The Morphine–Thebaine Group of Alkaloids. Part V. The Absolute Stereochemistry of the Morphine, Benzyl*isoquinoline, *Aporphine, and Tetrahydroberberine Alkaloids.*

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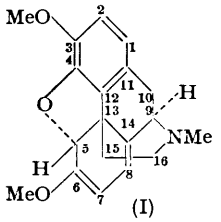
The absolute stereochemistry of the various asymmetric centres in the morphine alkaloids has been deduced. The change of optical rotation with polarity of solvents is of the same type in the benzyl*iso*quinoline and the tetrahydroberberine alkaloid series but there is an inversion in the aporphine alkaloids. The benzyl*iso*quinoline, aporphine, and tetrahydroberberine alkaloids that accompany the morphine and sinomenine alkaloids in Nature are enantiomorphous with the latter.

With the syntheses of morphine (Gates and Tschudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1109; Elad and Ginsburg, *ibid.*, 1954, **76**, 312) Gulland and Robinson's formula for morphine (*J.*, 1923, 980; *Mem. Proc. Manchester Lit. Phil. Soc.*, 1925, **69**, 79) received final confirmation. These syntheses did not, however, establish the stereochemical arrangement of the various asymmetric centres. The stereochemistry of the morphine alkaloids was first discussed by Schöpf (*Annalen*, 1927, **452**, 211) who suggested that the nitrogen-containing ring was *trans* to the oxide ring as in (I). His argument was influenced by the observation (Freund and Speyer, *J. prakt. Chem.*, 1916, **94**, 135; Schöpf and Borkowsky, *Annalen*, 1927, **452**,

* Part IV, preceding paper.

249) that 14-hydroxydihydrocodeinone methine (II) on Hofmann degradation gave a cyclic ether " dihydrohydroxycodeone " (III). The *cis*-relationship of the 14-hydroxy-group and the ethanamine chain was thus established, but there was no unequivocal evidence that the hydroxyl group in 14-hydroxycodeinone had the same steric arrangement as the hydrogen atom at $C_{(14)}$ in morphine and codeine. The vital nature of this missing link becomes apparent when the stereochemistry of dihydrocodeinone is considered (see below). Lutz and Small (*J. Org. Chem.*, 1939, **4**, 220) provided evidence that strongly suggested, but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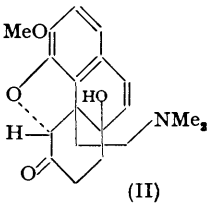
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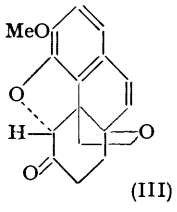
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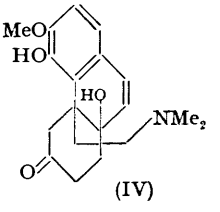
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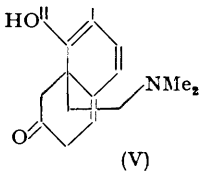
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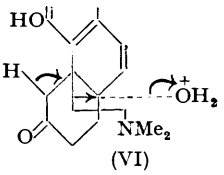
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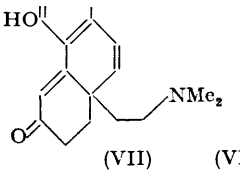
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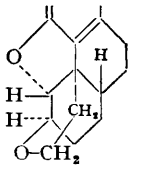
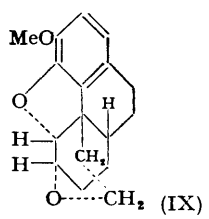

(VIII)

did not prove, that $C_{(14)}$ has the same stereochemistry in these compounds. We have noticed, however, one unexplained reaction in the literature that may be relevant to this problem.

Schöpf and Borkowsky (*loc. cit.*) reported that the methine (IV), unlike other 14-hydroxy-compounds, is readily dehydrated by warm hydrobromic acid to a substance formulated as (V), but the hydrobromide so produced is quite different from that of the authentic methine (V) (Bentley, Robinson, and Wain, *J.*, 1952, 958) and from the other tautomerides described by us (preceding paper). Indeed, from its reported resistance to aerial oxidation it cannot possibly be any of the thebainone methines and must accordingly be a rearrangement product. If the OH group is *trans* to the ethanamine chain (cf. VI), this could be most readily viewed as a concerted dehydration and rearrangement to metathebainone methine (VII). We have found that the hydrobromide of (VII) corresponds exactly with that obtained by Schöpf, particularly in crystallising with a fractional molecule of water that cannot be removed in *vacuo* at 120°. However, non-stereospecific dehydrations with rearrangement are known (cf. the conversion of borneol and *iso*borneol into camphene by 50% sulphuric acid; Konowalov, *J. Russ. Phys. Chem.*, 1900, **32**, 76; Gobulov, *ibid.*, 1912, **44**, 1061), and any thought that this rearrangement allows a distinction in favour of (VI) rather than (IV) was dispelled by the fact that dissolution of any of the thebainone methines in 40% hydrobromic acid and subsequent treatment with aqueous sodium hydroxide afforded the deep yellow colour characteristic of metathebainone derivatives in alkali. This, however, is not a preparative method for metathebainone methine.

