The Morphine–Thebaine Group of Alkaloids. Part III. The Structure of the Codeimethines, and Related Topics.*

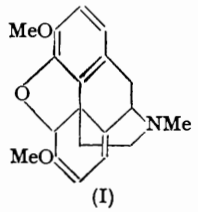
By K. W. Bentley and A. F. Thomas.

[Reprint Order No. 6056.]

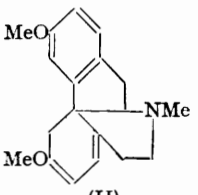
The structures adduced for α- and β-codeimethine by earlier workers have been confirmed and an alternative structure tentatively advanced for the α-isomer by Robinson disproved. A new α-dihydrocodeimethine has been prepared by the reduction of codeine methiodide and of α-codeimethine with sodium and liquid ammonia, reactions that also involve the production of a compound belonging to the deoxycodeine series. A new type of nitrogen-free substance has been prepared by the degradation of neopine dihydromethine.

In the arguments leading up to the now accepted structure for phenyldihydrothebaine Robinson (*Nature*, 1947, **160**, 815) stated that the only structure for thebaine other than the accepted one (I) capable of explaining formation of the former compound is (II), and that this type of structure in the morphine series is ruled out by the ultraviolet absorption of β-codeimethine which is consistent with the presence of the chromophore Ph·C:C·C:C; this is in agreement with the structure (III) for this compound and cannot be accommodated on a spiran structure of type (II). At the same time it was stated: "According to Dr. Strauss the ultraviolet absorption spectrum of α-codeimethine is not styrenoid and would be consistent with the arrangement Ph·C·C:C·C:C," and this grouping is embodied in the structure (IV) for the α-isomer instead of the formerly accepted (V).

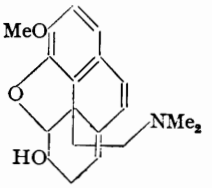
Now structure (IV) for α-codeimethine implies that the Hofmann degradation of codeine methiodide takes place under the influence of the 7 : 8-double bond rather than of the aromatic nucleus, which seems improbable. Further, a compound (IV) would be expected to isomerise readily in alkaline solution to (V) (cf. eugenol to *iso*eugenol). The



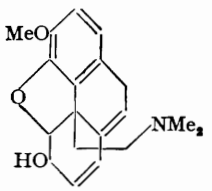
(I)



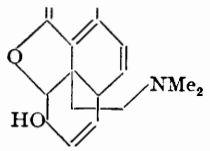
(II)



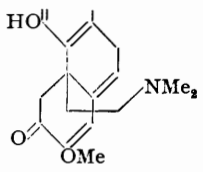
(III)



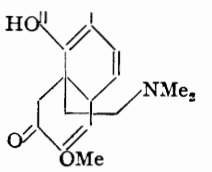
(IV)



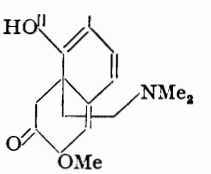
(V)



(VI)



(VII)



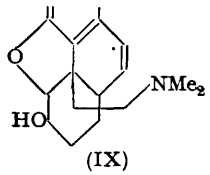
(VIII)

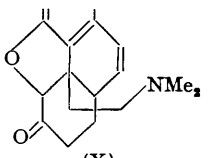
only previous case in which the three isomers of the types (III), (IV), and (V) have been isolated is in the degradation of sinomenine methiodide. There the tendency to give a 9 : 14 double bond under the influence of the C:C·CO system would be expected to be greater than with codeine methiodide, and the product (IV) would be expected to be more stable in alkali than (IV). In fact sinomenine *achro*methine (VI) is isolated only under carefully controlled conditions and is very readily isomerised to sinomenine *roseo*methine (VII) and sinomenine *violeo*methine (VIII) (Goto and Shishido, *Bull. Chem. Soc. Japan*, 1931, **6**, 79).

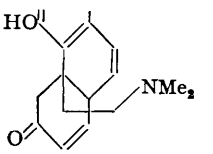
It is difficult to reconcile the structure (IV) for α-codeimethine with the production

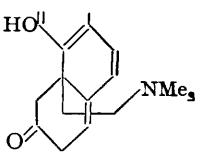
* Part II, *J.*, 1952, 972.

on mild reduction over nickel (von Braun and Cahn, *Annalen*, 1927, **451**, 55) of the same compound (IX) as is obtained by the degradation of dihydrocodeine methiodide (Freund, Melber, and Schlesinger, *J. prakt. Chem.*, 1920, **101**, 1), during which reaction it is inconceivable that the double bond appears at any position other than 9 : 10. One explanation of this could be that the compound (IV) is converted under the influence of the catalyst into its isomer (V), which is then reduced at the isolated double bond to (IX). In an attempt to realise this hypothetical isomerisation by heating α-codeimethine in alcoholic solution with Raney nickel, the products were dihydrocodeine methine (IX) and dihydro-


