Calc'd for $C_{26}H_{26}O_4$: C, 77.6; H, 6.51.
Found: C, 77.5; H, 6.56.

(+) *α-Hexahydrophenyldihydrothebaine dihydroisomethine.* Three grams of pure (+) α-isomethine (XXI) in 50 ml. of alcohol with 50 ml. of *N* hydrochloric acid and 400 mg. of platinum oxide absorbed 917 ml. of hydrogen (calc'd for 4 moles, 848 ml.). Removal of alcohol and isolation with ammonia and ether gave long white needles (from 75% alcohol), m.p. 108–108.5°, $(\alpha)_D^{20}$ −24.2° (alcohol, *c*, 1.78); brilliant yellow-green fluorescence in alcoholic solution.

Anal. Calc'd for $C_{26}H_{37}NO_3$: C, 75.8; H, 9.06.
Found: C, 75.7; H, 9.21.

The *methiodide* from methanol had m.p. 207–208°, $(\alpha)_D^{20}$ −14.7° (alcohol, *c*, 1.16).

Anal. Calc'd for $C_{27}H_{40}INO_3$: I, 22.9. Found: I, 22.9.

This salt is isomeric with the N-methomethiodides of (+) and (−) hexahydrophenyltetrahydrothebaimines.

(+) *α-Phenyldihydrothebaine methine* (VI). The normal methine, isolated as described under the degradation of (+) α-phenyldihydrothebaine, was purified as perchlorate, and recrystallized as base from 75% methanol; m.p. 126–127°, $(\alpha)_D^{20}$ −46.5° (alcohol, *c*, 0.86).

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.7; H, 7.45.

The *perchlorate* crystallized solvated from ethanol, melting range 106–120° (gas evolution), and had $(\alpha)_D^{20}$ −60.3° (alcohol, *c*, 0.26), $(\alpha)_D^{20}$ −34° (acetone, *c*, 1.12).

Anal. Calc'd for $C_{26}H_{30}ClNO_7 + C_2H_5OH$: C, 61.1; H, 6.60; C_2H_5OH, 8.4.
Found: C, 60.8; H, 6.81; loss at 110°, 8.0.

The *methiodide* was prepared in ethyl acetate and purified from methanol, m.p. 244° (evac. tube), $(\alpha)_D^{20}$ −51.5° (alcohol, *c*, 0.41).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.4; H, 5.91.
Found: C, 59.4; H, 6.18.

The normal methine is soluble in alkali, and couples to a red dye with diazosulfanilic acid. It is unaffected by boiling with concentrated HCl (recovery 95%), in contrast to the isomethine. For hydrogenation, see under (+) phenyltetrahydrothebaimine.

rac. Vinylphenyldihydrothebaol (XXIV). (+) α-Phenyldihydrothebaine methine is so resistant to degradation that boiling the methiodide with 40% KOH gives only the methohydroxide, long, yellow, felted needles. Distillation of this in the oil-pump vacuum at 160° gave *rac.* vinylphenyldihydrothebaol, m.p. 149.5°, $(\alpha)_D^{20}$ 0.0° (ethyl acetate, *c*, 0.39), identical with the racemate (?) obtained by combination of the (+) and (−) isomers [see degradation of (−) δ-phenyldihydrothebaine].

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19; 2 OCH_3, 17.3.
Found: C, 80.5; H, 6.48; OCH_3, 17.1.

(+) *δ-Phenyldihydrothebaine* (III). The alcoholic mother liquor from preparation of (+) α-phenyldihydrothebaine hydrochloride (*ex* 100 g. of thebaine) was concentrated at 40° *in vacuo* to a heavy syrup; this was dissolved in 100 ml. of water, base liberated with ammonia, and taken into ether. The residue from the ether crystallized on dilution with a little alcohol, yield 9.8 g. (7.8% based on thebaine), pale lavender, m. *ca.* 140°; crystallized twice from abs. alcohol, white needles, m.p. 143.5°, $(\alpha)_D^{20}$ −110° (U.S.P. $CHCl_3$, *c*, 1.10); $(\alpha)_D^{20}$ −131° (*c*, 0.87, acetone). Occasionally the color was persistent, but could be removed by passing through the hydrochloride (3*N* HCl and sat'd NH_4Cl).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.1; H, 6.98.
Found: C, 76.9; H, 7.15.

