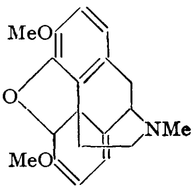
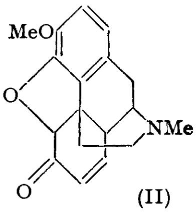
172. *The Morphine–Thebaine Group of Alkaloids. Part I. The Isomerism of the Thebainones.*

By K. W. Bentley and A. E. Wain.

A fourth thebainone has been prepared, by hydrolysis of dihydrothebaine-ϕ with acid. Structures have been allotted to all four isomers on the basis of infra-red and ultra-violet absorption data.

The reduction of thebaine (I) (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160; Schöpf and Borkowsky, *Annalen*, 1927, **458**, 148) and of codeinone (II) (Knorr, *Ber.*, 1905, **38**, 3171) with stannous chloride and concentrated hydrochloric acid, and catalytic hydrogenation of thebaine in >5N-hydrochloric acid (Cahn, *J.*, 1933, 1038) result in the production of a phenolic unsaturated ketone, originally called thebainone, but subsequently renamed metathebainone when it was realised that this base no longer contains the thebaine skeleton, having suffered migration of the side chain from $C_{(13)}$ to $C_{(14)}$, and is in fact (III) (Schöpf and Borkowsky, *loc. cit.*).


(I)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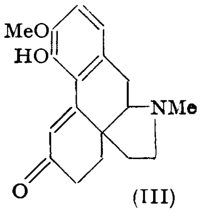
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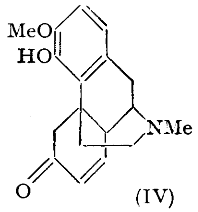
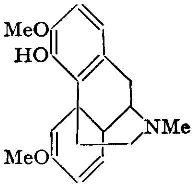

(IV)

Subsequently the true thebainone (IV) was isolated from the stannous chloride–hydrochloric acid reduction of thebaine and codeinone under slightly different conditions (Schöpf and Hirsch, *Annalen*, 1931, **489**, 224) and later (Small and Morris, *J. Amer. Chem. Soc.*, 1932, **54**, 2122; 1934, **56**, 2159) shown to be identical with the "sulphur-free ketone" obtained by the hydrolysis of β-ethylthiocodide (Pschorr, *Annalen*, 1910, **373**, 15). It has since also been prepared by hydrolysis of thebainone enol methyl ether (V) (Small and Browning, *J. Org. Chem.*, 1939, **3**, 618), and by the catalytic rearrangement of codeine (VI) (Weiss and Weiner, *J. Org. Chem.*, 1949, **14**, 194). Thebainone has been shown to have the structure (IV) by its smooth catalytic hydrogenation to dihydrothebainone (VII) (Schöpf and Hirsch, and Small and Browning, *loc. cit.*).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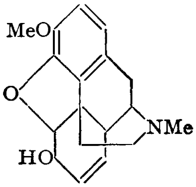
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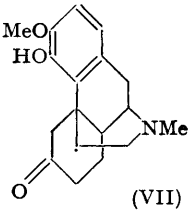
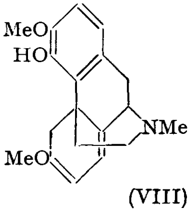
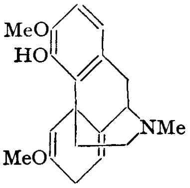

(VII)

Two other thebainones were isolated by Small and Browning from the products of hydrolysis of dihydrothebaine-ϕ [at that time believed to be (VIII), but now known to be (IX) (Stork, *J. Amer. Chem. Soc.*, 1951, **73**, 504)]. One of these (obtained by hydrolysis with potassium hydrogen sulphate) was believed to be the $C_{(14)}$ epimer of thebainone and was named β-thebainone, on the basis of its hydrogenation to β-dihydrothebainone and the degradation of the latter to a methine, dihydromethine, and nitrogen-free product (β-thebenone), during the whole course of which the isomerism between the two series persisted. β-Thebainone has since been obtained by hydrolysis of β-dihydrothebaine (Schmid and Karrer, *Helv. Chim. Acta*, 1950, **33**, 863) [first thought to be the $C_{(14)}$ epimer of (V), but now known to be (VIII) (Stork, *loc. cit.*)].