(IX)

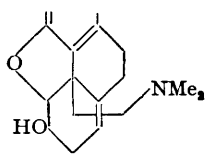

(X)

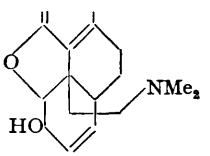

(XI)

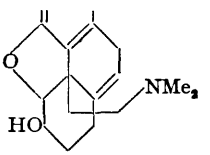

(XII)

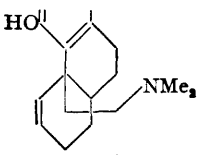
codeinone methine (X) (cf. the arrangement of codeine to dihydrocodeinone under the influence of noble metal catalysts; Knoll and Co., D.R.-P., 365,683/1921, 380,919/1922, 607,931, 617,238, 623,821/1934; *Friedlander*, **14**, 1301 1302; **21**, 652; **22**, 583, 584); a third, phenolic, substance, presumably thebainone-A methine (XI) (cf. the rearrangement of codeine to thebainone-A under slightly different conditions; Weiss and Weiner, *J. Org. Chem.*, 1949, **14**, 194) was also produced but proved so sensitive to aerial oxidation that isolation and purification was never achieved [cf. the sensitivity of thebainone-B methine (XII); Bentley, Robinson, and Wain, *J.*, 1952, 958; Bentley and Cardwell, following paper].

The reduction of α- and β-codeimethine with sodium and liquid ammonia was next investigated, as here the temperature precludes initial conversion of α- into β-methine. Under these conditions, (IV) would be expected to suffer 1 : 4-reduction of the conjugated system to give (XIII) whilst (V) and (III) would undergo reduction only of the double


(XIII)


XIV)


(XV)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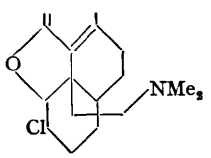
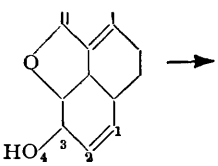
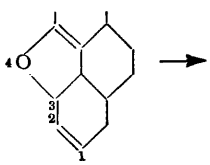
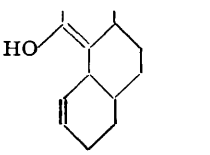

(XVII)


(XVIII)

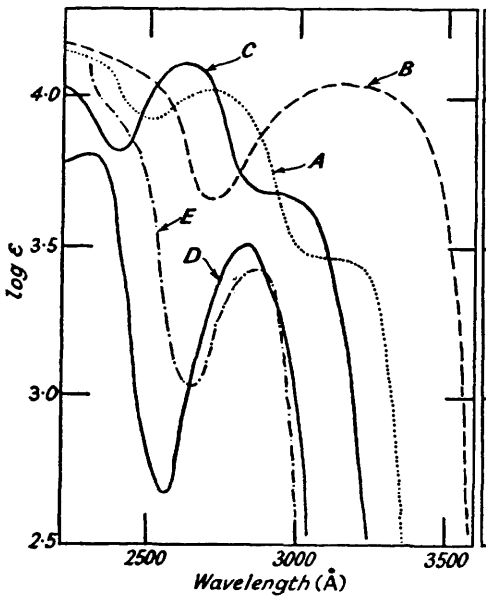

(XIX)


(XX)

bond conjugated with the aromatic nucleus, yielding (XIV) and (XIII) respectively. Alternatively (V) could undergo 1 : 4-reduction of the conjugated diene system, giving (XV). The sodium–ammonia reduction of β-codeimethine was expected to give the same product, (XIII) or (XV), as has already been obtained by the sodium and alcohol reduction of α-codeimethine (Vongerichten, *Ber.*, 1899, **32**, 1047; 1901, **34**, 2722), the mild catalytic (von Braun and Cahn, *loc. cit.*) and sodium amalgam (Mosettig, *J. Org. Chem.*, 1940, **5**, 401) reduction of β-codeimethine, and the sodium–ammonia reduction of neopine methiodide (Bentley and Wain, *J.*, 1952, 972), whilst the product (XIV) would be a new compound and should also be accessible by the sodium–ammonia reduction of codeine methiodide.