The *perchlorate*, prepared in alcohol with 20% alcoholic perchloric acid, was much more soluble than that of the (+) α isomer, 1 g. in 18 ml. of boiling alcohol; purified from alcohol-ether, m.p. 209–213°, $(\alpha)_D^{24}$ −44.5° (alcohol, *c*, 1.23).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.4; H, 5.92.

The *methiodide* was prepared in ethyl acetate, purified from methanol, m.p. 206–208°, $(\alpha)_D^{23}$ −43° (alcohol, *c*, 0.72). It was solvated, calc'd for CH_3OH: 5.7; for $2H_2O$: 6.3. Loss at 100°: 5.8.

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.68.
Found: C, 58.6; H, 5.92.

(+) *δ-Phenyldihydrothebaine isomethine* (IX). (+) δ-Phenyldihydrothebaine methiodide was boiled for 15 min. with 30% aqueous KOH, the potassium salt of the product hydrolyzed with ammonium chloride, and extracted with ether. The ether residue crystallized from 70% alcohol in long prisms, m.p. 117–119°, $(\alpha)_D^{25}$ +153° (alcohol, *c*, 0.63); yield 70%. It sublimed in long, feathery crystals at 140°/0.1 mm., m.p. unchanged.

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.4, 77.1; H, 7.75, 7.10.

The *perchlorate* was prepared in alcohol with 20% alcoholic perchloric acid, purified from abs. alcohol; solvated, m.p. 114–116°, $(\alpha)_D^{23}$ +89.6° (alcohol, *c*, 0.67).

Anal. Calc'd for $C_{26}H_{30}ClNO_7 + 2C_2H_5OH$: C, 60.4; H, 7.10; C_2H_5OH, 15.5.
Found: C, 60.3; H, 6.81; loss at 100°, 15.5.

The *methiodide*, prepared in ethyl acetate and purified from abs. alcohol-ether, had the m.p. 202–203°, $(\alpha)_D^{24}$ +108° (alcohol, *c*, 0.99).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.5; H, 5.91.
Found: C, 59.7; H, 6.17.

Degradation of (+) *δ-phenyldihydrothebaine isomethine.* Treatment of the methiodide of IX with boiling sodium ethoxide yielded (+) vinylphenyldihydrothebaol (XIX), identical with that from the parallel degradation of the (+) α-isomethine (XXI). It showed $(\alpha)_D^{24}$ +46.6° (ethyl acetate, *c*, 0.58), m.p. 149°, mixed m.p. 149°.

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19.
Found: C, 80.8; H, 6.14.

(+) *δ-Phenyldihydrothebaine dihydroisomethine* (X). The (+) δ-isomethine (IX) in dilute acetic acid with platinum oxide took up one mole of hydrogen rapidly. The product was liquid, and was converted to the methiodide, purified from alcohol-ether; m.p. 217–219° (gas), $(\alpha)_D^{23}$ +145° (alcohol, *c*, 0.32).

Anal. Calc'd for $C_{27}H_{34}INO_3$: I, 23.2. Found: I, 22.9.

Degradation of the methiodide with sodium ethoxide solution gave 50% yield of (+) ethylphenyldihydrothebaol (XVIII), identical with that from the (+) α-dihydroisomethine (XXII). It showed $(\alpha)_D^{23}$ −76.0° (ethyl acetate, *c*, 0.27), m.p. 118°, mixed m.p. 118°; sublimed for analysis.

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71.
Found: C, 80.2; H, 6.75.

Cyclization and degradation of (+) *δ-isomethine* (IX → XXVII). A solution of the (+) δ-isomethine (IX) in conc'd HCl was boiled for five minutes, treated with NaOH, and the oily, non-phenolic product converted to the methiodide, m.p. 170–173°, $(\alpha)_D^{26}$ −3.8° (alcohol, *c*, 1.05). [Compare properties of the isomer drived from XXVI in the (+) α-series.] Degradation with boiling sodium ethoxide eliminated the isomerism; the N-free end-product was identical with *rac.* phenyl-6-methoxythebentriene (XXVII), m.p. and mixed m.p. 161–162°, $(\alpha)_D^{25}$ 0.0° (acetone, *c*, 0.38).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19.
Found: C, 80.3; H, 6.25.