This illustrates the ambiguity attached to all chemical attempts to probe the stereochemistry of the morphine alkaloids. This was recognised by Rapoport and Lavigne (*J. Amer. Chem. Soc.*, 1953, **75**, 5329) in their degradations of the isomeric thebenones, but the ambiguity is also present in the work of Rapoport and Payne (*ibid.*, 1952, **74**, 2630) who found that exhaustive methylation of dihydro*iso*codeine affords 2% of a product, codiran (VIII), in which the residue of the ethanamine chain has cyclised with the 6-hydroxyl group. Together with the previous proof (Rapoport and Payne, *J. Org. Chem.*, 1950, **15**, 1093) of the *trans*-relation of the 5- and the 6-oxygen atom in dihydro*iso*codeine this led to a *trans*-arrangement of the oxide and nitrogen rings in codeine. A study of models reveals the ambiguity, for the cyclic product (VIII) is highly strained, whilst a strainless model of the isomeride (IX) can be constructed. Thus the very low yield of codiran could

be due either to the difficulty of formation of the strained product (VIII) or to an abnormal reaction in which $-NMe_3^+$ is replaced by –OH and the resulting ethanol chain performs a substitution by inversion at $C_{(6)}$ leading to the strain-free form (IX).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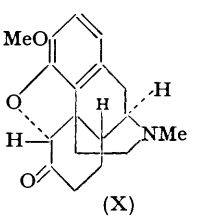
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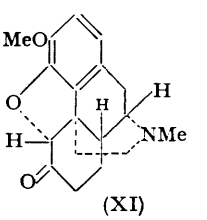
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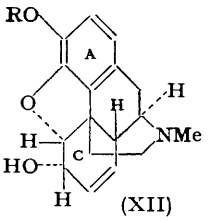
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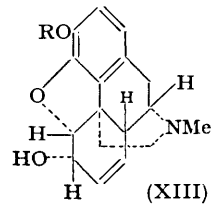
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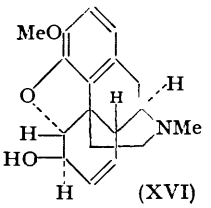
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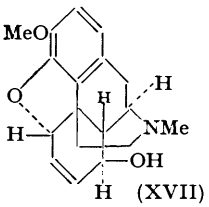
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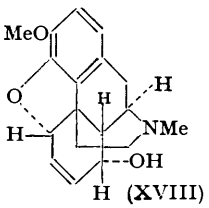
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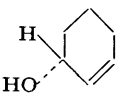
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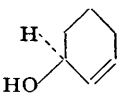

(XV)

In view of these ambiguities we investigated the stereochemistry by physical methods. Only two stereochemical arrangements, (X) and (XI) (or their mirror images), need be considered for (—)-dihydrocodeinone [which is known to have the same stereochemistry at $C_{(14)}$ as morphine and is not epimerised at $C_{(5)}$ by alkali (Schöpf, *loc. cit.*)], as a study of models shows that inversion at $C_{(5)}$ [or, of course, at $C_{(14)}$] in (X) or (XI) leads to a highly strained oxide ring. This disposes of Stork's attempt (" The Alkaloids," Academic Press Inc., New York, 1952, Vol. II, 171) to deduce the stereochemistry of morphine without reference to Schöpf and Borkowsky's work on 14-hydroxycodeinone. If the hydroxyl group in 14-hydroxydihydrocodeinone has the same configuration as the $C_{(14)}$ hydrogen atom in dihydrocodeinone then the latter must be (X); if this is not established then there are no *a priori* grounds for rejecting (XI). Stork's subsequent attempt (*op. cit.*, p. 190) to deduce a *trans*-relation of the oxide ring and ethanamine chain as in (X) by postulating a concerted *trans*-elimination mechanism in reactions leading to acetylmethylmorphol is equally unsatisfactory, for to maintain this argument he subsequently (*op. cit.*, p. 191) overlooks the fact that the Hofmann degradation of α- and β-codeimethine to methylmorphenol involves a *cis*-elimination of the ethanamine chain and the hydrogen atom from position 5.

