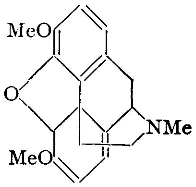
171. *The Reduction of Thebaine and Dihydrothebaine by Sodium and Ammonia.*

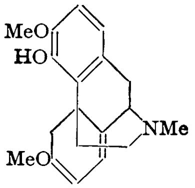
By K. W. Bentley, Sir Robert Robinson, and A. E. Wain.

The sodium–liquid ammonia reduction of thebaine has been shown to give phenolic dihydrothebaine * in excellent yield, and the sodium–liquid ammonia reduction of dihydrothebaine affords dihydrothebainone Δ^5-enol methyl ether. The latter is also obtained by the catalytic reduction of phenolic dihydrothebaine, and shown to be different from the compound prepared in the latter way by Small and Browning (*J. Org. Chem.*, 1939, **3**, 618). Phenolic dihydrothebaine has been degraded to a nitrogen-free substance. Wolf–Kishner reduction of thebenone and β-thebenone yields isomeric phenols. The reduction of thebaine is concentrated hydrochloric acid with zinc affords a bimolecular substance of unknown constitution.

The reduction of organic compounds by sodium dissolving in liquid ammonia, with or without an additional proton source such as alcohol, has been shown to follow in many cases a course similar to that of the reduction with sodium and alcohol (Birch, *J.*, 1945, 809; *Nature*, 1946, **158**, 585). As the reduction of thebaine (I) by the latter process results in reductive scission of the allylic ether group and production of "phenolic dihydrothebaine" * (Freund and Holtoff, *Ber.*, 1899, **32**, 168; Small and Browning, *J. Org. Chem.*, 1939, **3**, 618), the reduction of thebaine under the conditions of the sodium–liquid ammonia method was investigated. The reduction (Bentley and Robinson, *Experientia*, 1950, **6**, 353) proceeded very rapidly in the absence of alcohol to give dihydrothebaine-*ϕ* in yields of up to 90%, thus providing a much more convenient method of preparing the base than that available hitherto. Dihydrothebaine-*ϕ* has been formulated as (II) (Small and Browning, *loc. cit.*) and we adopted this view until it was found to be inconsistent with the failure of attempts to convert the base into derivatives of 14-bromothebainone (III) by methods analogous to those used for the preparation of 14-bromocodeinone (IV) from thebaine (Freund, *Ber.*, 1906, **39**, 844) and of attempts to add benzoquinone or maleic anhydride to the base, its methiodide, and methyl ether methiodide. Stork (*J. Amer. Chem. Soc.*, 1951, **73**, 504) has shown from a study of the ultra-violet and infra-red absorption spectra of thebaine, β-dihydrothebaine (Schmid and Karrer, *Helv. Chim. Acta*, 1950, **33**, 863), and dihydrothebaine-*ϕ* that (II) is in fact the structure of β-dihydrothebaine, whilst dihydrothebaine-*ϕ* is to be represented by the only other feasible formula, (V), and must arise in the sodium–liquid ammonia reduction by 1 : 4-addition of electrons to the allylic ether system.



(I)



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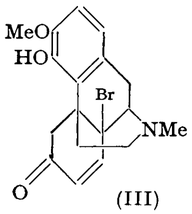

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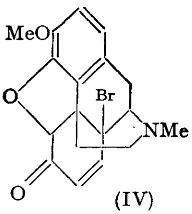

(IV)

Contrary to the statement of Freund and Holtoff (*loc. cit.*) dihydrothebaine-*ϕ* methiodide is readily degraded by hot alkali to a methine base, shown by ultra-violet and infra-red spectral measurements to be (VI) (Fig. 2), the 5 : 6-double bond having moved into conjugation under the influence of the hot alkali in a manner analogous to the well-known

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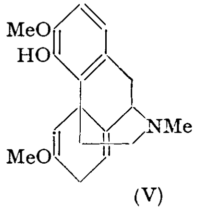
* The term "phenolic dihydrothebaine" accords with no recognised system of nomenclature and is especially cumbrous in the case of derivatives. We suggest the use of the expression dihydrothebaine-*ϕ* (not *ϕ*-dihydrothebaine, which could be confused with phenyldihydrothebaine).

Secondly, we propose to adopt the name "codeimethine" instead of the familiar "methylmorphimethine." This alternative appears simple and logical. It also avoids ambiguity in the case of certain derivatives.

isomerisation of α-codeimethine (VIII) to β-codeimethine (IX) (Gulland and Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, 1925, **69**, 79). The base (VI) should thus be termed



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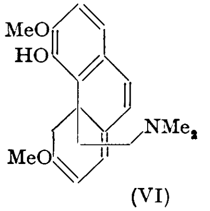

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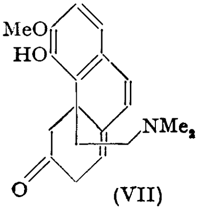
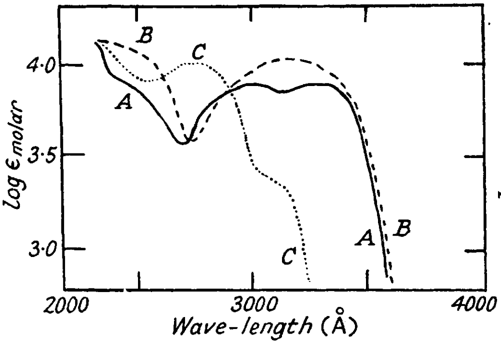


(VII)

β-dihydrothebaine methine, though its production by the Hofmann degradation of β-dihydrothebaine has not yet been attempted owing to the inaccessibility of the base. Hydrogenation of (VI) proceeded rapidly with absorption of two molecules of hydrogen, to give, probably, a mixture of stereoisomers since no crystalline derivatives could be obtained.