(−) *δ-Phenyldihydrothebaine* (IV). Solvent free (+) α-phenyldihydrothebaine (168 g.) was sealed in an evacuated flask and held at 200° ± 2° for 80 hours. The fluorescent yellow resin, while still warm, was brought into 250 ml. of alcohol, seeded with a sample from a sample from a small test run, and held at 3° for 2 days. The crystals were washed white with cold alcohol, m.p. 138–140°, 27 g. (16%); recrystallized twice from abs. alcohol, white needles, m.p. 143.5°, $(\alpha)_D^{20}$ +110° (U.S.P. $CHCl_3$, *c*, 1.10); $(\alpha)_D^{20}$ +131° (acetone, *c*, 0.66).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.1; H, 6.99.
Found: C, 76.9; H, 7.29.

The base is alkali-soluble; gives no ferric chloride test, but forms a brilliant red dye with diazosulfanilic acid; indifferent to catalytic hydrogenation in neutral solution.

From the alcoholic mother liquor (+) α-phenyldihydrothebaine was recovered as perchlorate in 70% of the possible yield.

(−) *δ-Phenyldihydrothebaine perchlorate* was prepared in, and purified from alcohol, m.p. 209–213°, $(\alpha)_D^{24}$ +42.8° (alcohol, *c*, 0.63).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.2; H, 6.09.

The *methiodide*, like its optical opposite, crystallized solvated from methanol (calc'd for CH_3OH: 5.7; for $2H_2O$: 6.3; found: loss at 100° 6.3). It had m.p. 206–208°, $(\alpha)_D^{20}$ +44° (alcohol, *c*, 0.32).

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.69.
Found: C, 58.8; H, 6.00.

(−) *δ-Phenyldihydrothebaine isomethine* (XXX). The methiodide of IV was degraded in 98% yield by boiling for 5 minutes with 30% KOH. The viscous potassium salt was hydrolyzed with ammonium chloride and extracted with ether, which left long leaflets. It was purified as perchlorate, regenerated, and crystallized from 60% alcohol; m.p.-117–119°, $(\alpha)_D^{20}$ −154° (alcohol, *c*, 0.92). It sublimed at 140°/0.1 mm. in long feathery crystals.

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.2; H, 7.59.

The perchlorate crystallized from abs. alcohol solvated, m.p. 114–116°, $(\alpha)_D^{26}$ −90° (alcohol, *c*, 0.69). The solvent-free salt could not be brought to satisfactory analytical purity.

Anal. Calc'd for $C_{26}H_{30}ClNO_7$: C, 61.9; H, 6.00.
Found: C, 61.2; H, 6.06.

The methiodide, purified from abs. alcohol-ether melted at 202–203°, $(\alpha)_D^{25}$ −105° (alcohol, *c*, 0.40).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.4; H, 5.91.
Found: C, 59.4; H, 5.80.

(−) *Vinylphenyldihydrothebaol* (XXIII). The (−) δ-isomethine methiodide was degraded like its (+) analog, and the product purified from alcohol; m.p. 149.5–150°, $(\alpha)_D^{22}$ −47.4° (ethyl acetate, *c*, 0.17).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19.
Found: C, 80.2; H, 6.07.

Equal amounts of this compound and the (+) analog (XIX) were mixed and crystallized from alcohol. The product had $(\alpha)_D^{20}$ 0.0° (ethyl acetate, *c*, 0.21), m.p. 146–147°, and is probably identical with the racemic compound (XXIV) from degradation of the (+) α normal methine; mixed m.p. 146–147°.

Conversion of (−) *δ-phenyldihydrothebaine to* (+) *α-phenyldihydrothebaine* IV → II. Three grams of pure IV in a sealed tube under oil-pump vacuum was held at 200° ± 4° for 60 hrs. The product was a dark glass, in contrast to the reverse transformation, II → IV; this perhaps resulted from the inadvertant use of a soft-glass tube. It was taken up in 8 ml. of hot abs. alcohol and seeded with IV; a small amount crystallized but could not be purified enough for positive identification.

The dark mother liquor was acidified with 60% perchloric acid; brown crystals, 2.2 g. (59%). It was digested with carbon in 125 ml. of alcohol, large glassy colorless crystals; analytical sample by two more crystallizations; m.p. 248° (vac., dec.), $(\alpha)_D^{20}$ +37° (alcohol, *c*, 0.209).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.3; H, 5.93.

Further identification by x-ray diffraction pattern (Fig. 1).

(−) *α-Phenyldihydrothebaine* (V). Pure (+) δ-Phenyldihydrothebaine (7.6 g.) in a sealed tube under a high vacuum was heated at 200° ± 2° for 50 hours. The pale yellow glassy product was dissolved in 10 ml. of abs. alcohol and seeded with the (+) δ-isomer. After 12 hours at 0°, the crystals were washed with 5 ml. of cold alcohol; recovery 1.8 g. (23%), m.p. 138°.