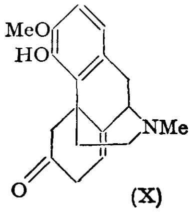
The other isomer of thebainone was obtained in very erratic and unsatisfactory yield by the hydrolysis of dihydrothebaine-ϕ with warm sulphurous acid, was named α-thebainone, and was tentatively allotted the structure (X). Small and Browning further reported that hydrolysis of dihydrothebaine-*ϕ* with mineral acid gave only " coloured varnish-like substances," and suggested that under these conditions changes in addition to the simple hydrolysis of the enol ether group had occurred. By carrying out the hydrolysis with alcoholic hydrobromic acid we have isolated as hydrobromide a fourth thebainone, further characterised as its picrate, and we have been able to show that the same substance is produced by hydrolysis of dihydrothebaine-*ϕ* with aqueous hydrochloric or perchloric acids. The free base rapidly degenerates to highly coloured substances. This thebainone was hydrogenated as the hydrobromide in aqueous solution, affording a 90% yield of dihydrothebainone.



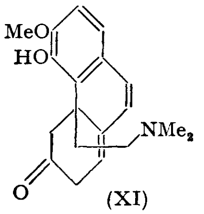
(VIII)



(IX)



(X)



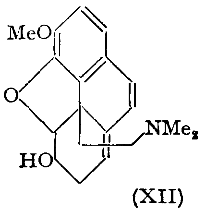
(XI)

It is clear that the existence of four isomeric thebainones can only be reasonably explained on the assumption that in one of them the nitrogen-containing ring has been broken with the introduction of a double bond between $C_{(9)}$ and $C_{(10)}$, and it seemed very probable that this has occurred during the production of Small and Browning's α-thebainone [compare the hydrolysis of dihydrothebaine-*ϕ* methiodide by hot sulphurous acid to the hydriodide of the base (XI), erroneously named α-thebainone methine (Bentley and Robinson, *Experientia*, 1950, **6**, 353)]. On the basis of this explanation two of the thebainones should be αβ-unsaturated and two βγ-unsaturated ketones. This question could not be settled by investigation of the ultra-violet absorption spectra of the thebainones as the ultra-violet absorption of the carbonyl group is masked in the morphine series by that of the aromatic nucleus, so attention was directed to the infra-red absorption of the four isomers. The following values were found for the carbonyl absorption frequencies in the infra-red:

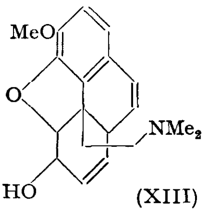
Thebainone perchlorate	1677 cm.$^{-1}$
β-Thebainone perchlorate	1671 cm.$^{-1}$
α-Thebainone perchlorate	1709 cm.$^{-1}$
New thebainone hydrobromide	1711 cm.$^{-1}$

These frequencies are slightly lower than normal, probably owing to hydrogen bonding in the solids, but they are clearly divided into two pairs, those of thebainone and β-thebainone being attributable to a carbonyl group conjugated with a double bond, whilst those of α-thebainone and the new thebainone are attributable to a normal non-conjugated carbonyl group.

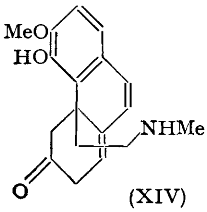
The absorption of the four compounds in the ultra-violet was next studied and found to allow a clear differentiation between α-thebainone and the other three isomers. The absorption curves of thebainone, β-thebainone, and the new thebainone are close to that of dihydrothebaine-*ϕ* (Fig. 1), the absorption in these cases being attributable to the guaiacol nucleus only; the spectrum of α-thebainone shows greatly increased absorption, and absorption at longer wave-lengths, as in the case of β-codeimethine (XII) and the base



(XII)



(XIII)



(XIV)

(XI) in which two double bonds are conjugated with the aromatic nucleus, the absorption being greater than with α-codeimethine (XIII) in which only one double bond is conjugated with the nucleus (Fig. 2). These results leave no doubt that the new thebainone has the structure originally allotted by Small and Browning to α-thebainone, whilst the latter must now be allotted the structure (XIV).