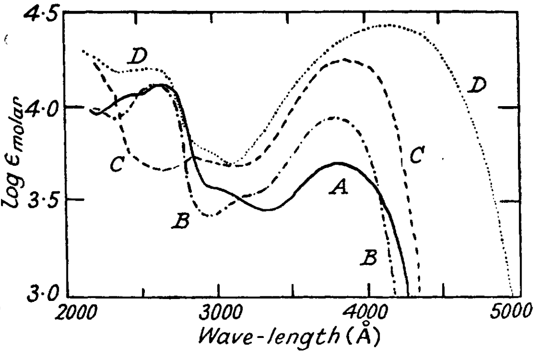
Hydrolysis of (VI) with mineral acid gave thebainone-B methine (VII), the ultra-violet absorption spectrum of which closely resembles that of β-codeimethine * (IX) whilst that of α-codeimethine (VIII) in which only one double bond is conjugated with the aromatic nucleus is markedly dissimilar (Fig. 1). The piperonylidene derivative of (VII) shows an intense absorption band in the region 3000—5000 Å, indicative of the presence of a highly conjugated system (Fig. 2).

FIG. 1.



——— *A, Thebainone-B methine* (VII).
— — — *B, β-Codeimethine* (IX).
. . . . . *C, α-Codeimethine* (VIII).

FIG. 2.



——— *A, β-Dihydrothebaine methine* (VI).
—.—.— *B, 6-Methoxythebentriene.*
— — — — *C, Product of reduction of thebaine with zinc and concentrated hydrochloric acid.*
. . . . . . *D, Piperonylidenethebainone B methine.*

These results are sufficient to eliminate the isomeric αβ-unsaturated ketone structure for thebainone-B methine. Hydrolysis of dihydrothebaine-*ϕ* methiodide with hot sulphurous acid was reported by Freund and Holtoff (*loc. cit.*) to give "*iso*dihydrothebaine" (m. p. 138°; hydriodide, 235°; methiodide, 205°) whereas we find that the reaction affords thebainone-B methine (m. p. 184°; hydriodide, 215°; methiodide, 210°) in good yield. The same reaction occurs under the influence of warm mineral acid. Dihydrothebaine-*ϕ* methyl ether methiodide has also been degraded to a methine base (Freund and Holtoff, *loc. cit.*), which on hydrolysis affords thebainone-B methyl ether methine.

The nitrogen-containing ring of dihydrothebaine-*ϕ*, which shows a tendency to break on treatment with sulphurous acid, to give thebainone-C (X) (Bentley and Wain, following

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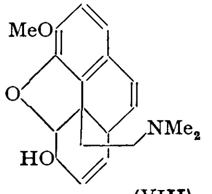
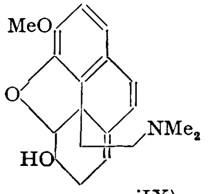
* The ultra-violet absorption of α-codeimethine was at one time thought to be inconsistent with a styrenoid constitution (cf. Robinson, Anniversary Address Roy. Soc., 1947) but a further examination of models such as eugenol and *iso*eugenol, and their derivatives, has removed this obstacle. The spectra remain somewhat anomalous and fuller elucidation of the subject is needed.

communication), is apparently so further weakened by conversion into the methiodide that fission of the ring can occur very readily. Thebainone-B methiodide undergoes degradation to (VII) in the same way, and a preliminary experiment indicates that β-dihydrothebaine methiodide also suffers degradation by acids to the salt of a sensitive base. The intermediate in all these reactions is doubtless thebainone-B methiodide,



(VIII)



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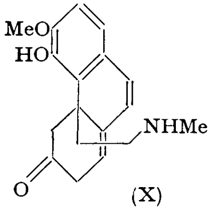
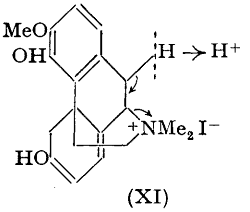


(X)

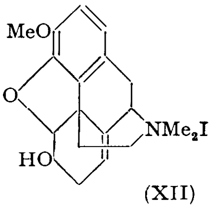


(XI)

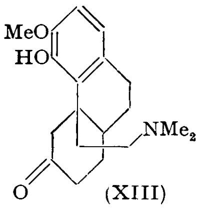
which in its enolic form (XI) allows the formation of a conjugated system by fission of the nitrogen ring with the introduction of a 9 : 10-double bond. Neopine methiodide (XII), which cannot develop a similar conjugated system, is unaffected by hot acids. It is noteworthy that thebaine methiodide does not undergo a similar degradation, but this is possibly related to the ease with which thebaine undergoes other rearrangements in acid solution.

Hydrogenation of thebainone-B methine resulted in production of β-dihydrothebainone dihydromethine (XIII), further characterised by conversion into β-thebenone (XIV), these products being identical with those obtained by Small and Browning (*loc. cit.*) from β-thebainone, hydrogen addition at $C_{(14)}$ occurring in the configuration abnormal in the morphine series. Hofmann degradation of (VII) involved the loss of a volatile base, but the nitrogen-free substance could not be isolated.

