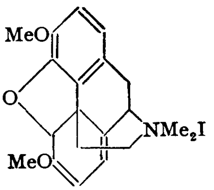
173. *The Morphine–Thebaine Group of Alkaloids. Part II.* The Reduction of Certain Quaternary Salts.*

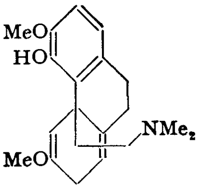
By K. W. Bentley and A. E. Wain.

Sodium–liquid ammonia reduction of the methiodides of alkaloids of the morphine group has been shown to result in reductive scission of the nitrogen-containing ring, except in the case of dihydrothebainone Δ^5-enol methyl ether methiodide, which is reconverted into the parent base. In this way thebaine has been degraded to a nitrogen-free product.

QUATERNARY ammonium salts in the *iso*quinoline series have been reduced catalytically to dimethyl-2-*o*-tolylethylamines (Emde and Kull, *Arch. Pharm.*, 1936, **274**, 173) and degraded by sodium amalgam reduction to dimethyl-2-vinylbenzylamines (Emde, *Annalen*, 1912, **391**, 173), and Clayson (*J.*, 1949, 2016) has shown that sodium–liquid ammonia reduction of such quaternary salts follows the course of the catalytic reduction. As the morphine alkaloids are derivatives of *iso*quinoline the methiodides of some of these have been submitted to the sodium–liquid ammonia reduction, and in this way thebaine methiodide (I) has been shown to undergo reduction to dihydrothebaine-*ϕ* dihydromethine (II) in 70% yield; the same substance is obtained by similar reduction of dihydrothebaine-*ϕ* methiodide, and its methyl ether from dihydrothebaine-*ϕ* methyl ether methiodide. A further application of this reduction to the methiodide of (II) led to complete elimination of the nitrogen atom and production of 13-ethyl-7 : 8 : 9 : 13-tetrahydro-4-hydroxy-3 : 6-dimethoxyphenanthrene (III), a very unstable substance which spontaneously decomposed in a very short time. Hofmann degradation of the methiodide of (II) afforded 6-methoxytheben-5 : 8-diene (IV).



(I)



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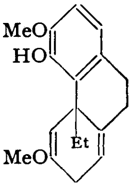

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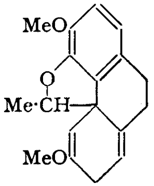

(IV)

Catalytic reduction of dihydrothebaine-*ϕ* dihydromethine proved to be more difficult than that of dihydrothebaine-*ϕ*; as in the case of neopine and thebainone-B, in which the double bond occupies the same position as in (II) (Bentley and Wain, Part I of this series), reduction only occurred at a measurable rate at temperatures above 70°, under which conditions a base, presumably dihydrothebainone dihydromethine Δ^5-enol methyl ether (Δ^5-tetrahydrothebaine methine) (V), was obtained. The latter on hydrolysis yielded what appears to be the low-melting form of dihydrothebainone dihydromethine obtained by Cahn (*J.*, 1926, 2570) and Schöpf (Annalen, 1927, **452**, 266, footnote).

Hydrolysis of dihydrothebaine-*ϕ* dihydromethine with aqueous hydrochloric acid yielded thebainone-B dihydromethine (VI) (carbonyl absorption frequency in the infra-red 1699 cm.$^{-1}$, compared with 1709 and 1711 cm.$^{-1}$ for the unconjugated carbonyl groups in thebainones-C and B, and 1677 and 1671 cm.$^{-1}$ for the conjugated carbonyl groups in thebainone-A and β-thebainone-A; Bentley and Wain, *loc. cit.*). Hofmann degradation of the methiodide of (VI) afforded with difficulty an oil which proved to be a mixture, probably of isomeric dehydrothebenones (VII) and (VIII), as the 8 : 14-double bond may well migrate in part into conjugation with the carbonyl group under the influence of the hot concentrated alkali. Dihydrothebaine-*ϕ* methyl ether dihydromethine proved to be an oil and was not further investigated.