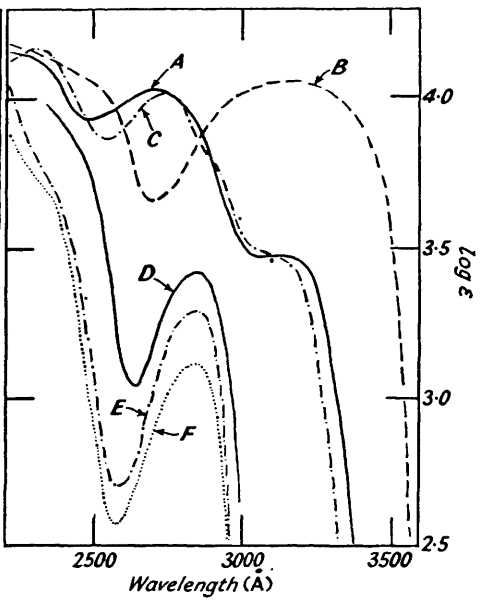
As expected, β-codeimethine was reduced in this way to give a good yield of the base (XIII) or (XV) whilst α-codeimethine gave 10—40% of a new base, codeine dihydromethine (α-dihydrocodeimethine-A) (XIV), and 40—60% of a phenolic substance, the amount of the former decreasing and of the latter increasing as the amount of sodium used for the reduction was increased. The same two compounds, with the same variation in yield, were obtained on reduction of codeine methiodide under the same conditions. The phenolic substance appears to be deoxydihydrocodeine-C dihydromethine (XVI) and may be identical with the compound prepared by Cahn (*J.*, 1926, 2562) by sodium–alcohol reduction of 6-chloro-α-tetrahydrocodeimethine (XVII), though Cahn appears to think the Δ^6-structure equally likely for his compound, and indeed the solubility properties of the two substances appear to be different. The mechanism for the production of (XVI) from

FIG. 1.



A, α-*Codeimethine*. *B*, β-*Codeimethine*. *C*, iso*Eugenol*. *D*, *Eugenol*. *E*, *Codeine*.

FIG. 2.



A, α-*Codeimethine*. *B*, β-*Codeimethine*. *C*, *Dihydrocodeine methine* (IX). *D*, *Codeine*. *E*, *Codeine dihydromethine* (XIV). *F*, $\Delta^{9(14)}$-*Dihydrocodeimethine* (XV).

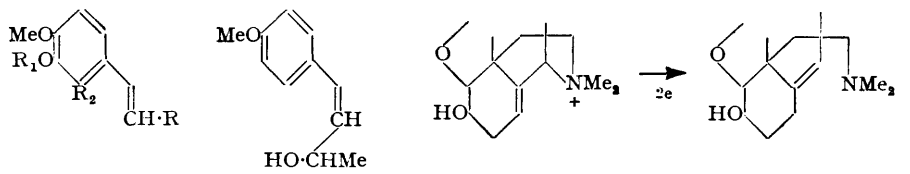
(XIV) is probably as set out in (XVIII) ⟶ (XX). Catalytic reduction of the dihydromethine (XIV) gave α-tetrahydrocodeimethine, also obtained by sodium–ammonia reduction of dihydrocodeine methiodide.

The reduction of morphine methiodide with sodium, ammonia, and alcohol apparently follows a similar course, giving a catechol derivative, the isolation of which from the resulting alkaline solution proved impossible owing to the excessively rapid aerial oxidation (cf. *apo*morphine in alkaline solution). By reasoning from the above, codeine on reduction in the same way would be expected to give first deoxycodeine-C and finally deoxydihydrocodeine-C, but only codeine and the merest trace of phenolic matter could be recovered from this reduction. The sodium–ammonia reduction of 6-acetyl*neo*morphine methiodide apparently gives the morphine analogue of (XIII), but this could not be characterised.

The results of these reductions favour the structure (V) rather than (IV) for α-codeimethine and the ultraviolet absorption spectra do in fact confirm this. Fig. 1 shows the spectra of α-codeimethine, β-codeimethine, codeine, eugenol, and *iso*eugenol. The spectra

of the codeine derivatives show a slight shift to longer wavelengths in comparison with eugenol and *iso*eugenol, but that of α-codeimethine is clearly analogous to that of *iso*eugenol and not to that of eugenol. Further Braude (personal communication) points out that the chromophore of α-codeimethine is (XXI) and the maxima are at 2750 and 3100 Å; for the analogous alcohol (XXII) the maxima are at 2610 and 2920 Å (Braude, *J.*, 1947, 1087); introduction of the *m*-alkoxy- and the *o*-alkyl substituent displaces the two bands by 140 and 180 Å respectively. Such shifts do not appear to be unusual if (XXII) and 2′-methylstyrylmethanol (Braude, *loc. cit.*, max. 2550 and 2880 Å) are compared with 1-styrylethanol (Braude, *loc. cit.*, max. 2510 and 2810 Å). In fact the combined shifts due to *p*-methoxy and *o*-methyl would be 100 + 40 = 140 Å and 100 + 70 = 180 Å on the shorter and longer-wavelength bands respectively, in exact agreement with the figures above.