It may be noted here that production of a compound allotted the structure (VII) by the degradation of 14-hydroxydihydrothebainone methine (XV) was reported by Schöpf and and Borkowsky (*Annalen*, 1927, **452**, 248), but, whereas (VII) has been shown to give β-dihydrothebainone dihydromethine on hydrogenation, Schöpf and Borkowsky's base gave a different substance that was not analysed.



(XII)



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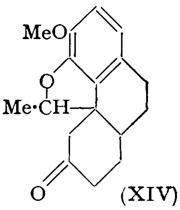
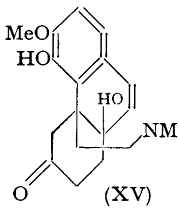


(XIV)



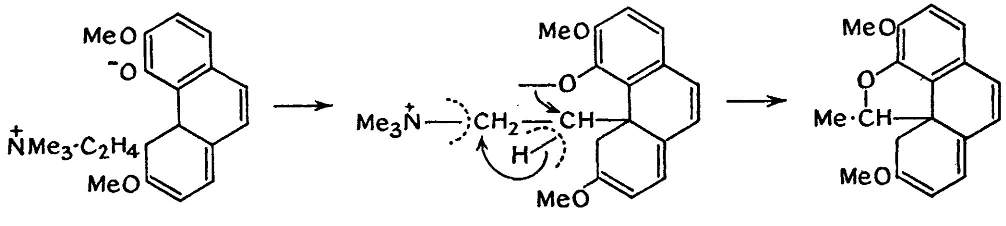
(XV)

β-Dihydrothebaine methine (VI) undergoes further Hofmann degradation with loss of trimethylamine and production of 6-methoxythebentriene (XVII) which retains the residue of the nitrogen-containing ring as part of a cyclic ether of thebenone type. Apparently production of this cyclic ether system stabilises the product as when this is impossible, in the methyl ether of (VI), loss of the side chain occurs and 3 : 4 : 6-trimethoxyphenanthrene is obtained (Freund, *Ber.*, 1905, **38**, 3234). It is reasonable therefore to assume that during the degradation of (VI) a vinyl group does not appear as such at $C_{(13)}$, as this would result in immediate loss of ethylene as in the methyl ether series, there being no plausible mechanism by which a vinyl group could cyclise with the phenolic hydroxyl group in alkaline solution. The ease of loss of trimethylamine in degradations resulting in thebenone ring closure suggests that the same mechanism is operative in all cases. This mechanism is very probably (XVI) ⟶ (XVII) as illustrated.

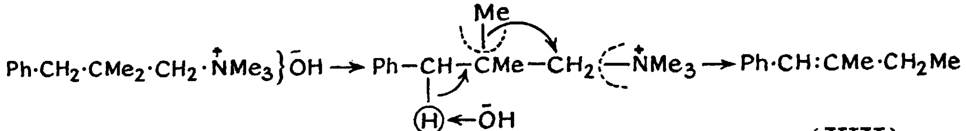
In a similar manner (XVIII) degrades as shown to (XIX) (Robinson, unpublished work).

Hydrolysis of 6-methoxythebentriene yielded theben-8(14) : 9-dien-6-one (XX) which is very sparingly soluble in all solvents and has not been subjected to reduction.

When the $C_{(14)}$-epimeric ketones thebenone and β-thebenone (XIV) were reduced under the drastic conditions of Huang-Minlon's modification of the Wolf–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) demethylation accompanied reduction, the products being morphoran and β-morphoran (XXI) respectively, though in one reduction of thebenone a small amount of the methyl ether of morphoran was obtained.



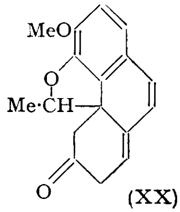
(XVI) Migration of H⁻ (XVII)



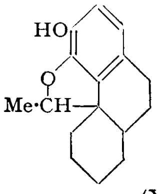
$$\text{Ph·CH}_2\text{·CMe}_2\text{·CH}_2\text{·}\overset{+}{\text{N}}\text{Me}_3\}\bar{\text{O}}\text{H} \longrightarrow \text{Ph–}\underset{\text{(H)}\leftarrow\bar{\text{O}}\text{H}}{\text{CH}}\text{–}\overset{\text{Me}}{\text{C}}\text{Me–CH}_2\text{–}\overset{+}{\text{N}}\text{Me}_3 \longrightarrow \text{Ph·CH:CMe·CH}_2\text{Me}$$

(XVIII) Migration of Me⁻ (XIX)

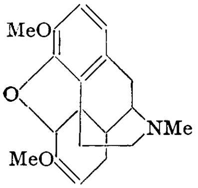
Attempts to oxidise dihydrothebaine-*ϕ* to a bimolecular derivative by silver nitrate (Goto, *J. Chem. Soc. Japan*, 1929, **50**, 603) led to a mixture, but as nitric acid is produced during this oxidation hydrolysis in part to thebainone derivatives may well occur.