Dihydrothebaine methiodide (IX) was next submitted to reduction with sodium in ammonia and found to give an intractable mixture of bases, not all of which were soluble in

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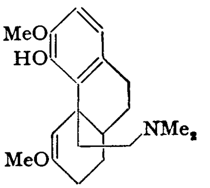
* Part I, preceding paper.

alkali; the analytical data for the mixture indicated that it contained less hydrogen than corresponds to (V). When however dihydrothebainone Δ^5-enol methyl ether methiodide (Δ^5-tetrahydrothebaine methiodide) (X) (Bentley, Robinson, and Wain, *J.*, 1952, 958),



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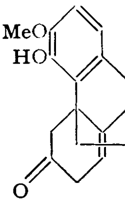

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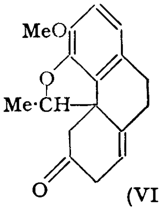

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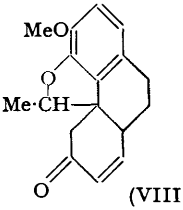
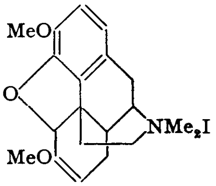


(VIII)

the expected intermediate in the sodium–ammonia reduction of dihydrothebaine methiodide, was reduced in this way only the undegraded parent base was recovered from the reaction in good yield. Presumably some reduction of the nitrogen-containing ring in dihydrothebaine methiodide occurs before scission of the cyclic ether, and dihydrothebaine dihydromethine (XI), which would be the product of such a reaction, is so sparingly soluble that no reduction takes place in liquid ammonia, as was verified by a separate experiment. This would account for the production of a non-phenolic substance during the reduction of dihydrothebaine methiodide. Neopine methiodide (XII) on reduction under these conditions affords an excellent yield of neopine dihydromethine (XIII), identical with the product of sodium–alcohol reduction of α-codeimethine (XIV) (Vongerichten, *Ber.*, 1899, **32**, 1047; 1901, **34**, 2722) and the product of sodium amalgam reduction (Mosettig, *J. Org. Chem.*, 1940, **5**, 401) or mild catalytic reduction (von Braun and Cahn, *Annalen*, 1927, **451**, 55) of β-codeimethine (XV). The reduction of codeine methiodide appears to follow the same course, but other changes occur in addition, and this and similar reductions will be the subject of a later discussion.



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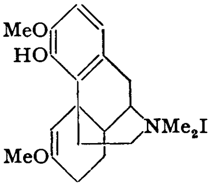

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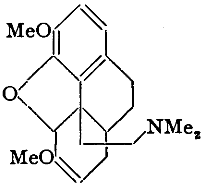

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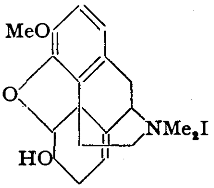

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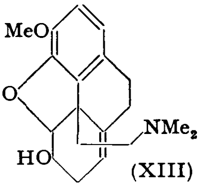

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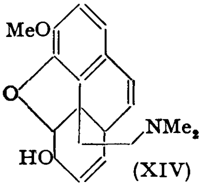

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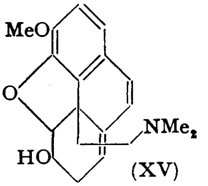

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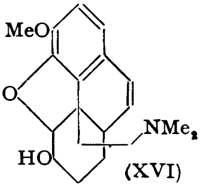

(XVI)

The reductive scission of the nitrogen-containing ring in the quaternary salts of the morphine alkaloids appears to proceed most smoothly when there is a double bond in the βγ-position relative to the nitrogen, *i.e.*, when the base is an allylamine (*e.g.*, thebaine, dihydrothebaine-*φ*, dihydrothebaine-*φ* methyl ether and neopine methiodides).

The methiodide of (XIII) is remarkably stable towards alkaline degradation, being unaffected by prolonged boiling in a concentrated potassium hydroxide solution, and only slowly suffering degradation by sodium *cyclo*hexyloxide in boiling *cyclo*hexanol (to give a mixture). This Hofmann degradation will be investigated more fully to determine whether any methylation of the alcoholic hydroxyl group occurs, as in the degradation of dihydrocodeine methine (XVI) (Rapoport, *J. Org. Chem.*, 1948, **13**, 714).

EXPERIMENTAL

(M. p.s are uncorrected.)