Furthermore Fig. 2 gives the spectra of α-codeimethine, β-codeimethine (III), codeine dihydromethine (XIV), the base (XV) (see below), dihydrocodeine methine (IX) and codeine, which again prove that the α-methine is correctly represented by (V) and not by (IV).

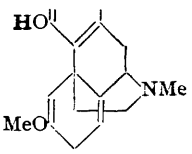


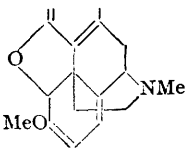
(XXI) (XXII) (XXIII) (XXIV)

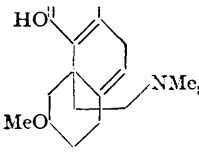
Bentley and Wain (*loc. cit.*) allotted structure (XIII) rather than (XV) to the product of sodium–ammonia reduction of neopine methiodide, as the same substance is obtained by the reduction of α-codeimethine with sodium and boiling alcohol, conditions that would favour rapid conversion of (XV) into (IX). However, production of (XV) from neopine methiodide, (XXIII) ⟶ (XXIV), would be analogous to the production of (XXV) from (XXVI). Accordingly neopine dihydromethine and dihydrothebaine-φ dihydromethine (Bentley and Wain, *loc. cit.*) were heated with alcoholic sodium ethoxide at 90—100° for 8 hours; both were recovered unchanged, suggesting structures (XIII) and (XXVIII) for these bases since (XXVII) would be expected to give (XXIX). However dihydrothebaine-φ dihydromethine, when heated for 3 hours at 100° with 5N-hydrochloric acid, gave no αβ-unsaturated ketone (infrared spectrum), and similarly the product of hydrolysis gave no αβ-unsaturated ketone when heated with alcoholic sodium ethoxide for 1 hour. These results indicate that the product of hydrolysis of dihydrothebaine-φ dihydromethine is not an αβ-unsaturated ketone; it is accordingly allotted structure (XXX) rather than (XXXI); dihydrothebaine-φ dihydromethine is therefore (XXVII), and neopine dihydromethine is (XX). The infrared spectrum of dihydrothebaine-φ dihydromethine supports this conclusion, for it differs from that of dihydrothebaine-φ in the region 5·8—7·0 μ and in particular does not show the bands at 5·9 and 6·0 μ characteristic of the 1 : 4-dihydroanisole system (see Stork, *J. Amer. Chem. Soc.*, 1952, **74**, 768). It is now easier to understand why it was found much more difficult to hydrogenate dihydrothebaine-φ dihydromethine (XXVII) and the product of hydrolysis (XXX) than to hydrogenate dihydrothebaine-φ (XXV) and thebainone-B (XXXII) (Bentley and Wain, *loc. cit.*). The structures of other degradation products prepared by Bentley and Wain must similarly be revised.

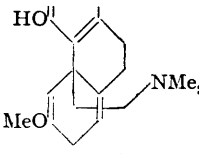
As previously stated (Bentley and Wain, *loc. cit.*) the degradation of the methiodide of (XV) by sodium *cyclo*hexyloxide in boiling *cyclo*hexanol affords a mixture, now shown by chromatography to consist of methylmorphenol (*ca.* 20%), a nitrogen-free substance of structure (XXXIII) or (XXXIV) (*ca.* 50%), and a by-product from the *cyclo*hexanol series (*ca.* 25%). The structure (XXXIII) or (XXXIV) was allotted to the major product, for its ultraviolet absorption closely resembles that of α-codeimethine, indicating the conjugation of one double bond with the nucleus, and also the infrared absorption indicates the presence of a hydroxyl group.

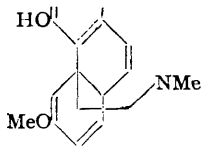
Attack at the carbon atom β to the nitrogen by a *cyclo*hexyloxide ion probably results in elimination of the side-chain to give (XXXIII, but $\Delta^{8(14)}$); migration of the double bond into the *iso*eugenol position followed by the addition of a proton would then afford (XXXIII). This structure is regarded as the most probable, for the tendency for the double bond to migrate to the 13 : 14-position may well be the real driving force behind the elimination of the side-chain. Alternatively the double bond could migrate to the 9 : 10-position, this being followed by elimination of the side-chain to give (XXXIV). It may

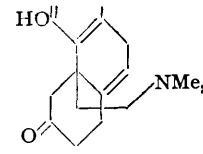

(XXV)