The mother liquor was brought to acidity with 60% perchloric acid, and the crystals washed with 20 ml. of cold alcohol, pure white, 6.7 g. (74%). The salt was purified from alcohol, solubility boiling 1 g./65 ml. like the (+) α-salt; m.p. 248° (vac., dec.), $(\alpha)_D^{20}$ −8.0° (acetone, *c*, 1.25), $(\alpha)_D^{20}$ −35° (alcohol, *c*, 0.20).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.1; H, 5.96.

The base liberated from the salt was a colorless glass like its optical opposite; $(\alpha)_D^{20}$ −10° (alcohol, *c*, 0.22). No attempt was made to prepare the crystalline solvated form, whose indefinite properties make it worthless for identification.

The methiodide was purified from methanol, m.p. 216°, $(\alpha)_D^{26}$ −43.6° (alcohol, *c*, 0.27).

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.69.
Found: C, 60.0; H, 6.06.

(−) *α-Phenyldihydrothebaine isomethine.* A suspension of 2.4 g. of (−) α-methiodide

in 10 ml. of 30% KOH was boiled 5 min. The separated resin was treated with ether and dilute ammonium chloride. The residue from the ether, in 5 ml. of hot alcohol was made acid to Congo with 10% aqueous $HClO_4$; yield of solvated, white salt, 2.3 g. (95%). It was recrystallized from 7 ml. of alcohol, filtering from 150 mg. of undegraded (−) α-phenyldihydrothebaine perchlorate, $(\alpha)_D^{20}$ −35.5°. The crystals from the filtrate melted at 112–118°, gas evol., but probably contained some of the normal methine salt, for $(\alpha)_D^{20}$ was +168°. It was fractionated from alcohol to free it of the more soluble normal methine, and yielded the pure isomethine perchlorate, m.p. 111–116°, $(\alpha)_D^{20}$ +197° (alcohol, *c*, 0.61). At 100°/0.1 mm. it lost 6.6%, calc'd for C_2H_5OH, 8.4%.

Anal. Calc'd for $C_{26}H_{30}ClNO_7$: C, 62.0; H, 6.00.
Found: C, 61.9; H, 6.18.

The base liberated from the perchlorate was crystallized from 75% alcohol, m.p. 101°, $(\alpha)_D^{20}$ +281° (alcohol, *c*, 1.12).

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.1; H, 7.33.

(+) *Phenyltetrahydrothebaimine* (VIII). Thirty grams of (+) α-phenyldihydrothebaine (II) in 220 ml. of *N* acetic acid with 20 ml. of 5% gum arabic solution and 60 ml. of palladous chloride solution (1% Pd) absorbed 1 mole (1750 ml.) of hydrogen in 20 minutes and stopped abruptly. The catalyst-free solution was washed with ether, and the base liberated with ammonia in the presence of a trace of sodium dithionite, and extracted with ether. The product was purified from ethyl acetate, and 75% alcohol; yield 23 g. (85%), pentagonal plates (Fig. 3). It had the m.p. 120–121°, $(\alpha)_D^{20}$ −35.0° (acetone, *c*, 1.14), $(\alpha)_D^{20}$ −4.2° (10% acetic acid, *c*, 1.19). It gave no ferric chloride test, but was soluble in alkali, and gave a red dye with diazosulfanilic acid. x-Ray diffraction pattern, Fig. 6.

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.3; H, 7.66.

The reduction of (+) δ-phenyldihydrothebaine was carried out similarly, except that 18 hours was required. The product was identical with that described above, m.p. and mixed m.p. 121°, $(\alpha)_D^{20}$ −32.7° (acetone, *c*, 2.63).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.7; H, 7.30.

(+) *Phenyltetrahydrothebaimine N-methomethiodide* (VII). When VIII was warmed in benzene with methyl iodide, white crystals of the N-methomethiodide separated in 46% yield, the remainder staying in solution as the secondary base hydriodide (from which VIII could be recovered). VII melted at 235° (evac. tube) and was dimorphous; after grinding gently, m.p. 250–253°; $(\alpha)_D^{24}$ −5.2° (*c*, 2.67, methanol), $(\alpha)_D^{24}$ −3.3° (*c*, 2.11, ethanol).

Anal. Calc'd for $C_{27}H_{34}INO_3$: C, 59.2; H, 6.26.
Found: C, 59.2; H, 6.71.