Dihydrothebaine-ϕ Dihydromethine.—(*a*) Sodium (17·2 g.) was added in thin slices to a mechanically stirred solution of thebaine methiodide (76 g.) in liquid ammonia (1500 ml.) during 1 hour, a permanent blue colour being finally obtained. During the reduction the solution first became pale green, a cream-coloured precipitate separated, and the colour then became deep red, changing through purple to the blue colour indicative of the presence of excess of sodium. The mixture was stirred for a further 5 minutes, the excess of sodium removed by the addition of solid ammonium chloride, and the solution cautiously poured into cold water (1·5 l.). A bulky flesh-coloured precipitate separated, but dissolved completely on addition of sodium hydroxide. Precipitation of the base was effected by the addition of 2N-hydrochloric acid, the solution remaining strongly alkaline with ammonia throughout. The base was taken up in ether (2 l.), and the ethereal solution washed twice with water, dried ($MgSO_4$), and evaporated, giving 50 g. of crude material. The base is very soluble in almost all solvents, the best for recrystallisation being ether, from which the recovery is only about 50%. Recrystallisation from ether yielded *dihydrothebaine-ϕ dihydromethine* (20 g.), m. p. 88—89°, $[\alpha]_D^{17}$ + 94·5° (in ethanol) (Found: C, 72·2, 72·3; H, 8·3, 8·3; N, 3·8; C-Me, 0·0. $C_{20}H_{27}O_3N$ requires, C, 72·8; H, 8·2; N, 4·2; C-Me, 0·0%).

A further 15 g. of the base was recovered by evaporating the mother-liquors to small bulk and cooling the residue in a freezing mixture; from the mother-liquors from this recovery 5·35 g. of thebainone-B dihydromethine were obtained on hydrolysis, making the total recoverable yield from thebaine 69%.

Dihydrothebaine-ϕ dihydromethine methiodide is readily soluble in water and in ethanol, but addition of sodium perchlorate to an aqueous solution precipitated the crystalline *methoperchlorate*, obtained as colourless needles, m. p. 253°, on recrystallisation from water (Found: C, 55·9; H, 6·5. $C_{20}H_{27}O_3N,CH_3ClO_4,\frac{1}{2}H_2O$ requires C, 55·8; H, 6·6%).

(*b*) Dihydrothebaine-ϕ methiodide (5 g.) was dissolved in liquid ammonia (150 ml.) in a Dewar flask, and sodium (0·91 g.) added, with mechanical stirring, in thin slices, a permanent blue colour being obtained. The mixture was stirred for a further 5 minutes, the excess of sodium removed by the addition of ammonium chloride, and the base isolated as above, in a yield of 2·81 g. of pure material, m. p. 88°, undepressed by the addition of a specimen of the base prepared by the reduction of thebaine methiodide.

Dihydrothebaine-ϕ Methyl Ether Dihydromethine.—Dihydrothebaine-ϕ methyl ether methiodide (5 g.) in liquid ammonia (200 ml.) was reduced as above with sodium (0·85 g.), the colour of the mixture changing through mauve and purple to deep blue. The base, isolated in the same way as dihydrothebaine-ϕ dihydromethine, proved to be a clear amber oil (3·6 g.), obtained as a pale amber glass on distillation, b. p. 63°/0·04 mm. (Found: C, 73·9; H, 8·5. $C_{21}H_{29}O_3N$ requires C, 73·5; H, 8·4%).

No crystalline derivatives could be obtained from this base, which has not been further investigated.

13-*Ethyl*-7 : 9 : 10 : 13-*tetrahydro*-4-*hydroxy*-3 : 6-*dimethoxyphenanthrene.*—Methyl iodide (5 g.) was added to a solution of dihydrothebaine-ϕ dihydromethine in alcohol (20 ml.), and the solution warmed on the water bath for 10 minutes, evaporated to 10 ml., poured into liquid ammonia (800 ml.), and treated with ethyl alcohol (10 ml.). Sodium (1·68 g.) was added in thin slices during 30 minutes to the stirred solution, traces of unchanged sodium were removed by ammonium chloride, and the mixture was poured cautiously into water (300 ml.). The phenol was precipitated by addition of 2N-hydrochloric acid, the solution remaining strongly alkaline with ammonia throughout. The precipitate was isolated by ether-extraction as a pale yellow oil, yielding a semi-opaque glass on distillation, b. p. 150—155°/0·05 mm. (Found: C, 75·2; H, 8·0. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%). The *phenol* was soluble in alkali, and the solution gave an immediate blood-red colour on the addition of diazobenzenesulphonic acid. Within 3 weeks the phenol had completely decomposed to a black tar.