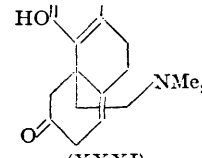

(XXVI)

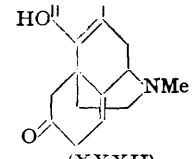

(XXVII)


(XXVIII)


(XXIX)

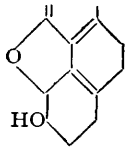

(XXX)

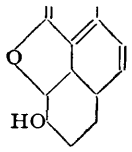

(XXXI)

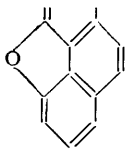

(XXXII)

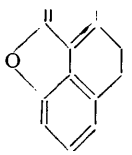
be noted that in this type of elimination the side-chain becomes joined at the β-carbon atom to the reacting anion by an ether link as was originally believed to be the case in the degradations of substances with a free 4-hydroxyl group, resulting in the thebenone type of cyclic ether (Bentley, Robinson, and Wain, *loc. cit.*).* The second product of this elimination reaction would be $C_6H_{11}\cdot O\cdot CH_2\cdot CH_2\cdot NMe_3\}I$, which could then suffer normal Hofmann degradation to give trimethylamine and *cyclo*hexyl vinyl ether, and indeed the by-product of the degradation, clearly still a mixture, appears to contain this substance contaminated with *cyclo*hexanol, as the infrared absorption obtained shows bands characteristic of the groupings C·O·C:C (9·43μ) and ·CH:CH_2 (10·32 and 10·88μ).

The compound of structure (XXXIII) would be expected, on the basis of Emde's conclusions (*Helv. Chim. Acta*, 1930, **13**, 1035), to be lævorotatory, whereas the compound of structure (XXXIV) might be dextro- or lævo-rotatory. The degradation product was strongly dextrorotatory.


(XXXIII)


(XXXIV)


(XXXV)


(XXXVI)

Methylmorphenol (XXXV) could arise from (XV) by normal Hofmann degradation, dehydration, and extrusion of the 13-vinyl group, giving the diphenyl (XXXVI), followed by aerial oxidation.

Treatment of neopine hydrobromide in formic acid with hydrogen peroxide afforded 1-bromoneopine; an attempt to prepare 1-bromothebaine in a similar way from thebaine hydrobromide yielded 14-hydroxycodeinone.

* The thebenone type of substance is now believed to contain a six-membered cyclic ether system (Rapoport, *J. Amer. Chem. Soc.*, 1953, **75**, 5329; Bentley and Cardwell, unpublished results), but the later results scarcely justify a dogmatic assertion " ***in the absence of further evidence*** " by Stork (*loc. cit.*) that they contain six-membered ethers. ***In the absence of further evidence*** all that could then be said was that no evidence was available to decide between the five- and the six-membered ether structures.

Experimental

α-Codeimethine, prepared by degradation of codeine methiodide, formed rods, m. p. 118·5° (lit., 119°), on recrystallisation from aqueous ethanol. The *perchlorate* was obtained as prisms, m. p. 183°, from 90% ethanol, $[\alpha]_D^{20}$ −116·4° (2% in H_2O) (Found : C, 55·0 ; H, 6·0. $C_{19}H_{23}O_3N,HClO_4$ requires C, 55·2 ; H, 5·9%).

Small (*J. Org. Chem.*, 1947, **12**, 359) reports that neopine methiodide is recovered unchanged from hot alcoholic potassium hydroxide. However we found that degradation is rapid when 35% sodium hydroxide solution (150 ml.) is added to neopine methiodide (5 g.) in water (250 ml.) at 100° (cf. van Duin, Robinson, and Smith, *J.*, 1926, 903), giving β-codeimethine, prisms (from ethanol), m. p. 134° (lit., 134°). The *perchlorate*, was obtained as plates, m. p. 152° (decomp.), from aqueous ethanol, $[\alpha]_D$ +242° (2% in 50% EtOH) (Found : C, 54·2; H, 5·6. $C_{19}H_{23}O_3N,HClO_4,\frac{1}{2}H_2O$ requires C, 54·0; H, 5·9%).

Rearrangement of α-Codeimethine.—A solution of α-codeimethine (10 g.) in ethanol (100 ml.) was neutralised to litmus with hydrochloric acid and boiled with Raney nickel (5 g.) for 2 hr., the solution filtered, and perchloric acid (5 ml.) added. Mauve-coloured crystals separated which, three times crystallised from 50% ethanol, gave *dihydrocodeinone methine perchlorate* as colourless elongated plates, m. p. 267° (Found : C, 55·2; H, 5·8; Cl, 8·9. $C_{19}H_{23}O_3N,HClO_4$ requires C, 55·2; H, 5·8; Cl, 8·6%). The substance was non-phenolic and the infrared spectrum showed that it is a ketone. The base was not crystalline, but was converted into the methiodide, prisms, m. p. 282° (lit., 280°) (from aqueous ethanol) (Found : C, 52·7; H, 5·7; I, 27·6. Calc. for $C_{19}H_{23}O_3N,MeI$: C, 52·7; H, 5·7; I, 27·9%).