Structures (X) and (XI) for dihydrocodeinone may be expanded to (XII and XIII; R = H) respectively for (—)-morphine. The former was derived from Schöpf's expression for thebaine (I) by Fieser and Fieser (" Natural Products Related to Phenanthrene," Reinhold, New York, 1949, p. 23) and is supported by the work of Rapoport and his co-workers (*loc. cit.*); the latter formula is, however, not excluded by the chemical evidence.

At our suggestion Mrs. D. M. Crowfoot-Hodgkin and Mrs. M. Mackay very kindly undertook an *X*-ray investigation, and their proof that (—)-morphine is (XII) or its mirror image, and not (XIII) (R = H), is given in the following paper. We, however, probed the relative stereochemistry by determining the absolute stereochemistry at as many centres as possible: our results established that (—)-morphine is (XII; R = H) and not the enantiomorph.

Absolute Stereochemistry at $C_{(5)}$.—Mills (*J.*, 1952, 4976) has shown that, in the terpene series, allylic alcohols containing the *cyclo*hexenol structure (XIV) are less lævorotatory than those containing the epimeric structure (XV). This method was successfully extended

to the steroids and, assuming that the same arguments may be applied to semi-boat rings (see below), we have now used it with success in the morphine series. Codeine (XII; R = Me), $[\alpha]_D$ −112° ($CHCl_3$), is less lævorotatory than *iso*codeine (XVI), $[\alpha]_D$ −151° ($CHCl_3$); and ψ-codeine (XVII), $[\alpha]_D$ −97° (EtOH), is less lævorotatory than *allo*-ψ-codeine (XVIII), $[\alpha]_D$ −235° (EtOH); this suggests that these bases have the absolute stereochemistry shown in the formulæ. This argument assumes that the hydroxyl groups in codeine and *allo*-ψ-codeine are *cis* to the 5-oxygen atom. This is certainly true for codeine (Rapoport and Payne, *loc. cit.*) and the orientation in other cases may be deduced. Ring C is roughly coplanar with the nitrogen ring in (XII) and with ring B in (XIII). In both cases, hydroxyl groups of the same orientation with reference to the oxide ring or $C_{(14)}$ will have the same conformation (axial or equatorial) with reference to the coplanar bicyclic systems. Compounds derived by sodium and alcohol reduction of $C_{(6)}$- and $C_{(8)}$-ketones (α-*iso*morphine, *iso*codeine, dihydrothebainol-A, γ-*iso*morphine, ψ-codeine, dihydro-ψ-codeine-A) should have equatorial hydroxyl groups (Barton, *J.*, 1953, 1027). The epimeric compounds (morphine, codeine, dihydrothebainol-B, β-*iso*morphine, *allo*-ψ-codeine) might be expected to have axial hydroxyl groups and this is almost certainly true for compounds in which the oxide ring is broken. In morphine, however, the 6-hydroxyl group can become equatorial with reference to the planar bicyclic system if ring C has a semi-boat rather than a semi-chair configuration, and the *X*-ray analysis (see following paper) shows that morphine does have a semi-boat ring C. Thus in so far as *iso*codeine is more stable than codeine this is due to a change of ring C from a boat to a chair configuration rather than a change in orientation of the 6-hydroxyl group.

Absolute Stereochemistry at $C_{(13)}$ *and* $C_{(14)}$.—The nitrogen-containing ring must be *cis*-fused to the hydrophenanthrene system; hence determination of the absolute stereochemistry at either $C_{(13)}$ or $C_{(9)}$ allows a distinction between (XII) and (XIII). Bick (*Nature*, 1952, **169**, 756) pointed out that the rearrangement of morphine to *apo*morphine (XIX) leaves only one asymmetric centre. In principle Leithe's extension (*Ber.*, 1930, **63**, 1498) of Clough's method (*J.*, 1918, **113**, 526) may be used to determine the absolute stereochemistry of the latter base. Bick reported that the rotations of *apo*codeine and *apo*morphine became less lævorotatory as the solvent polarity increased and on this basis assigned to *apo*morphine and hence to morphine an absolute stereochemistry at $C_{(9)}$ that, with our determination at $C_{(6)}$, leads to (XIII; R = H) for morphine. If this were correct then rings A, B, and C would be coplanar and there would be an enantiomorphous resemblance between rings C and B of the morphine alkaloids and rings A and B of the steroids. We therefore compared the rotations of cholestane (XX) and 2- and 4-oxygenated cholestanes with those

TABLE 1.