6-*Methoxytheben*-5 : 8-*diene* (IV).—Dihydrothebaine-ϕ dihydromethine methiodide (from 1·1 g. of the base) was boiled with a solution of potassium hydroxide (15 g.) in air-free water (250 ml.) in a nitrogen atmosphere until evolution of amine ceased (about 3 hours), the mixture was cooled, and the liquid was decanted from the residual gum. The latter was shaken with ether and very dilute acetic acid, the ethereal layer separated, washed twice with water, then dried ($MgSO_4$), and the ether removed by distillation, leaving the *diene* as a light brown oil (0·76 g.). This was obtained as a pale yellow glass on distillation, b. p. 255—265° (bath-temp.)/8 mm. (Found: C, 76·2; H, 7·0. $C_{18}H_{20}O_3$ requires C, 76·1; H, 7·0%). The diazobenzenesulphonic acid reaction was negative.

Hydrogenation of Dihydrothebaine-φ Dihydromethine.—Dihydrothebaine-φ dihydromethine (2 g.) in alcohol (50 ml.) was shaken under hydrogen in the presence of palladised strontium carbonate. No absorption of hydrogen was noticed after 3½ hours at room temperature. Hydrogen absorption at a measurable rate began at 70°, and proceeded until one mol. of hydrogen had been absorbed. After filtration, the alcohol was removed by evaporation, leaving a clear very pale yellow glass (1·8 g.) which was obtained as a colourless glass on distillation, b. p. 185°/0·025 mm. (Found: C, 72·1; H, 8·5. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·7%). This substance is presumably *dihydrothebainone dihydromethine Δ^5-enol methyl ether* (*Δ^5-tetrahydrothebaine dihydromethine*), as hydrolysis of a portion gave a base that on crystallisation from aqueous alcohol had m. p. 140°.

Thebainone-B Dihydromethine (VI).—Dihydrothebaine-φ dihydromethine (5 g.) was dissolved in warm N-hydrochloric acid (50 ml.), and the solution set aside for 10 minutes. On neutralisation with sodium carbonate in the presence of sodium dithionite (hydrosulphite) a flesh-coloured precipitate separated, and was collected at the pump, washed, and dried (3·6 g.). After three recrystallisations from aqueous alcohol, *thebainone-B dihydromethine* was obtained as almost colourless needles, m. p. 164° (Found: C, 72·0; H, 8·1. $C_{19}H_{25}O_3N$ requires C, 72·4; H, 7·9%). The *perchlorate*, prepared from the base and 60% perchloric acid in alcohol, was obtained as colourless prisms, m. p. 244—246°, on recrystallisation from water (Found: C, 54·6; H, 6·4; Cl, 7·8. $C_{19}H_{25}O_3N,HClO_4$ requires C, 54·9; H, 6·3; Cl, 8·5%). The *hydrobromide* was prepared in alcoholic solution and recrystallised from alcohol as colourless needles, m. p. 256—257° (Found: C, 57·6; H, 6·6; Br, 19·5. $C_{19}H_{25}O_3N,HBr$ requires C, 57·6; H, 6·6; Br, 20·0%). The *picrate* was precipitated from an aqueous solution of the hydrobromide by the addition of a solution of sodium picrate, and was obtained as clusters of bright yellow needles, m. p. 178—180°, on recrystallisation from alcohol (Found: C, 55·3; H, 5·2; N, 10·4. $C_{25}H_{28}O_{10}N_4$ requires C, 55·2; H, 5·1; N, 10·3%). The *methiodide*, prepared in alcohol, was obtained as colourless needles, m.p. 238°, on recrystallisation from 95% alcohol (Found: C, 51·6; H, 6·0; I, 27·2. $C_{19}H_{25}O_3N,CH_3I,\frac{1}{2}H_2O$ requires C, 51·5; H, 6·0; I, 27·3%). The *oxime* was obtained as colourless needles, m. p. 186—187°, on recrystallisation from 50% aqueous acetone (Found: C, 69·1; H, 8·2; N, 8·3. $C_{19}H_{26}O_3N_2$ requires C, 69·1; H, 7·9; N, 8·5%).