From the mother-liquors of the perchlorate, dihydrocodeine methine perchlorate gradually separated as prisms, m. p. 206° (lit., m. p. 203°) (Found : C, 55·3; H, 6·5. Calc. for $C_{19}H_{25}O_3N,HClO_4$: C, 55·0; H, 6·3%). The final mother-liquors left contained material almost wholly soluble in alkali (giving therein an intense red colour with diazotised sulphanilic acid), but the solution rapidly darkened in air, and the phenolic base could not be isolated. When this rearrangement was carried out without the addition of acid, the solution rapidly absorbed oxygen and became deep purple, with consequent diminution in yield.

Reduction of α-Codeimethine.—(*a*) Sodium (2 g.) was added in slices to a solution of α-codeimethine (5 g.) in liquid ammonia (350 ml.) and ethanol (50 ml.), with vigorous stirring. The mixture was poured into water (250 ml.), and the whole saturated with ammonium chloride and extracted three times with ether. The combined extracts were washed, dried, and evaporated, leaving a viscous oil. With 60% perchloric acid (2 ml.) in ethanol (18 ml.) this gave *codeine dihydromethine perchlorate* which, recrystallised three times from aqueous ethanol, was obtained as felted needles, m. p. 210°, $[\alpha]_D$ −33·4° (2% in H_2O) (Found : C, 54·7; H, 6·5; Cl, 8·3. $C_{19}H_{25}O_3N,HClO_4$ requires C, 55·0; H, 6·3; Cl, 8·6%). The base was an oil and was converted into the *methiodide*, prisms, m. p. 265° (from aqueous ethanol) (Found : C, 52·5; H, 6·3. $C_{19}H_{25}O_3N,MeI$ requires C, 52·5; H, 6·5%). Both salts differed in their infrared spectra from the neopine dihydromethine salts.

From the mother-liquors from the perchlorate a base was obtained as elongated plates, m. p. 158° [from light petroleum (b. p. 60—80°) and from ether], $[\alpha]_D$ +21·5° (2% in $CHCl_3$) (Found : C, 75·4, 75·3; H, 9·0, 9·2; N, 4·1. $C_{19}H_{27}O_2N$ requires C, 75·6; H, 9·0; N, 4·6%). This substance, *deoxydihydrocodeine-C dihydromethine*, was soluble in alkali, and the alkaline solution gave an intense red colour with diazotised sulphanilic acid. The base gave a green-blue colour with ferric chloride. It is readily soluble in organic solvents with the exception of low-boiling light petroleum. In this reduction 2 g. each of dihydrodeoxycodeine-C dihydromethine and codeine dihydromethine were obtained.

(*b*) α-Codeimethine (5 g.) was reduced as above with sodium (3 g.), ethanol (25 ml.), and liquid ammonia (300 ml.) ; 3·5 g. of dihydrodeoxycodeine-C dihydromethine and 1 g. of codeine dihydromethine were obtained.

(*c*) α-Codeimethine (5 g.) was reduced with sodium (5 g.), alcohol (50 ml.), and liquid ammonia (300 ml.) ; only dihydrodeoxycodeine dihydromethine (3·9 g.) was recovered.

Reduction of Codeine Methiodide.—(*a*) Codeine methiodide (10 g.) was reduced as above with sodium (4 g.), ethanol (150 ml.), and liquid ammonia (500 ml.) ; 4 g. of codeine dihydromethine and 2·5 g. of dihydrodeoxycodeine-C dihydromethine were obtained.

(*b*) Codeine methiodide 10 g.), reduced with sodium (15 g.), ethanol (200 ml.), and liquid ammonia (700 ml.), gave only dihydrodeoxycodeine-C dihydromethine (5 g.).

Reduction of β-Codeimethine.—β-Codeimethine (6 g.) was reduced with sodium (3 g.), ethanol

(25 ml.), and liquid ammonia. The oily product slowly solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave neopine dihydromethine as prisms, m. p. 88—89° (lit., 86—88·5), $[\alpha]_D$ −105° (1% in EtOH) (Found : C, 72·6; H, 8·0. Calc. for $C_{19}H_{25}O_3N$: C, 72·3; H, 8·0%). Neopine dihydromethine prepared by Bentley and Wain (*loc. cit.*) recrystallised readily when seeded with this product and had identical properties. The perchlorate of the base obtained by the reduction of β-codeimethine had m. p. 216° and the methiodide, m. p. 251—253°, both alone or mixed with the corresponding salts prepared by Bentley and Wain.