Cholestane derivative	$[\alpha]_D$	Δ	Alkaloid	$[\alpha]_D$	Δ
Cholestane [1]	+24·5°	—	Tetrahydrodeoxycodeine (XXII)	−34°	—
-2β-ol [2]	+33	+ 8·5°	Dihydrothebainol-B (XXV)	−36·5	− 2·5°
-2α-ol [2]	+36	+11·5	Dihydrothebainol-A (XXVI)	−46·2	−12·2
-2-one [2]	+49	+24·5	Dihydrothebainone (XXVII)	−80	−46
-4β-ol [3]	+29·9	+ 5·4	Tetrahydro*allo*-ψ-codeine (XXVIII)	−58	−24
-4α-ol [4]	+ 2·8	−21·7	Tetrahydro-ψ-codeine (XXIX)	−17·8	+16·2
-4-one [2]	+29·5	+ 5·0	Tetrahydro-ψ-codeinone (XXX)	+ 8·0	+42

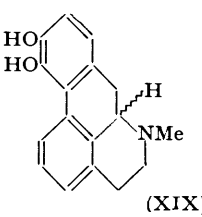
Steroid rotations in chloroform, alkaloid rotations in ethanol.

[1] Stavely and Bergmann *J. Org. Chem.*, 1937, **1**, 567. [2] Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 524, 727. [3] Furst and Scotoni, *ibid.*, 1953, **36**, 1382. [4] Plattner, Petrizilka, and Lang, *ibid.*, 1944, **27**, 513.

Alkaloid references: see Bentley, "The Chemistry of the Morphine Alkaloids," The Clarendon Press, Oxford, 1954.

of tetrahydrodeoxycodeine (XXI on the basis of XIII for morphine) and its oxygenated derivatives. The results are given in Table 1; with one exception the introduction of functional groups produces changes of rotation of opposite sign to the corresponding changes in the cholestane series, the one exception occurring when a polarisable group (CO) is near to the asymmetric centre ($C_{(9)}$) that is not present in the steroids. We thus have strong evidence that the morphine alkaloids are enantiomorphous to the steroids, but

further examination reveals that this condition is also met by (XII); thus in (XXII) it is the hydrogenated *iso*quinoline system that is largely coplanar, the benzene ring being the angular substituent. Thus the parallelism shown in Table 1 establishes the absolute stereochemistry at $C_{(14)}$ but not that at $C_{(13)}$.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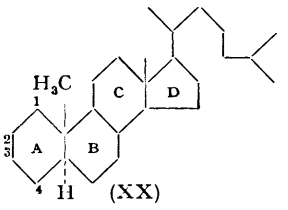
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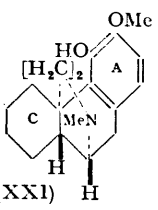
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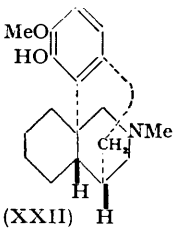
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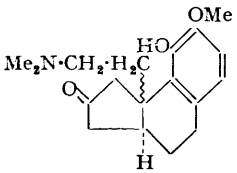
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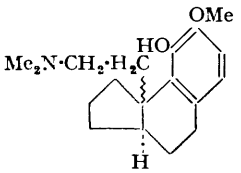
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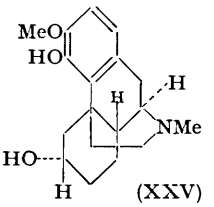
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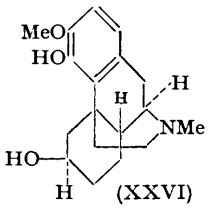
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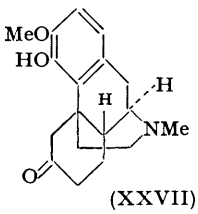
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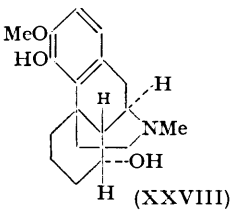
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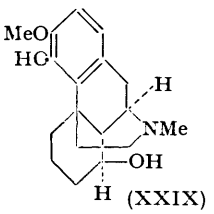
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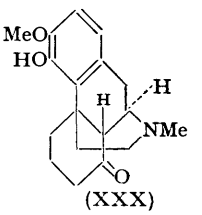

(XXX)