(+) Phenyltetrahydrothebaimine derived from the (+) δ-isomer gave the same dimorphous N-methomethiodide, m.p. 235° and 250–254°, $(\alpha)_D^{25}$ −5.8° (*c*, 1.21 methanol), $(\alpha)_D^{25}$ −3.5° (*c*, 1.73, ethanol); mixed m.p., because of the grinding, 250–254°.

(+) α-Phenyldihydrothebaine normal methine (VI) was hydrogenated (one mole) in ethanol with platinum oxide, and the oily dihydromethine (XII) converted to the methiodide, yield quantitative. It was identical with the two N-methomethiodides described above, m.p. 235° and 251–254°, no depression in mixture with either; $(\alpha)_D^{25}$ −5.4° (*c*, 3.30 methanol), −3.9° (*c*, 2.85, ethanol).

Anal. Calc'd for $C_{27}H_{34}INO_3$: C, 59.2; H, 6.26.
Found: C, 59.1; H, 6.79.

(−) *Phenyltetrahydrothebaimine* (XII). (−) δ-Phenyldihydrothebaine (IV), 5 g., m.p. 142°, absorbed 1 mole of hydrogen in 4 hours under the conditions described for reduction of the (+) α and (+) δ compounds (II and III). The product was isolated and purified essentially as above, giving 4.5 g. of faintly pink (colloidal palladium) pentagonal plates (Fig. 4) of m.p. 121°, $(\alpha)_D^{20}$ +35.5° (acetone, *c*, 1.01). The color could be removed by sublimation *in vacuo* at 150°, needle clusters, m.p. 121°, $(\alpha)_D^{20}$ +35.4°.

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.5, H, 7.88.

The N-methomethiodide melted at 235° (evac. tube) and had $(\alpha)_D^{20}$ +5.3° (methanol, *c*, 2.31).

Anal. Calc'd for $C_{27}H_{34}INO_3$: C, 59.2; H, 6.26.
Found: C, 59.1; H, 6.05.

The high-melting dimorphous form of this compound corresponding to that described in the (+) series (prepared seven years earlier and in a different Laboratory) could not be obtained, nor (lacking seed) was it possible to repeat the transformation with samples of the (+) compounds.

XIII from (−) *α-phenyldihydrothebaine.* The amorphous base was liberated from 2 g. of pure V perchlorate, and reduced in dilute acetic acid as described for the other isomers. One mole of hydrogen (122 ml., 28°) was absorbed in 2.5 hours. The purple (colloidal Pd) solution was decolorized, saturated with ether, and the base precipitated crystalline with ammonia (seeding with XIII obtained from reduction of IV, above); 1.5 g. (94%). It was purified from ethyl acetate, m.p. and mixed m.p. 120.5–121°. Sublimed for analysis, $(\alpha)_D^{20}$ +35.5° (acetone, *c*, 1.00); +4.9° (10% acetic acid, *c*, 1.02).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.6; H, 7.35.

rac. Phenyltetrahydrothebaimine (XIV). Equal amounts of the imines from the (+) α and (−) δ series were dissolved in boiling alcohol; in several attempts mixed crystals of m.p. 105–108° were obtained. Through unknown factors, the racemate suddenly crystallized from the hot solution in long crystal bundles (Fig. 5) of m.p. 134°, $(\alpha)_D^{20}$ 0.0° (acetone, *c*, 0.6).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.7; H, 7.82.

The imines from the (+) δ, (−) α, the (+) δ, (−) δ, and (+) α, (−) α series were pairwise dissolved in boiling alcohol and seeded with the above racemate; crystals separated immediately from the boiling solution. These three racemates were identical with that above, m.p. 134°, $(\alpha)_D^{20}$ 0.0° ± 0.1° (acetone, *c*, 0.5, 0.8, 0.8). The four racemates were mixed in the six possible combinations, and showed in each the sharp m.p. 134°.

CRYSTALLOGRAPHIC EXAMINATION

The optical crystalline properties of the (+), (−), and racemic phenyltetrahydrothebaimines were determined by Dr. Geo. L. Keenan.

"(+) *Phenyltetrahydrothebaimine.* Appearance in Ordinary Light: The significant habit is thin plates, five-sided in outline and usually referred to as uniterminal or hemimorphic.

Characters Shown in Parallel Polarized Light (crossed nicols): The elongated forms show parallel extinction. The polarization colors are brilliant and striking. The hemimorphic plates usually extinguish sharply and many irregular fragments remain bright when the microscope stage is revolved with nicols crossed.