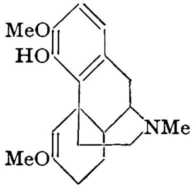
(XX)



(XXI)



(XXII)



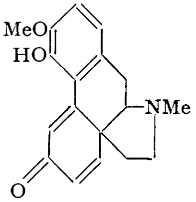
(XXIII)

Following the success of the sodium–liquid ammonia reduction of thebaine, dihydrothebaine (XXII) was reduced in the same way to obtain dihydrothebainone Δ-^{5}enol methyl ether (XXIII). [Stork (*loc. cit.*) points out that the allocation of structures to the Δ^5- and Δ^6-enol methyl ethers of dihydrothebainone by Small and Browning (*loc. cit.*) must be reversed, as these were based on a misconception of the structure of dihydrothebaine-*ϕ*. The revised nomenclature is used throughout this account.] From this reduction a hard granular crystalline solid, m. p. 145—146°, $[\alpha]^{17}_{D}$ —61·5° (in alcohol), was obtained, whereas Small and Browning report this enol ether, obtained by the catalytic reduction of dihydrothebaine-*ϕ*, as plates, m. p. 127—128°, $[\alpha]^{27}_{D}$ —8·0° (in alcohol). A repetition of the catalytic reduction of dihydrothebaine-*ϕ* over palladised strontium carbonate as catalyst (Small and Browning used platinum oxide) resulted in the same compound, m. p. 145—146°, as granular crystals, though these were mixed with a certain amount of gummy impurity, possibly the $C_{(14)}$-epimer of (XXIII). The compound from both sources gave dihydrothebainone in 95% yield on hydrolysis.

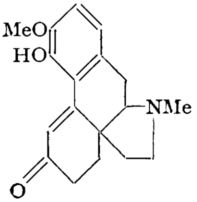
We regard this product, obtained in two independent ways, as the genuine dihydrothebainone Δ^5-enol methyl ether, and presume that Small and Browning's substance of lower melting point and rotation is a mixture, possibly with dihydrothebaine-*ϕ*, $[\alpha]^{18}_{D}$ +31·4°, though they report a very good yield of dihydrothebainone on hydrolysis of their compound. Dihydrothebainone Δ^5-enol methyl ether is presumably the intermediate in the reported reduction of dihydrothebaine to dihydrothebainone by sodium and amyl alcohol (Freund, Speyer, and Guttmann, *Ber.*, 1920, **53**, 2250), the enol ether being hydrolysed to the ketone during isolation of the product.

When thebaine is dissolved in concentrated hydrochloric acid a deep red-orange solution is obtained. This is believed to contain (XXIV) (Robinson, *Nature*, 1947, **160**, 815) which on reduction catalytically (Cahn, *J.*, 1933, 1038) or with stannous chloride (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160; Schöpf and Borkowsky, *Annalen*, 1927, **458**, 148) yields metathebainone (XXV). Reduction of this halochromic solution with zinc has now been shown to give a bimolecular derivative containing no keto-group, the ultra-violet spectrum of which shows strong absorption in the same region as for β-dihydrothebaine methine (VII) and 6-methoxythebentriene (XVII) (Fig. 2), from which it is concluded that the aromatic nuclei are probably joined through two double bonds. The substance is phenolic and couples readily with diazonium salts, but nothing further is known about its constitution.

(XXIV)



(XXV)



EXPERIMENTAL.

Dihydrothebaine-φ (V).—Thebaine (110 g.) was suspended in liquid ammonia (1100 ml.) in a 1600-ml. Dewar flask, and clean sodium (17·6 g.) added in thin slices with mechanical stirring, the transitory orange colour first noted being finally replaced by a permanent deep blue colour (35 minutes). The solution was stirred for a further 10 minutes, the excess of sodium removed by the addition of a few drops of alcohol, and the solution cautiously poured into cold water (1000 ml.). A small amount of precipitate was formed but dissolved immediately on addition of sodium hydroxide solution. The phenolic base was precipitated by addition of either solid carbon dioxide or 2N-hydrochloridic acid, the solution remaining strongly ammoniacal throughout. The former method gave a somewhat purer product. The base was taken up in ether (5 l.), the extract washed well to remove ammonia, and the ether partly removed by distillation, whereupon the base separated as a white or very pale pink solid; this was collected when the extract had been concentrated to 400—500 ml. The yield was 87 g. of material sufficiently pure for most purposes. A further 12 g. of less pure material could be recovered from the ethereal solution. The remainder of the product was a red tar.

On recrystallisation from ethyl acetate–light petroleum (b. p. 80—100°) dihydrothebaine-φ was obtained as colourless prisms, m. p. 154° alone or mixed with a specimen prepared by sodium–alcohol reduction of thebaine (Small and Browning, *loc. cit.*). It had $[\alpha]_D^{18}$ + 31·4° (Found: C, 73·2; H, 7·3; N, 4·3; OMe, 17·5. Calc. for $C_{19}H_{23}O_3N$: C, 72·9; H, 7·3; N, 4·5; OMe, 19·8%). The *picrate* was obtained as rosettes of slender yellow needles, m. p. 176° (decomp.), on recystallisation from alcohol containing 10% of benzene (Found: C, 55·4; H, 4·8; N, 10·3. $C_{25}H_{26}O_{10}N_4$ requires C, 55·4; H, 4·8; N, 10·3%).

O-*Acetyldihydrothebaine-φ*.—Dihydrothebaine-φ gave a black tar on treatment with acetyl chloride or acetic anhydride in pyridine, but the O-*acetyl* derivative was obtained by passing a stream of keten through a solution of the base (10 g.) in dry ether (800 ml.) for 6 hours, during which the solution became milky and a small quantity of brown tar separated. This tar dissolved when the mixture was shaken with water. The ethereal layer was separated, shaken with dilute potassium hydroxide solution (6 × 150 ml.), washed with water, dried (Na_2SO_4), and evaporated. The crystalline residue was recrystallised from light petroleum (b. p. 80—100°) (charcoal), giving O-*acetyldihydrothebaine-φ* as rosettes of slender, colourless prisms, m. p. 139° (3·5 g.) (Found: C, 71·3; H, 6·8. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%). The *picrate* was obtained as minute, canary-yellow prisms, m. p. 180° (decomp.), on crystallisation from 2-ethoxyethanol (Found: C, 55·1; H, 4·8; N, 9·9. $C_{27}H_{28}O_{11}N_4$ requires C, 55·5; H, 4·8; N, 9·6%).