Reduction of Codeine Dihydromethine.—A solution of codeine dihydromethine (2 g.) in ethanol (50 ml.) was shaken with palladised strontium carbonate under hydrogen at room temperature and atmospheric pressure until absorption ceased. The catalyst and solvent were removed, leaving an oil, which afforded a perchlorate, prisms, m. p. 217° (from 90% ethanol), $[\alpha]_D$ −33·4° (2·5% in 50% EtOH) (Found : C, 53·5; H, 6·7. Calc. for $C_{19}H_{27}O_3N,HClO_4,\frac{1}{2}H_2O$; C, 53·5; H, 6·8%), and a methiodide, needles, m. p. 221° (from aqueous alcohol) (Found : C, 50·3; H, 6·7. Calc. for $C_{19}H_{27}O_3N,MeI,H_2O$: C, 50·3; H, 6·8%), both m. p.s being undepressed on admixture with the α-tetrahydromethine derivatives.

Reduction of Dihydrocodeine Methiodide.—Dihydrocodeine methiodide (8 g.) was reduced with sodium (5 g.), ethanol (100 ml.), and liquid ammonia (300 ml.) as described above; and the product (5 g.) consisted only of α-tetrahydrocodeimethine (perchlorate, prisms, m. p. and mixed m. p. 217°; methiodide, needles, m. p. and mixed m. p. 221°).

Reduction of Morphine Methiodide.—Morphine methiodide (10 g.) was reduced by sodium (10 g.), liquid ammonia (300 ml.), and ethanol (100 ml.). When all the methiodide had dissolved a red colour developed. This was destroyed as each fresh slice of sodium was added, but reappeared as soon as the sodium had completely dissolved. Pouring the ammoniacal solution into water gave a homogeneous solution which very rapidly darkened in air. No base was recovered.

Reduction of 6-O-*Acetylneomorphine Methiodide.*—6-*O*-Acetylneomorphine (6 g.) was converted into the *methiodide*, triangular and oblong prisms, m. p. 244°, $[\alpha]_D$ +24° (1·1% in H_2O) (Found : C, 51·5; H, 5·4. $C_{19}H_{21}O_4N,MeI$ requires C, 51·2; H, 5·2%), which was difficult to crystallise. The methiodide (5 g.) was reduced with sodium (0·75 g.) and liquid ammonia (150 ml.). The mixture was poured into saturated ammonium chloride solution, and the product extracted with chloroform. After removal of the chloroform the product was obtained as a dark brown gum, that was sublimed at 180°/0·08 mm., being then obtained as minute colourless crystals that very rapidly degenerated to an orange solid, m. p. *ca.* 18° finally giving a tar, on exposure to the air. No satisfactory analytical figure could be obtained for this substance, which is believed to be neomorphine dihydromethine. The picrate and methiodide were oils, and all the other salts appear to be very soluble in the solvents used for their preparation.

Degradation of Neopine Dihydromethine Methiodide.—Neopine dihydromethine methiodide (prepared from β-codeimethine) was degraded as described by Bentley and Wain (*loc. cit.*) to an oil (4 g.) that was passed in benzene (120 ml.) and light petroleum (b. p. 40—60°) down a column of activated alumina (70 g.). A wide band having a purple fluorescence was eluted from the column first, with 3 : 2 ⟶ 4 : 1 benzene–light petroleum (b. p. 40—60°); it was obtained as a white wax, which after further chromatography gave methylmorphenol, m. p. 60°, elongated prisms, m. p. 62° (undepressed on admixture with a specimen prepared from α-codeimethine) on recrystallisation from light petroleum (b. p. 40—60°) (Found : C, 81·2; H, 4·3. Calc. for $C_{15}H_{10}O_2$: C, 81·1; H, 4·5%). The *picrate* was prepared in ethanol and obtained as red needles, m. p. 119°, decomposing on attempted recrystallisation and only stable in the presence of excess of picric acid.

From the original chromatogram a second product was eluted with solvents from benzene (90%) to pure benzene; it was a pale yellow oil (0·9 g.) with a pale blue fluorescence. On distillation it was colourless, b. p. 120°/0·05 mm., n_D^{20} 1·6518, $[\alpha]_D$ = 0·0° (Found : C, 79·1; H, 11·25%).