Characters Shown in Convergent Polarized Light (crossed nicols): The substance is biaxial and optic axis figures are commonly shown with positive optic sign.

Refractive Indices: The significant refractive indices are: $\alpha = 1.568$, $\beta = 1.630$, $\gamma = 1.698$; all ± 0.002. The α and β values are most commonly found on the substance.

As would be expected, the physical isomer, (−) *phenyltetrahydrothebaimine*, has identical optical crystallographic properties as those described above."

"*Racemic* (+−) *Phenyltetrahydrothebaimine.* Appearance in Ordinary Light: The significant habit is rod-shaped, some of the elongated forms breaking up into irregular fragments when powdered for microscopic examination. Many of the elongated forms also have blunt, spear-shaped terminations, others square ends.

Characters Shown in Parallel Polarized Light (crossed nicols): The extinction is parallel and the sign of elongation is negative. With crossed nicols, many of the elongated forms are observed to be thin, showing low order whites, the thicker rods exhibiting more brilliant polarization colors.

Characters Shown in Convergent Polarized Light (crossed nicols): The substance is biaxial, the interference figure showing the plane of the optic axes, with positive optic sign. The axial angle (2 E) is quite small, the interval between the melatopes being readily observed within the microscopic field.

Refractive Indices: The significant refractive indices are: $\alpha = 1.638$, $\beta = 1.640$, $\gamma = 1.698$; all ± 0.002. The α value is usually shown lengthwise on elongated forms and the β value crosswise.

The racemate, therefore, is distinctly different microscopically from the isomers already described."

(+) *Hexahydrophenyltetrahydrothebaimine* (XVI). Six grams of (+) α-phenyldihydrothebaine in 50 ml. of alcohol with 100 ml. of *N* hydrochloric acid absorbed four moles of hydrogen in 50 hours (platinum oxide). The product was isolated in the usual way and purified from ethyl acetate, yield nearly quantitative; slender, colorless prisms, m.p. 129–130.5°, $(\alpha)_D^{28}$ −8.5° (alcohol, *c*, 0.73). Analysis showed partial hydration, so it was sublimed in the oil-pump vacuum, 140°.

Anal. Calc'd for $C_{25}H_{35}NO_3$: C, 75.4; H, 8.90.
Found: C, 75.4; H, 9.05.

The same product was obtained by hydrogenation of (+) δ-phenyldihydrothebaine under these conditions, absorption 4 moles, yield quantitative; m.p. and mixed m.p. 129–130.5°, $(\alpha)_D^{25}$ −9° (alcohol, *c*, 1.0).

The *hydrochloride* crystallized from ethanol-ether in slender prisms, m.p. 253–255° (gas evol.), $(\alpha)_D^{28}$ −17.6° (alcohol, *c*, 0.25).

Anal. Calc'd for $C_{25}H_{36}ClNO_3$: C, 69.2; H, 8.36.
Found: C, 69.3; H, 8.24.

Reduction of (+) phenyltetrahydrothebaimine derived from either (+) α- or (+) δ-phenyldihydrothebaine, absorption 3 moles, yielded the same substance, m.p. and mixed m.p. 129–130.5°, $(\alpha)_D^{25}$ −9.0° (alcohol, *c*, 1.0).

N-methomethiodide. (+) Hexahydrophenyltetrahydrothebaimines from the four sources described gave identical N-methomethiodides (in benzene), yield 41%; m.p. 231–232.5°, $(\alpha)_D^{29}$ −4.8° (alcohol, *c*, 0.31).

Anal. Calc'd for $C_{27}H_{46}INO_3$: C, 58.6; H, 7.38; I, 22.9.
Found: C, 58.5: H, 7.33; I, 22.9.

The benzene mother liquor contained the hydriodide of the unchanged secondary base, which was recovered in 46% yield.

(+) *Vinylhexahydrophenyltetrahydrothebaol* (XX). This was obtained by sodium ethoxide degradation of the N-methomethiodides of XVI derived from both the (+) α and (+) δ series; colorless needles from 75% alcohol, m.p. 75.5–77°, $(\alpha)_D^{29}$ −22.7° (ethyl acetate, *c*, 0.33).

Anal. Calc'd for $C_{24}H_{30}O_3 + 1/4H_2O$: C, 77.7; H, 8.39; 2 OCH_3, 16.7; H_2O 1.2.
Found: C, 77.8; H, 8.50; OCH_3, 16.7; loss at 100° 0.7.