The nomenclature of the thebainones is now seen to be in a state of confusion; for example, β-thebainone refers to a compound with one configuration at $C_{(14)}$, but α-thebainone does not refer to its epimer, and β-thebainone is a closer relative of thebainone than is the α-isomer. We propose, therefore, the re-naming of all four thebainones as indicated below: *

Old name	New name	Structure
Thebainone	Thebainone-A	(IV)
β-Thebainone	β-Thebainone-A	(IV) $C_{(14)}$-epimer
" New thebainone "	Thebainone-B	(X)
α-Thebainone	Thebainone-C	(XIV)

The name " α-thebainone methine " given to (XI) by Bentley and Robinson (*loc. cit.*) is now an obvious misnomer, as the nitrogen ring is already broken in " α-thebainone; " in fact (XI) is related to thebainone-B and its correct name is thebainone-B methine.

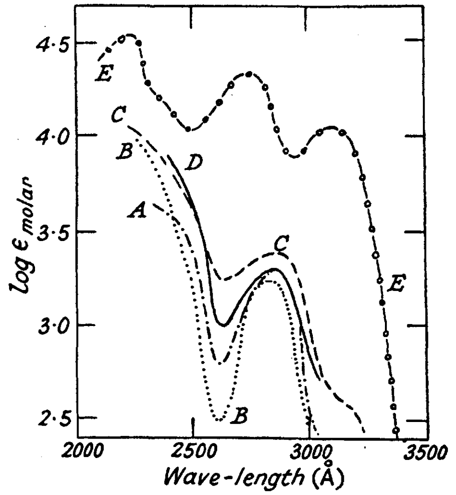
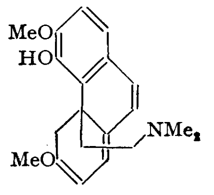
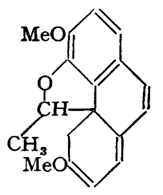


FIG. 1.

A, New thebainone obtained by hydrolysis of dihydrothebaine-φ with mineral acid.
B, Dihydrothebaine-φ.
C, β-Thebainone.
D, Thebainone.
E, α-Thebainone.

On the basis of structure (IX) for dihydrothebaine-φ it is clear that thebainone-B must be an intermediate in the hydrolysis of this base to β-thebainone-A with potassium hydrogen sulphate, and in fact it is gradually converted into the latter in an aqueous solution of potassium hydrogen sulphate. The hydrolysis of dihydrothebaine-φ to thebainone-C, however, must be an independent process, as no trace of this base (easily recognised by its intense eosin-red colour with concentrated sulphuric acid, with which the other three isomers give only a pale straw colour) is formed when thebainone-B is kept in sulphur dioxide

(XV)




(XVI)

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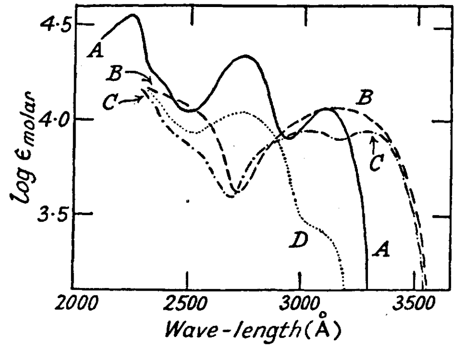
* Where the position of the ethylenic linkings is now known with certainty, *e.g.*, in the thebainone and deoxycodeine series, ambiguity can be avoided by use of Δ to specify these positions. For instance, thebainone-A (IV) may be called Δ^7-thebainone, dihydrothebaine-φ (IX) may be called $\Delta^{6:8}$-dihydrothebaine, and dihydrothebainone Δ^5-enol methyl ether [(XXIII) of the preceding paper] may be called Δ^5-tetrahydrothebaine.—ED.

solution for several weeks. Tentative experiments indicate that thebainone-B methiodide is degraded to the hydriodide of (XI) by hot sulphurous acid in the same way as is dihydrothebaine-ϕ methiodide.