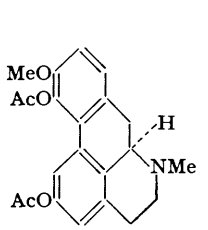
When the nitrogen ring is broken a further test should be possible, but in the absence of relevant optical data for the required pairs of compounds it is necessary to contract ring C in the alkaloids before a test can be made. In the sinomenine series (enantiomorphous with morphine) dihydrosinomenilone dihydromethine (XXIII), $[\alpha]_D$ −24·6° ($CHCl_3$) (Goto and Takubo, *Annalen*, 1932, **499**, 169), is much more lævorotatory than dihydrosinomenilan dihydromethine (XXIV), $[\alpha]_D$ +45·6° (Goto and Shishido, *ibid.*, 1933, **507**, 296). In the steroids A : B-*trans*-indanones have far more positive rotations than the corresponding indanes; hence sinomenilone derivatives cannot have the ethanamine chain *trans* to the hydrogen at $C_{(14)}$, and sinomenine methines must be of the coprostane type and morphine methines must be enantiomorphous with coprostane and not with cholestane. We thus provisionally conclude that morphine must be (XII).

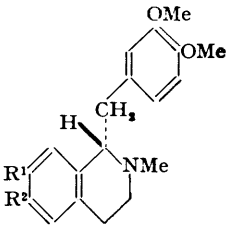
TABLE 2. *Specific rotations in various solvents.*

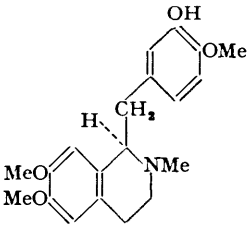
Substance	CS_2	*cyclo*-Hexane	Benzene	Pyridine	$CHCl_3$	EtOH	Base in N-HCl or hydrochloride in H_2O
(−)-Phenylethylamine [3]	—	−42·6°	—	—	−35·2°	−30·4°	−5·4°
(−)-*N*-Ethyl-1-phenylethylamine [3]	—	—	—	—	—	−53·2	−12·2
(−)-Tetahydro-*N*-methyl*iso*quinoline [3]	—	−79·9	—	—	−71·6	−71·5	−34·0
1-Benzyltetrahydro-*N*-methyl*iso*quinoline [3]	−65·8°	−46·8	−35·3°	−25·2°	+30·0	+64·0	+72·0
(+)-Laudanosine [1]	− 8·0	—	+ 2·2	+ 8·3	+52	+90	+102
(−)-Diacetylmorphothebaine [4]	−173	—	−92	−106	−82	−66	−39
(−)-Tetrahydroprotoberberine [3]	—	−462	—	—	−386	−377	−255
(+)-Glaucine [4]	+115	+125	—	+99	+138	+120	+110

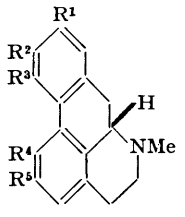
[1] Leithe, *Ber.*, 1930, **63**, 1498. [2] *Idem*, *ibid.*, p. 2343. [3] *Idem*, *Ber.*, 1931, **64**, 2827. [4] This paper.

Absolute Stereochemistry at $C_{(9)}$.—Bick's allocation of absolute stereochemistry at $C_{(9)}$ now requires re-examination. The possibility that the rotatory changes of *apo*morphine and *apo*codeine were due to variations in phenolic betaine concentration with solvent polarity was excluded by the examination of diacetylmorphothebaine (XXXI). This base showed an increase in lævorotation with increasing solvent polarity (Table 2), and, in agreement with


(XXXI)

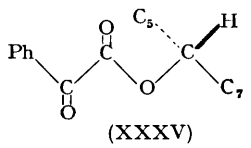

(XXXII)

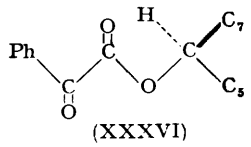

(XXXIII)

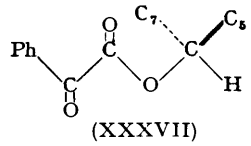

(XXXIV)

Bick's conclusion, appears to have the same absolute stereochemistry as (+)-laudanosine (XXXII; $R^1 = R^2 = Me$), which has been related (see Table 2) to (−)-1-phenylethylamine and thence by oxidation to (+)-alanine (Leithe, *Ber.*, 1930, **63**, 2343; 1931, **64**, 2827). This relation can be tested, as Faltis and Adler (*Arch. Pharm.*, 1951, **284**, 281) have prepared (−)-glaucine from (−)-laudanosine. (+)-Glaucine (XXXIV; $R^3 = H$, $R^1 = R^2 = R^4 = R^5 = OMe$) should therefore, if Bick is correct, show a similar variation of rotation with solvent polarity to (−)-diacetylmorphothebaine. For the three most polar solvents (+)-glaucine (we are grateful to Dr. R. H. F. Manske for the gift of a sample) shows the opposite variation, and therefore belongs to the opposite series from (−)-diacetylmorphothebaine, which must accordingly be (XXXI) and morphine must be (XII; R = H).