It was sublimed at 140°/0.1mm.

Anal. Calc'd for $C_{24}H_{30}O_3$: C, 78.7; H, 8.25.
Found: C, 78.6; H, 8.69.

It coupled with diazotized aniline to give an orange-red dye; it also formed an acetyl derivative of m.p. 79–80.5° and $(\alpha)_D^{25}$ −26.6° (ethyl acetate, *c*, 0.23).

(−) *Hexahydrophenyltetrahydrothebaimine* (XXXI) was prepared by reduction of (−) δ-phenyldihydrothebaine (4 moles of hydrogen) in the same manner as the optical opposite. The product had m.p. 128–129.5°, $(\alpha)_D^{25}$ +10.0° (alcohol, *c*, 0.90). The *N-methomethiodide* had m.p. 231–232°, $(\alpha)_D^{25}$ +6.6° (alcohol, *c*, 0.60). It gave on degradation (−) *vinylhexahydrophenyltetrahydrothebaol* (XXXII), m.p. 70–75°, $(\alpha)_D^{26}$ +35.4°; which could not be brought to analytical purity because of scarcity.

(+) *Vinylphenyltetrahydrothebaol* (XI). Degradation of (+) phenyltetrahydrothebaimine N-methomethiodide (VII) with sodium ethoxide solution gave 72% yield of N-free

product, crystallized from 75% alcohol, m.p. 85.5–87°, $(\alpha)_D^{29}$ −58.7° (alcohol, *c*, 0.43). Acetylation in pyridine gave the *acetyl derivative*, rectangular prisms from methanol, m.p. 102–104°, $(\alpha)_D^{28}$ −48.5° (ethyl acetate, *c*, 0.27).

Anal. Calc'd for $C_{26}H_{26}O_4$: C, 77.6; H, 6.51; 2 OCH_3, 15.4.
Found: C, 77.7; H, 6.84; OCH_3, 15.6.

On reduction (platinum oxide) of this in ethyl acetate containing acetic acid, two moles of hydrogen were absorbed, giving *acetylethylphenylhexahydrothebaol*, m.p. 80°, alone or in mixture with the product obtained from (+) α-phenyldihydrothebaine isomethine (XXI → XIX → XVIII → XVII); $(\alpha)_D^{25}$ −29° (ethyl acetate, *c*, 0.31).

Norphenyldihydrothebaine. A solution of 12 g. of (+) α-phenyldihydrothebaine in 40 ml. of 48% hydrobromic acid was refluxed for 30 min. The hydrobromide of norphenyldihydrothebaine separated on cooling, in 85% yield, as faintly pink crystals. These were purified from water (pasty) or alcohol and ether; m.p. 200–210°, $(\alpha)_D^{29}$ +31.4° (alcohol, *c*, 0.4).

Anal. Calc'd for $C_{23}H_{24}BrNO_3+3H_2O$: C, 55.6; H, 6.09; OCH_3, 0.0; Br, 18.1; H_2O, 10.9.
Found: C, 56.1; H, 6.23; OCH_3, 0.0; Br, 18.5; loss at 110°, 12.7.

The base was precipitated with bicarbonate and extracted (sparingly soluble) into ether in the presence of sodium dithionite; it was purified from 50% alcohol, m.p. 130–136°, $(\alpha)_D^{29}$ +12.3° (alcohol, *c*, 0.3).

Anal. Calc'd for $C_{23}H_{23}NO_3 + 0.5H_2O$: C, 74.6; H, 6.53; H_2O, 2.4.
Found: C, 74.3; H, 6.40; loss at 110°, 1.9.

Methylation. A solution of norphenyldihydrothebaine in methanol-ether (1:2) was treated with excess diazomethane. The product was an oil, whose hydrobromide (from alcohol) had the m.p. 86.5–89° (gas evol. at 97°); $(\alpha)_D^{28}$ +21.4° (alcohol, *c*, 0.3).

Anal. Calc'd for $C_{26}H_{30}BrNO_3$: 3 OCH_3, 19.2. Found (dried sample): OCH_3, 20.9.

The *methiodide*, from methanol, had m.p. 195–197°, $(\alpha)_D^{28}$ +19.2° (alcohol, *c*, 0.34).

Anal. Calc'd for $C_{27}H_{32}INO_3$: 3 OCH_3, 17.0. Found: OCH_3, 16.4.