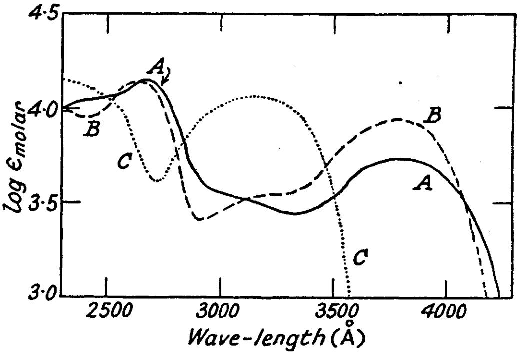
Although Stork (*loc. cit.*) has shown that dihydrothebaine-ϕ is to be represented by the structure (IX) and not by (VIII) (a formulation in agreement with our observation of its failure to undergo Diels–Alder addition of benzoquinone or maleic anhydride), there is no doubt on the basis of the ultra-violet absorption spectra (Fig. 3) that the methine base obtained by the degradation of its methiodide and the nitrogen-free product (6-methoxythebentriene) have the structures (XV) and (XVI) allotted to them by Bentley and Robinson (*loc. cit.*), which were based as much on these spectra as on their methods of preparation. Doubtless the 5 : 6-double bond moves into conjugation with those at positions 8 : 14 and 9 : 10 under the influence of the hot alkali during the Hofmann degradation.

FIG. 2.



A, *α-Thebainone.* *C*, (XI).
B, *β-Codeimethine.* *D*, *α-Codeimethine.*

FIG. 3.



A, (XV). *B*, (XVI). *C*, (XII).

EXPERIMENTAL

(M. p.s. are uncorrected.)

Thebainone-B (X).—Dihydrothebaine-ϕ (5 g.) was dissolved in hot ethanol (20 ml.), the solution was cooled to 30°, and 48% hydrobromic acid (3 ml.) was added. After 10 minutes the solution deposited a large quantity of minute prisms when scratched. The solid (5 g.) was collected, washed well with cold alcohol and finally with ether, and stored in a vacuum-desiccator. The hydrobromide is apparently indefinitely stable when dry, but rapidly degenerates to a tar if left wet with alcohol. *Thebainone-B hydrobromide*, m. p. 205—207°, is sparingly soluble in organic solvents but very soluble in water and has $[\alpha]_D^{20}$ +15·84° (in water) (Found: C, 56·7; H, 5·9; Br, 20·8. $C_{18}H_{21}O_4N,HBr$ requires C, 56·8; H, 5·8; Br, 21·0%). The base was obtained, as a pale yellow gum that rapidly degenerated on attempted crystallisation, by precipitation from a solution of the hydrobromide by potassium hydrogen carbonate in presence of sodium dithionite (hydrosulphite) and extraction with ether. The *picrate*, obtained by adding a solution of sodium picrate to an aqueous solution of the hydrobromide, formed bright yellow prisms, m. p. 183°, on recrystallisation from 2-ethoxyethanol (Found: C, 54·3; H, 4·9; N, 10·2. $C_{24}H_{24}O_{10}N_4$ requires C, 54·5; H, 4·55; N, 10·6%). The same picrate was obtained by hydrolysis of dihydrothebaine-ϕ with aqueous hydrochloric acid, precipitation of the product as the sparingly soluble gummy perchlorate, dissolution of the latter in hot water, and addition of aqueous sodium picrate. No other crystalline salts have been prepared from thebainone-B.

Thebainone-A (IV).—This was prepared by Schöpf and Hirsch's method (*loc. cit.*) and purified through the *perchlorate*. This was obtained as colourless plates, m. p. 149—150° (on recrystallisation from water), $[\alpha]_D^{21}$ −28·2° (in 50% alcohol) (Found: C, 51·6, 52·1; H, 6·2, 6·1. $C_{18}H_{21}O_3N,HClO_4,H_2O$ requires C, 52·7; H, 5·8%).