This conclusion can be put to the test. The absolute stereochemistry at $C_{(6)}$ is satisfactorily established by interlocking optical evidence. The weakest link is the evidence on the absolute stereochemistry at $C_{(9)}$. Application of Prelog's method (*Helv. Chim. Acta*, 1953, **36**, 308) to the optical rotation of the atrolactic acid resulting from the treatment of the phenylglyoxylyl ester of dihydrocodeine with methylmagnesium iodide, paradoxically gives no information about the absolute stereochemistry at $C_{(6)}$, but if the stereochemistry at this centre is regarded as settled the result does allow a distinction between (XII and XIII; R = H) for morphine. The three conformations of the phenylglyoxylate are (XXXV), (XXXVI), and (XXXVII) the groups in order of size being $C_{(5)} > C_{(7)} > H$. If dihydrocodeine were as (XIII, 7 : 8-dihydro; R = Me) then, as shown by models, as in the cases studied by Prelog, attack by the Grignard reagent on conformation (XXXV) would be from above and on conformations (XXXVI) and (XXXVII) from below, leading, on


(XXXV)

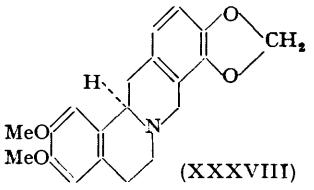

(XXXVI)


(XXXVII)

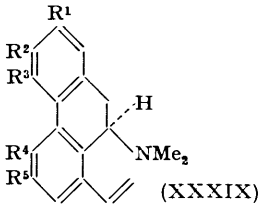
hydrolysis, to an excess of (+)-atrolactic acid. However, models show that the conformation (XXXVII) is impossible with the structure (XII, 7 : 8-dihydro; R = Me) for dihydrocodeine, and that moreover in conformation (XXXI) attack from below is seriously hindered by the 3-methoxyl group, so that attack from above will be accentuated and will more than compensate for the slightly preferred attack from below shown by configuration (XXXVI). Thus an excess of (−)-atrolactic acid should be obtained on hydrolysis. The atrolactic acid isolated from this sequence of reactions had $[\alpha]_D^{18}$ −5·73°, thus confirming the structure (XII; R = H) for morphine. The arrangement of groups deduced by Schöpf, by Fieser and Fieser, by Rapoport and his co-workers (*loc. cit.*), and by Bose (*Chem. and Ind.*, 1954, 130) is thus confirmed.

The ambiguity observed earlier in the optical comparison of steroids and hydrogenated

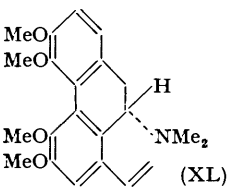
codeine derivatives and the observation that benzyl*iso*quinolines and aporphine alkaloids have the same stereochemistry when their rotatory variations with solvent polarity are opposite, illustrate a principle that is sometimes neglected. In comparisons of optical data the spatial arrangements of the molecules must be studied. Thus, in the benzyl*iso*quinolines the preferred conformation will be that (XXXIII) in which the benzene nucleus is



(XXXVIII)



(XXXIX)



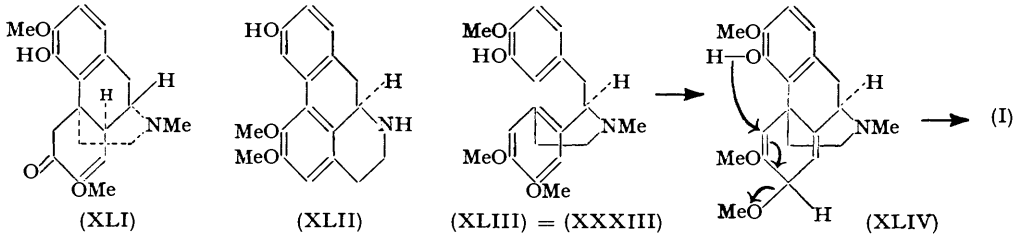
(XL)

remote from the unsaturated ring of the tetrahydro*iso*quinoline. Cyclisation to a tetrahydroberberine (XXXVIII) then involves little geometrical change. In conformity with this, Leithe (*Ber.*, 1934, **67**, 1261) has prepared (−)-tetrahydroprotoberberine (deoxy-XXXVIII) from (−)-benzyltetrahydro*iso*quinoline and has shown that in these two compounds the optical rotation changes with solvent polarity in the same manner. Cyclisation to an aporphine, however, involves a major change of shape, hence it is not surprising that the dependence of rotation on solvent polarity also changes.