Hofmann Degradation of Thebainone-B Dihydromethine Methiodide.—Thebainone-B dihydromethine methiodide (1·4 g.) was boiled with 30% aqueous potassium hydroxide (30 ml.) until evolution of amine ceased (about 45 minutes), and the solution was cooled, acidified with hydrochloric acid, and extracted four times with chloroform (50 ml. portions). The extracts were washed with water, then dried, and the chloroform was removed, leaving a dark red oil, obtained as a yellow glass on distillation, b. p. 200—210° (bath-temp.)/0·075 mm. This substance was clearly a mixture, presumably of isomeric dehydrothebenones (the double bond having moved into conjugation with the carbonyl group in part under the influence of the hot alkali) as on storage for several weeks it was resolved into a crystalline solid and a dark yellow gum, both of which seem to be readily soluble in the same solvents, and have not yet been separated (Found, for mixture: C, 76·4; H, 6·8. Calc. for $C_{17}H_{18}O_3$: C, 75·5; H, 6·7%). The diazobenzenesulphonic acid reaction was negative for this compound, which was insoluble in aqueous alkali.

Reduction of Dihydrothebaine Methiodide.—Dihydrothebaine methiodide (18 g.) was reduced by sodium (2·85 g.) in liquid ammonia (400 ml.), and the product isolated as before. This proved to be an intractable mixture of bases, not all of which were soluble in alkali, one component apparently being crystalline, but it has not yet been possible to separate the mixture. No dihydrothebainone Δ^5-enol methyl ether could be isolated from the mixture (Found, for the mixture: C, 72·5; H, 8·3. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·8. $C_{20}H_{27}O_3N$ requires C, 72·9; H, 8·2. Calc. for $C_{19}H_{25}O_3N$: C, 72·8; H, 7·8%).

Reduction of Dihydrothebainone Δ^5-Enol Methyl Ether Methiodide.—This salt (5·5 g.) was dissolved in liquid ammonia (200 ml.) and reduced with sodium (2·37 g.). The product, isolated in the usual way, was obtained as colourless granular prisms (2·7 g.), m. p. 144—146°, undepressed on addition of dihydrothebainone Δ^5-enol methyl ether.

Neopine Dihydromethine (XIII).—Neopine methiodide (10 g.) was reduced by sodium (1·15 g.) in liquid ammonia (300 ml.), the excess of sodium removed by the addition of a few drops of alcohol, and the solution poured cautiously into water (300 ml.). The resulting aqueous solution was saturated with ammonium chloride and extracted with ether (3 × 200 ml.), and the combined ethereal extracts were washed, dried, and evaporated, leaving a brown oil that was converted in part into the methiodide, pale yellow elongated prisms, m. p. 263° (from 90%

alcohol), $[\alpha]_D^{19}$ −31·3° (in water) (Found: C, 50·1; H, 6·0; I, 27·2. Calc. for $C_{19}H_{25}O_3N,MeI,H_2O$: C, 50·5; H, 6·3; I, 26·8%); the m. p. was not depressed by addition of the methiodide of neopine dihydromethine prepared by sodium–alcohol reduction of α-codeimethine. The *perchlorate*, prepared in alcohol, was obtained as colourless pointed prisms, m. p. 216—217°, $[\alpha]_D^{20}$ −27·7° (in 50% alcohol) on recrystallisation from 95% alcohol (Found: C, 55·3; H, 6·7; Cl, 8·5. $C_{19}H_{25}O_3N,HClO_4$ requires C, 54·9; H, 6·3; Cl, 8·5%).

Hofmann Degradation of Neopine Dihydromethine Methiodide.—This methiodide (0·5 g.) was boiled with 40% aqueous potassium hydroxide for 1 hour, during which no trace of amine was evolved, and on cooling the salt crystallised. 5 G. of the methiodide were accordingly boiled under reflux with a solution of 2 g. of sodium in 60 ml. of *cyclo*hexanol until evolution of amine ceased (about 3 hours), the *cyclo*hexanol was removed by steam-distillation, and the residue was extracted with ether, which on evaporation left a brown viscous oil from which no definite fraction could be isolated on distillation.

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