Attempted oximation. Norphenyldihydrothebaine, suspended in water, was heated with two equivalents of hydroxylamine hydrochloride at 100° for 75 min. The base went into solution and on cooling colorless needles of a hydrochloride separated. The base recovered from this melted at 132–137°, no depression in mixture with starting material.

Phenyldihydrothebaine methyl ether, obtained by the action of diazomethane on (+) α-phenyldihydrothebaine was a sirup, whose hydrobromide melted at 86–88° (gas evol. at 99°) and had $(\alpha)_D^{28}$ +21.9° (alcohol, *c*, 0.33).

Anal. Calc'd for $C_{26}H_{30}BrNO_3$: 3 OCH_3, 19.2. Found: OCH_3, 18.9.

The *methiodide* had the m.p. 196–197.5°, $(\alpha)_D^{28}$ +20.7° (alcohol, *c*, 0.34).

Anal. Calc'd for $C_{27}H_{32}INO_3$: 3 OCH_3, 17.0. Found: OCH_3, 16.7.

DEGRADATION OF THE METHYLDIHYDROTHEBAINONES

Methyldihydrothebainone methine. A suspension of 3.3 g. of methyldihydrothebainone methiodide (7) in 20 ml. of 30% KOH was boiled vigorously for 15 min. The resinous product was hydrolyzed with water and CO_2, and brought into ether, which yielded 1.5 g. of crystals (66%); from ethyl acetate, felted needles, m.p. 164–165° (darkens); $(\alpha)_D^{20}$ +163° (alcohol, *c*, 1.0); diazosulfanilic acid test intense red.

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.9; H, 8.25.
Found: C, 72.6; H, 8.22.

The *methiodide*, from methanol, had the m.p. 246–249° (evac. tube), $(\alpha)_D^{20}$ +117° (alcohol, *c*, 0.51).

Anal. Calc'd for $C_{21}H_{30}INO_3$: C, 53.5; H, 6.41.
Found: C, 53.2; H, 6.81.

Methyldehydrothebenone. The above methine methiodide was degraded by boiling for 5 min. with 30% KOH. The suspension of granular material was acidified with HCl, and the precipitate recrystallized from alcohol (88% yield), and sublimed at 150°/0.1 mm., m.p. 183–184°; $(\alpha)_D^{20}$ +262° (acetone, *c*, 0.52); diazosulfanilic acid test negative.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.09.
Found: C, 75.7; H, 7.40.

Isomethyldihydrothebainone methine. Isomethyldihydrothebainone (7) was converted to the methiodide in boiling acetone, and the hygroscopic crystals immediately boiled for 15 min. with 30% KOH. The resin was treated with water and CO_2 and brought into benzene, which yielded 0.8 g. of pink crystals; purified from ethyl acetate and sublimed at 150°/0.1 mm., m.p. 193°, $(\alpha)_D^{20}$ +231° (alcohol, *c*, 0.2); diazosulfanilic acid test intense red.

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.9; H, 8.25.
Found: C, 72.5, 72.4; H, 8.90, 8.51.

Isomethyldehydrothebenone. The methine was converted to the amorphous methiodide, which was boiled 4 min. with 30% KOH. The resin was triturated with dil. HCl and ether; the ether gave a crystalline product in poor yield; from alcohol, m.p. 116.5–117°, $(\alpha)_D^{20}$ +252° (alcohol, *c*, 0.49); diazosulfanilic acid test negative.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.09.
Found: C, 75.9; H, 7.09.

SUMMARY

Phenylmagnesium bromide reacts with thebaine to give two isomeric phenyldihydrothebaines, designated as (+) α and (+) δ. By heat treatment the (+) α isomer rearranges to a (−) δ form, and the (+) δ isomer to a (−) α form. The isomerism of the α and δ series is shown to be due to a difference in configuration at the asymmetric atom to which nitrogen is attached.

By hydrogenolysis, the nitrogen-containing ring of the (+) α and (+) δ isomers is opened, to give a single (+) phenyltetrahydrothebaimine; the (−) α and (−) δ isomers give similarly a (−) phenyltetrahydrothebaimine. These optical antipodes form a well-defined racemate.

The degradation of the phenyldihydrothebaines through isomethines to nitrogen-free products is described. The great stability of the ring system, the retention of the vinyl group in the final step of exhaustive methylation, and other peculiarities of the phenyldihydrothebaines are not explicable on the basis of the accepted thebaine formula. Since thebaine is related to morphine through dihydromorphine dimethyl ether, this also casts doubt on the structure of morphine.

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