The proof that (+)-glaucine and (−)-morphothebaine are enantiomorphous suggests the assignment of all aporphine alkaloids that are dextrorotatory in ethanol or chloroform to the (−)-1-phenylethylamine series. All the 2 : 3 : 5 : 6-tetra-oxyaporphines [(+)-domesticine, (+)-dicentrine, (+)-laurotetanine, (+)-actinodaphnine, and (+)-boldine] that have been related to (+)-glaucine are represented by (XXXIV; $R^3 = H$, R^1, R^2, R^4, R^5 = OX) (for references see Henry, " The Plant Alkaloids," 4th Edn., Churchill, 1949). None of the 3 : 4 : 5 : 6-tetra-oxyaporphines has been related to the glaucine series, but in addition to the sign of rotation, which assigns to (+)-bulbocapnine, (+)-corydine, (+)-*iso*-corydine (artabotrinine), (+)-corytuberine, and (+)-suaveoline the structure (XXXIV) we note that aporphine alkaloids on Hofmann degradation give *iso*methines of opposite sign of rotation to the parent base. Thus *apo*morphine dimethyl ether, $[\alpha]_D$ −148°, gives an *iso*methine (XXXIX; $R^1 = R^4 = R^5 = H$, $R^2 = R^3 =$ OMe), $[\alpha]_D$ +139°. *iso*Corydine methyl ether (XXXIV; $R^1 = H$, $R^2 = R^3 = R^4 = R^5 =$ OMe), $[\alpha]_D$ +182°, gives an *iso*methine (XL), $[\alpha]_D$ −183°, and this confirms our assigmnent of the dextrorotatory aporphines to a series enantiomorphous to (−)-morphothebaine. In the trioxyaporphines, *iso*thebaine methyl ether, $[\alpha]_D$ +235°, gives an *iso*methine, $[\alpha]_D$ −284° (Klee, *Arch. Pharm.*, 1914, **252**, 211); hence despite the fact that the position of the oxygen atoms has not been clearly established we can assign *iso*thebaine to the series (XXXIV). In the dioxyaporphines, (−)-roemerine (5 : 6-methylenedioxyaporphine), $[\alpha]_D$ −77°, on demethylation, methylation, and degradation affords an *iso*methine, $[\alpha]_D$ +14°; we can therefore assign to (+)-roemerine the constitution (XXXIV; $R^1 = R^2 = R^3 = H$, $R^4R^5 = CH_2O_2$) despite the fact that a sample kindly provided by Professor L. Marion did not show a characteristic rotatory change with solvent polarity. These facts confirm our suggestion that the absolute stereochemistry of the aporphine alkaloids may now be assigned on the basis of the sign of rotation in ethanol or chloroform. The only doubtful case is anolobine (2-hydroxy-5 : 6-methylenedioxyaporphine) whose rotation ($[\alpha]_D$ −23°) is too low for unambiguous assignment.

Now that the absolute stereochemistry of the benzyl*iso*quinoline, morphine, aporphine, and tetrahydroberberine alkaloids is known an interesting pattern emerges. Sinomenine (XLI) is enantiomorphous at $C_{(9)}$ to (−)-sinactine (XXXVIII) and (−)-tuduranine (XLII), which are also found in *Sinomenium acutum* (Goto and Kitasato, *J.*, 1930, 1234; Goto, Inaba, and Nozaki, *Annalen*, 1937, **530**, 142). Similarly in *Papaver somniferum* thebaine (I), morphine (XII; R = H), and codeine (XII; R = Me) are accompanied by (+)-codamine (XXXII; $R^1 =$ OH, $R^2 =$ OMe) and (+)-laudanosine (XXXII; $R^1 = R^2 =$ OMe), and in *Papaver orientale* thebaine (I) and (+)-*iso*thebaine appear at different periods

of growth. In each case the morphine alkaloids are enantiomorphous at $C_{(9)}$ to those mentioned of the other series accompanying them. In addition Hesse (*Annalen*, 1870, **153**, 47; *Ber.*, 1871, **4**, 693; *Annalen*, 1894, **282**, 209) isolated laudanine [(±)-laudanidine] and (−)-laudanidine (XXXIII) from opium residues. As (−)-laudanidine is the only alkaloid of the same absolute stereochemistry as thebaine isolated from opium it is reasonable to accept it, or a less methylated base, as a precursor of thebaine in Robinson and Sugasawa's biogenetic scheme (*J.*, 1931, 3163). The oxide ring may then be built by an allylic expulsion of methoxyl (XL) ⟶ (XLI) ⟶ (I). It is significant that of the benzyl*iso*quinoline alkaloids present in opium only laudanidine has a free hydroxyl group suitable for oxide ring