Bromination of dihydrothebaine-φ or its acetyl derivative in glacial acetic acid in the presence of potassium acetate with one, two, or three molecular equivalents of bromine yielded intractable products.

Condensation of Thebaine Methiodide with Benzoquinone.—A solution of resublimed benzoquinone (0·3 g.) in chloroform (5 ml.) was added to a solution of thebaine methiodide (1 g.; m. p. 224°) in chloroform (5 ml.), a red colour immediately developing. The mixture was heated to boiling on the steam-bath and rubbed with a glass rod, whereupon a bright orange precipitate separated. This was collected, washed with chloroform, and dried. "*Thebaine-quinone*" *methiodide* was thus obtained as orange needles, m. p. 205° (decomp.) (Found: C, 55·6; H, 5·0; I, 23·3. $C_{26}H_{28}O_5NI$ requires C, 55·6; H, 5·0; I, 22·7%). The *adduct* was decomposed completely on recrystallisation from *cyclo*hexanone, to give thebaine methiodide, m. p. 224° alone or mixed with an authentic specimen (Found: C, 52·0; H, 5·3; I, 27·1. Calc. for $C_{20}H_{24}O_3NI$: C, 53·0; N, 5·3; I, 28·0%). Dihydrothebaine-ϕ and its methiodide were rather rapidly oxidised when warmed with benzoquinone in chloroform, and the base was decomposed on being heated with maleic anhydride in boiling benzene. Dihydrothebaine-ϕ methyl ether methiodide (Freund, *Ber.*, 1905, **38**, 3255), though not so rapidly oxidised, slowly darkened on being heated with benzoquinone. In no case could the production of any adduct be detected.

β-*Dihydrothebaine Methine* (VI).—Potassium hydroxide was added to a solution of recrystallised dihydrothebaine-ϕ methiodide (30 g.) in hot, air-free water, until oily drops formed in the resulting brown solution. The mixture was then refluxed for 30 minutes in an atmosphere of oxygen-free nitrogen. (Without this precaution the mixture rapidly became almost black and the product was extremely difficult to purify.) The mixture was then cooled in ice, and the liquid decanted from the brown glassy solid, which was washed twice with ice-cold water, and shaken with warm water (125 ml.) and ether (500 ml.). The solid dissolved in the ethereal layer, which was separated, washed with water (3 × 100 ml.), and dried (Na_2SO_4), and the ether was then evaporated. In this way β-*dihydrothebaine methine* was obtained as a brownish-yellow crystalline solid. It separated from light petroleum (b. p. 60—80°) as pale yellow, well-formed cubes, m. p. 99°, with a red-brown tint when viewed in thickness, or as small yellow prisms from methyl acetate (recovery not good) [Found: (From petroleum) C, 73·9; H, 8·0; N, 4·2. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·7; N, 4·3. (From methyl acetate) C, 70·3; H, 7·7. $C_{20}H_{25}O_3N,0{\cdot}5CH_3{\cdot}CO_2CH_3$ requires C, 70·8; H, 7·7%]. It was readily soluble in all organic solvents except cold light petroleum. Its alcoholic solution gave an intense grey-violet colour with ferric chloride, and its alkaline solution an intense red colour with diazobenzenesulphonic acid. The methiodide, prepared in methanol, was very soluble in water and alcohols, but addition of aqueous sodium perchlorate to a solution of the salt in water precipitated the *methoperchlorate* which was obtained as apple-green, felted needles, m. p. 134°, on recrystallisation from 50% aqueous alcohol (Found: C, 56·8; H, 6·6; Cl, 8·2. $C_{21}H_{28}O_3N,ClO_4$ requires C, 57·1; H, 6·4; Cl, 8·0%).

β-*Dihydrothebaine methine picrate* was obtained as scarlet prisms, m. p. 159°, when alcoholic solutions of the base and picric acid were mixed in the correct proportions (Found: C, 55·8; H, 5·0; N, 10·0. $C_{26}H_{28}O_{10}N_4$ requires C, 56·1; H, 5·0; N. 10·1%). It decomposed on attempted recrystallisation from *iso*butanol. The picrate and the methoperchlorate appear to be stable but the free base decomposes, slowly in the dark, very rapidly in sunlight, to a black tar.

Reduction of β-*Dihydrothebaine Methine.*—β-Dihydrothebaine methine (3 g.) in alcohol (50 ml.) was shaken under hydrogen in presence of palladised strontium carbonate until absorption of hydrogen ceased (505 ml., 2 mols.). The solution was filtered from catalyst, during which process it assumed a deep violet colour which disappeared when the solution was evaporated. On distillation of the residue, the *tetrahydro*-derivative (a β-*hexahydrothebainemethine*) was obtained as a colourless oil, b. p. 200°/0·04 mm., $[\alpha]_D^{20}$ 0·0° (in alcohol) (Found: C, 72·3; H, 8·6. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·8%). No crystalline derivatives could be obtained.