β-*Thebainone-A* (IV).—This was prepared by Small and Browning's method (*loc. cit.*) and purified through the perchlorate, which is apparently dimorphic, as we obtained it as colourless prisms, m. p. 122—124° (reported as colourless six-sided plates, m. p. 149—157°). The base obtained from this low-melting form was recovered, on recrystallisation from aqueous acetone, as long colourless needles, m. p. 99—100°, $[\alpha]_D^{21}$ +112° (in acetone) [reported m. p. 98—99°, $[\alpha]_D^{27}$ +114° (in acetone)] (Found: C, 68·1; H, 7·3. Calc. for $C_{18}H_{21}O_3N,H_2O$: C, 68·1; H, 7·25%).

Thebainone-C (XIV).—This isomer was prepared as directed by Small and Browning for "α-thebainone," and, as reported, the preparation was very troublesome. In our hydrolysis a white crystalline solid separated when the solution was set aside. This was presumably the bisulphite addition compound of a mixture of thebainones-B and -C, as it readily dissolved when the solution was heated and could not then be recovered. This substance was collected and dissolved in hot water, the solution cooled, and the base isolated as recommended by Small and Browning; after recrystallisation from acetone, a portion was found to have m. p. 186—187° (reported for "α-thebainone" 185—186°). *Thebainone-C perchlorate* was prepared, by the addition of aqueous sodium perchlorate to a solution of the base in dilute hydrochloric acid, and was obtained as colourless leaflets, m. p. 200° (decomp.) on recrystallisation from water in presence of a very small quantity of sodium dithionite (Found: C, 54·6; H, 5·6. $C_{18}H_{21}O_3N,HClO_4$ requires C, 54·2; H, 5·5%).

Hydrogenation of Thebainone-B Hydrobromide.—Thebainone-B hydrobromide (3·8 g.) in water (100 ml.) was shaken under hydrogen in presence of palladised charcoal. Hydrogen absorption did not begin until the solution had been heated to 80°. (In a comparative experiment using neopine hydrobromide, in which the double bond occupies a similarly sheltered position, absorption only began at 75°.) When absorption of hydrogen ceased the solution was freed from catalyst by filtration and neutralised with potassium hydrogen carbonate solution, which when kept gave a crystalline precipitate of dihydrothebainone (2·7 g.), m. p. 148—150° (from aqueous ethanol), undepressed on admixture with an authentic specimen.

Isomerisation of Thebainone-B.—(*a*) Thebainone-B hydrobromide (1 g.) was kept overnight in a solution of potassium hydrogen sulphate (2 g.) in water (15 ml.), after which the base was isolated and converted into the perchlorate, which after four recrystallisations from water was obtained as colourless irregular prisms, m. p. 122—123°, or m. p. 121—123°, when mixed with a specimen of β-thebainone-A perchlorate.

(*b*) Thebainone-B hydrobromide (1 g.) was kept for 3 weeks with a saturated solution of sulphur dioxide at 15—25°, with occasional warming to 40°. A crystalline solid, probably the bisulphite addition commpound of thebainone-B, separated but dissolved on addition of water and warming to 35°. Addition of perchloric acid to this solution gave no precipitate, but warming to 100° and cooling precipitated an oily perchlorate. This gave only a pale straw colour on dissolution in concentrated sulphuric acid and is probably unchanged thebainone-B perchlorate. No crystalline perchlorate could be isolated from the reaction mixture.

Thanks are tendered to Mr. D. C. McKean for the measurement of the infra-red absorption spectra of the thebainones, which were done on the solid salts in suspension in "Nujol" using a rock-salt prism and a Perkin-Elmer spectrometer, model 12C; to Dr. F. B. Strauss for the measurement of the ultra-violet absorption spectra of the thebainones; and to the Ministry of Education for a grant to one of us (A. E. W.). We also thank Professor Sir Robert Robinson for his interest in this work.

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