By elution from the column with solvents from pure benzene to 4 : 1 benzene–chloroform a third product was obtained as a non-fluorescent amber glass, b. p. 170°/0·02 mm. [Found : C, 73·3; H, 7·0%; *M* (Rast), 261. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%; *M*, 244]. This substance, believed to be (+)-1 : 2 : 3 : 4 : 9 : 10-*hexahydro*-3-*hydroxy*-6-*methoxy*-4 : 5-*phenanthrylene oxide*, is strongly dextrorotatory in chloroform, but the solution darkened and accurate reading of the rotation was impossible.

Attempted Isomerisation of Neopine Dihydromethine and Dihydrothebaine-φ Dihydromethine.—Neopine dihydromethine (2·4 g.) was heated at 90—100° with a solution of sodium (2·5 g.)

in ethanol (60 ml.) for 8 hr., and the mixture was cooled, diluted with saturated ammonium chloride, and extracted five times with ether. The ether extracts afforded 2·0 g. of a brown oil that crystallised on trituration with light petroleum and seeding with neopine dihydromethine. It was obtained as colourless prisms, m. p. 87—88° undepressed on admixture with the starting material, after recrystallisation from light petroleum (b. p. 60—80°). The ultraviolet spectra of the starting material and recovered base were identical.

Dihydrothebaine-ϕ dihydromethine behaved similarly.

Hydrolysis of Dihydrothebaine-ϕ Dihydromethine.—This methine (5·0 g.) was heated at 100° with 5N-hydrochloric acid (20 ml.) for 3 hr., the solution neutralised with ammonia, and the precipitated base collected, washed and recrystallised from aqueous alcohol. Only $\Delta^{8(14)}$-dihydrothebainone methine (thebainone-B dihydromethine of Bentley and Wain) was obtained as almost colourless needles, m. p. 164°. Neither the crude product nor the recrystallised material showed infrared bands characteristic of αβ-unsaturated ketones; the only ketone band was found at 5·86 μ. Only tar was recovered when this ketone was heated for 1 hr. with sodium ethoxide solution; the infrared spectrum of the tar showed no bands attributable to an αβ-unsaturated ketone system.

1-*Bromoneopine.*—Neopine hydrobromide (3 g.), 30% formic acid (50 ml.), and 30% hydrogen peroxide (2 ml.) were set aside overnight. On neutralisation the solution gave 1-bromoneopine which recrystallised from aqueous ethanol as prisms (becoming faintly pink in air), m. p. 174°, $[\alpha]_D$ −42·1° (2·5% in EtOH) (Found: C, 57·1; H, 5·4; Br, 21·3. $C_{18}H_{20}O_3NBr$ requires C, 57·1; H, 5·3; Br, 21·2%). The *hydrogen tartrate*, prepared in ethanol, recrystallised from 96% ethanol, as prisms, m. p. 248° (decomp.), $[\alpha]_D$ 0·0° (in H_2O) (Found: C, 49·7; H, 5·0; Br, 14·2. $C_{18}H_{20}O_3NBr,C_4H_6O_6$ requires C, 50·0; H, 4·9; Br, 14·2%). The *methiodide*, prepared in ethanol, recrystallised from aqueous ethanol as prisms, m. p. 225°, $[\alpha]_D$ 0·0° (in H_2O) (Found: C, 43·9; H, 4·5; Hal, 39·2. $C_{18}H_{20}O_3NBr,MeI$ requires C, 43·8; H, 4·4; Hal, 39·8%). Degradation of the methiodide in aqueous alkali afforded 1-bromo-β-codeimethine, plates, m. p. 180° (from ethanol) (lit., 182°) $[\alpha]_D$ +193° (2·4% in $CHCl_3$) (Found: C, 57·8; H, 5·9; Br, 20·5. Calc. for $C_{19}H_{22}O_3NBr$: C, 58·1; H, 5·6; Br, 20·4%).

14-*Hydroxycodeinone.*—Thebaine hydrobromide (2 g.), 30% formic acid (10 ml.), and hydrogen peroxide (3 drops; 30%) similarly gave 14-hydroxycodeinone, prisms, m. p. 267° (from ethanol) (lit., 265°) (Found: C, 68·5; H, 6·1; Br, 0·0. Calc. for $C_{18}H_{19}O_4N$: C, 68·9; H, 6·1; Br, 0·0%).

We thank Sir Robert Robinson, O.M., F.R.S., for his interest in the work of this and the following two papers, Dr. F. B. Strauss and Mr. F. H. L. H. Hastings for the determination of the ultraviolet and infrared spectra, and the Ministry of Education for a grant (to A. F. T.). Part of this work was carried out during the tenure by one of us (K. W. B.) of an I.C.I. Fellowship.

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[*Received, January 22nd,* 1955.]