Thebainone-B Methine (VII),—(*a*) β-Dihydrothebaine methine (2 g.) was dissolved in 3N-hydrobromic acid (15 ml.) with warming, and, on cooling, a mass of colourless felted needles separated (2·2 g.). These were collected, washed with water, and recrystallised from water, giving *thebainone-B methine hydrobromide* as long colourless needles, m. p. 234° (decomp.) (Found: C, 58·1; H, 6·1; Br, 20·3. $C_{19}H_{23}O_3N,HBr$ requires C, 57·9; H, 6·1; Br, 20·3%). This gave an intense maroon colour with concentrated sulphuric acid, and its alcoholic solution gave a brown colour with ferric chloride, changing to a transient green on dilution with water. *Thebainone-B methine* was obtained as pale yellow needles on neutralisation of a warm solution of the hydrobromide with ammonia in presence of sodium dithionite (hydrosulphite). The solid was rapidly collected, washed, and dried *in vacuo*, during which processes it became violet. This colour became more intense during the recrystallisation from alcohol, which gave the methine as violet felted needles, m. p. 184°, stubbornly retaining solvent (Found: C, 72·0; H, 7·5; N, 4·1. $C_{19}H_{23}O_3N,0{\cdot}25EtOH$ requires C, 72·1; H, 7·5; N, 4·3%). The violet colour of the alcoholic solution was discharged by the addition of one drop of aqueous sodium dithionite but rapidly returned in the air. The *hydriodide* was obtained as almost colourless prisms by dissolving the base in warm dilute hydriodic acid and cooling the mixture. On recrystallisation from hot water with the addition of sodium dithionite it was obtained as colourless prisms, m. p. 214° (Found: C, 51·7; H, 5·3. $C_{19}H_{23}O_3N,HI$ requires C, 51·7; H, 5·4%). The *methiodide* prepared in benzene, crystallised from water as colourless needles, m. p. 210°, becoming blue on continued exposure to air (Found: C, 51·5; H, 5·8. $C_{20}H_{26}O_3NI,0{\cdot}5H_2O$ requires C, 51·7; H, 5·8%). The *piperonylidene* derivative was prepared by addition of sodium ethoxide to a hot alcoholic suspension of the hydriodide and piperonaldehyde, a blood-red solution being obtained. After 10 minutes this was diluted with four times its volume of water, and the precipitate was collected and recrystallised from alcohol, yielding dark brown-yellow plates, m. p. 192—193° (Found: C, 72·5; H, 6·2. $C_{27}H_{27}O_5N$ requires C, 72·5; H, 6·1%).

(*b*) Dihydrothebaine-*φ* methiodide (25 g.) was dissolved in boiling water (125 ml.), and sulphur dioxide passed through the solution for 15 minutes, during which the solution turned deep blue. The solution was boiled for a further 10 minutes to expel all sulphur dioxide, and allowed to cool, whereupon a mass of felted pale blue needles separated. These were collected, washed, and recrystallised from boiling water with the addition of sodium dithionite, affording thebainone-B methine hydriodide as colourless prisms, m. p. 214°. The m. p. of this salt, the hydrobromide (234°), and the free base (184°) were undepressed by addition of the corresponding derivatives prepared by the hydrolysis of β-dihydrothebaine methine.

Thebainone-B methine perchlorate was obtained as colourless prisms, m. p. 230° on recrystallisation from water, by addition of sodium perchlorate to a hot aqueous solution of the hydriodide (Found: C, 54·4; H, 5·8; Cl, 8·1. $C_{19}H_{23}O_3N,HClO_4,0{\cdot}5H_2O$ requires C, 54·1; H, 5·9; Cl, 8·4%).

(*c*) Dihydrothebaine-*φ* methiodide (1 g.) was dissolved in hot 5N-hydrochloric acid (10 ml.), and 10 drops of perchloric acid were added. On cooling, a mist of fine droplets appeared, but these rapidly solidified. The crystals were collected and recrystallised from water. They then had m. p. 230°, undepressed by the addition of thebainone-B methine perchlorate. The identity was further confirmed by comparison of their ultra-violet absorption spectra.

(*d*) Thebainone-B (Bentley and Wain, cf. following paper) was precipitated from an aqueous solution of the hydrobromide (2 g.) in the presence of sodium dithionite, the base taken up in ether, and methyl iodide added to the mixture. A sensitive methiodide separated. The ether was decanted and the mixture warmed with 5N-hydrochloric acid. Potassium iodide was added to the mixture, and the solution cooled, whereupon dark crystals of thebainone-B methine hydriodide separated. These were collected and recrystallised from water in the presence of sodium dithionite (charcoal). Insufficient material was obtained for full purification; it had m. p. 211°, undepressed by admixture with thebainone-B methine hydriodide, m. p. 214°.

Hydrogenation of Thebainone-B Methine.—Thebainone-B methine (10 g.) was suspended in alcohol (150 ml.) and shaken under hydrogen at room temperature and pressure in presence of palladised strontium carbonate until absorption of hydrogen ceased (1500 ml., 1·9 mols.). The solution was filtered from catalyst, which was washed twice with hot alcohol, and the combined solutions were evaporated. On cooling, β-dihydrothebainone dihydromethine crystallised and was collected (8 g.). It was obtained as almost colourless needles, m. p. 179° (alone or mixed with an authentic specimen), on recrystallisation twice from alcohol.

β-*Thebenone.*—The above base was converted into β-thebenone by Small and Browning's method (*loc. cit.*), the latter substance being obtained as almost colourless rods, m. p. 188°, on recrystallisation from alcohol (reported m. p. 189—190°). *Piperonylidene*-β-*thebenone*, prepared by the action of sodium ethoxide on a solution of β-thebenone and piperonaldehyde in hot alcohol, crystallised on cooling, and was obtained as golden-yellow plates, m. p. 189°, on recrystallisation from 2-ethoxyethanol (Found: C, 73·7; H, 6·0. $C_{25}H_{24}O_5$ requires C, 74·1; H, 5·9%).

Thebenone, prepared from dihydrothebainone dihydromethine (Wieland and Kotake, *Annalen*, 1925, **444**, 69) and recrystallised from alcohol, was obtained as almost colourless prisms, m. p. 135° (reported m. p. 134—136°). Its 2 : 4-*dinitrophenylhydrazone* was obtained as minute, orange prisms, m. p. 225°, on crystallisation from dioxan (Found: N. 12·2. $C_{23}H_{24}O_6N_4$ requires N, 12·4%).

β-*Dihydrothebaine methyl ether methine* (Freund, *Ber.*, 1905, **38**, 3255) was prepared by the Hofmann degradation of dihydrothebaine-*φ* methyl ether methiodide, in an atmosphere of nitrogen, the product being obtained as a pale, amber-coloured gum, from which, contrary to

Freund's statement, no crystalline methiodide could be obtained. No other derivative could be obtained crystalline. The base decomposed spontaneously on storage, with evolution of readily detectable amounts of amine.

O-*Methylthebainone-B Methine*.—(*a*) Dihydrothebaine-*ϕ* methyl ether methiodide (0·6 g.) was dissolved in hot water (5 ml.), and four drops of 60% perchloric acid were added. On cooling and scratching with a glass rod, almost colourless crystals of O-*methylthebainone-B methine perchlorate* separated (0·3 g.). These were collected and recrystallised from water, with the addition of a few mg. of sodium dithionite. The salt was thus obtained as colourless prisms, m. p. 169° (Found: C, 55·8; H, 6·0; Cl, 8·3. $C_{20}H_{25}O_3N,HClO_4$ requires C, 56·1; H, 6·1; Cl, 8·3%). This was shown to be the perchlorate of a base which was liberated on neutralisation of a hot solution with ammonia. The base could not be purified owing to its ready oxidation.

(*b*) β-Dihydrothebaine methyl ether methine (0·2 g.) was hydrolysed in the same way as dihydrothebaine-*ϕ* methyl ether methiodide, and found to yield the same perchlorate, m. p. 170°, undepressed by admixture with the perchlorate obtained from the latter hydrolysis.

6-*Methoxytheben*-6 : 8(14) : 9-*triene* (XVII).—β-Dihydrothebaine methine (15 g.) was refluxed with methyl iodide (10 ml.) in alcohol (20 ml.), and the alcohol evaporated. The resulting oily methiodide was dissolved in water (100 ml.), potassium hydroxide added to the hot solution until a brown oil separated, and the solution boiled until evolution of trimethylamine ceased. When the mixture was cooled in ice, the brown oil set to a glass, from which the liquid was decanted. The glass was washed with water and shaken with ether until no more would dissolve. After being dried (Na_2SO_4), the ethereal solution was evaporated, leaving a brown oil that solidified on trituration with light petroleum (b. p. 60—80°). The solid was collected and recrystallised from the same solvent (charcoal), giving 6-*methoxytheben*-6 : 8(14) : 9-*triene* as canary-yellow prisms, m. p. 88°, darkening slightly on exposure to sunlight (5 g.) (Found: C, 76·0; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·5; H, 6·39%). It was insoluble in alkali, and the diazobenzenesulphonic acid and ferric choride tests were negative. No picrate could be obtained, showing that the substance is not the isomeric 4-ethoxy-3 : 6-dimethoxyphenanthrene.

Theben-8(14) : 9-*dien*-6-*one* (XX).—Concentrated hydrochloric acid (1 ml.) was added to a solution of 6-methoxythebentriene (0·5 g.) in alcohol (10 ml.). During 30 minutes the solution deposited pale yellow crystals which were collected and well washed with alcohol and water (0·3 g.). On recrystallisation from a relatively large amount of dioxan (poor recovery), *theben*-8(14) : 9-*dien*-6-*one* was obtained as colourless prisms, m. p. 248° (Found: C, 75·7; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·0; H, 6·0%).

Morphoran (XXI).—Thebenone (1·5 g.) and 90% hydrazine hydrate (3·4 ml.) were added to a solution of sodium (1·8 g.) in diethylene glycol (50 ml.), and the mixture refluxed for an hour. Water was then distilled off until the b. p. of the mixture rose to 200°, whereafter the solution was refluxed for 6 hours, then cooled, and poured into water. No precipitate was obtained, but on acidification an oil separated, which was taken up in ether. Evaporation of the extract left a viscous oil that crystallised slowly on trituration with aqueous ethanol. After recrystallisation from this solvent, *morphoran* was obtained as large, iridescent, irregular, colourless plates, m. p. 103° (Found: C, 78·7; H, 8·3; OMe, 0·0. $C_{16}H_{20}O_2$ requires C, 78·6; H, 8·2%). Morphoran is readily soluble in most organic solvents, its alcoholic solutions give a green colour with ferric chloride, and its alkaline solutions an intense red colour with diazobenzenesulphonic acid.

In one experiment in which the time of reflux was limited to 3 hours a small amount of an alkali-insoluble by-product was obtained. This appears to be morphoran methyl ether (thebenan) and was obtained as colourless prisms, m. p. 86° on recrystallisation from alcohol, $[\alpha]_D^{20}$ 0·0° (methanol) (Found: C, 77·8; H, 8·3; OMe, 9·0. Calc. for $C_{17}H_{22}O_2,0{\cdot}25H_2O$: C, 77·7; H, 8·5; OMe, 11·8%). Goto and Mitsui (*Bull. Chem. Soc. Japan*, 1931, **6**, 197) give the antipode of thebenan as crystallising with $\frac{1}{2}H_2O$ and having $[\alpha]_D^{17}$ $-3{\cdot}1°$. The m. p. was not cited but their material was dried at 70°; Goto and Shishido (*ibid.*, 1935, **10**, 252) give the m. p. of (+)- and (−)-thebenan (anhydrous) as 48—54°; Cahn (*J.*, 1926, 2652) reports a compound of the same structure as an oil.

β-*Morphoran*, obtained in a similar way from β-thebenone, formed minute, almost colourless prisms, m. p. 148°, on crystallisation from 50% aqueous alcohol (Found: C, 78·3; H, 8·4%).

Oxidation of Dihydrothebaine-ϕ with Silver Nitrate.—Dihydrothebaine-*ϕ* (1 g.) in ethanol (10 ml.) was treated with excess of silver nitrate solution, and the mixture warmed on the water-bath for ½ hour and set aside overnight. The mixture was then filtered from the precipitated silver and poured into water, excess of ammonia was added, and the base was collected at the pump and dried. On crystallisation from toluene a light brown powder was obtained, decomposing slowly without melting on being heated above 200°. Two crystal types and an amorphous substance could be detected under the microscope. The analytical data were unsatisfactory.

Dihydrothebainone Δ^5-Enol Methyl Ether (XXIII).—(*a*) Dihydrothebaine (Small, Fitch, and Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 1457) (5 g.) was reduced with sodium (0·5 g.) in liquid ammonia (200 ml.), the excess of sodium removed by the addition of solid ammonium chloride, and the mixture cautiously poured into water (100 ml.). A small amount of precipitate formed, but this dissolved on the addition of sodium hydroxide. The phenolic base was precipitated by solid carbon dioxide and extracted with ether. The ethereal extract on evaporation left a very pale pink oil, that crystallised at once on being rubbed with methyl acetate, to give colourless crystals, m. p. 143—145° (4·7 g.). The *methyl ether* was obtained as large, hard, granular, colourless crystals, m. p. 145—146° (after three recrystallisations from methyl acetate), $[\alpha]_D^{17}$ $-61{\cdot}5°$ (in alcohol) (Found: C, 72·5; H, 7·9. $C_{19}H_{25}O_3N$ requires C, 72·8; H, 7·8%). The substance gave an intense red colour on treatment with diazobenzenesulphonic acid in alkaline solution. The *methiodide*, prepared in alcohol, was obtained as elongated prisms, m. p. 153°, on crystallisation from alcohol (Found: C, 52·3; H, 6·5. $C_{19}H_{25}O_3N,CH_3I$ requires C, 52·5; H, 6·1%).

(*b*) Dihydrothebaine-*φ* (5 g.) in alcohol (120 ml.) was shaken under hydrogen in the presence of palladised strontium carbonate at the room temperature until absorption of hydrogen ceased (about 20 hours). The filtered solution was evaporated, leaving a pink gum that crystallised when rubbed with methyl acetate. Dihydrothebainone Δ^5-enol methyl ether was obtained as colourless, granular crystals, m. p. 145—146° [undepressed when mixed with a specimen of the base prepared as in (*a*)], on recrystallisation from methyl acetate. The yield by this process was only about 50%, but the residue recovered from the methyl acetate mother-liquors contained considerably more of the base, as was shown by hydrolysis of the residue to dihydrothebainone in good yield.

The methiodide prepared in this way had m. p. 153°, undepressed on admixture with a specimen of the methiodide prepared as in (*a*).

Hydrolysis. Dihydrothebainone Δ^5-enol methyl ether (1 g.) was dissolved in warm 2N-hydrochloric acid (5 ml.). Crystals slowly appeared, and these passed into solution on dilution of the mixture to 25 ml. After 15 minutes the solution was neutralised with ammonia, and the precipitate collected and recrystallised from aqueous alcohol. Dihydrothebainone was obtained, m. p. 146—150° alone or mixed with an authentic specimen, m. p. 148—151° (yield before recrystallisation, 0·91 g.).

Reduction of Thebaine with Zinc and Concentrated Hydrochloric Acid.—Zinc turnings were added in portions of 0·5 g. each to a stirred solution of thebaine (5 g.) in concentrated hydrochloric acid (60 ml.), the temperature being kept below 30°. The orange-red colour of the solution first darkened, then became orange, and finally yellow, and deposited a yellow precipitate. The reduction occupied about 45 minutes. The mixture was poured into water (700 ml.), made alkaline with ammonia, and submitted to continuous ether-extraction. In this way, a yellow amorphous solid (2·4 g.) was obtained; it was freely soluble in organic solvents except ether and light petroleum. After three recoveries from light petroleum (b. p. 60—80°) it was amorphous and had m. p. *ca.* 202°. On one occasion fine yellow needles were obtained from aqueous methyl alcohol, and these had m. p. 264° but the quantity was insufficient for analysis. The substance was phenolic as shown by its solubility in alkali and the red colour given by the alkaline solution on treatment with diazobenzenesulphonic acid. The infra-red spectrum indicates that there is no carbonyl group in the molecule, and the molecular-weight determination of the amorphous substance indicated that the substance is bimolecular (Found: *M*, 559). Its solution in concentrated sulphuric acid is deep purple.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October* 31*st*, 1951.]