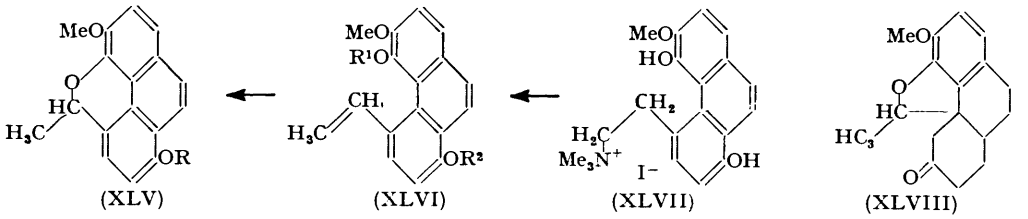
(XLI) (XLII) (XLIII) = (XXXIII) (XLIV)

formation. In *Papaver orientale*, as the plant ripens, the yield of thebaine increases, but when the plant begins to wither the yield of this alkaloid decreases and that of *iso*thebaine increases. This is consistent with the removal of (−)-laudanidine in the formation of thebaine and the accumulation of (+)-laudanidine which is subsequently used to make (+)-*iso*thebaine. On this basis, (+)-*iso*thebaine should be 2(or 4)-hydroxy-3 : 6(or 5)-dimethoxyaporphine. 2 : 3 : 6-Trimethoxyaporphine has been synthesised (Bentley and Blues, unpublished results) and is not identical with *iso*thebaine methyl ether; 3 : 4 : 6-trimethoxyaporphine has already been shown to be identical with morphothebaine dimethyl ether (Gulland and Haworth, *J.*, 1928, 2083). The work of Schlittler and Müller (*Helv. Chim. Acta*, 1948, **31**, 1119) indicates that *iso*thebaine is a 3 : 4 : 5-substituted aporphine, but this has been challenged by Kiselev and Konovalova (*J. Gen. Chem. U.S.S.R.*, 1949, **19**, 148). Further work on this problem is proceeding.

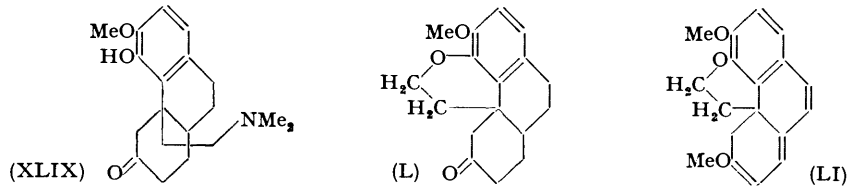
In view of its relevance to Rapoport and Lavigne's degradative work (*loc. cit.*) on the thebenones we have investigated the size of the oxide ring (formed by cyclisation of the 4-hydroxyl group with the ethanamine chain) in thebenol and thebenone derivatives by Kuhn–Roth *C*-methyl determinations. Gulland and Virden (*J.*, 1928, 921) assigned a six-membered oxide ring structure (XLV; R = H) to thebenol, the product of Hofmann degradation of *N*-methylthebenine methiodide (XLVII) (Freund, *Ber.*, 1894, **27**, 2961; Freund, Michaels, and Gobel, *ibid.*, 1897, **30**, 1356; Pschorr and Loewen, *Annalen*, 1910, **373**, 56). This structure, and a mechanism involving the intermediate vinyl compound (XLVI; $R^1 = R^2 = H$) were made very likely by the observation that the vinyl compound (XLVI; $R^1 = R^2 = Me$) cyclised to methebenol (XLV; R = Me) in warm acetic acid (Pschorr and Massaciu, *Ber.*, 1904, **37**, 2780). The structure has now been confirmed by the production of one molecular equivalent of acetic acid on Kuhn–Roth oxidation.

Cahn (*J.*, 1926, 2562) and subsequently Small, Sargent, and Bralley (*J. Org. Chem.*, 1947, **12**, 847) and Bentley, Robinson, and Wain (*J.*, 1952, 958) assigned a similar structure (XLVIII) to thebenone, the product of Hofmann degradation of dihydrothebainone dihydromethine (XLIX). In this case there is evidence (Bentley, Robinson, and Wain (*loc. cit.*) that a vinyl compound is not an intermediate, and the preparation of (LIII) from (LII) was cited as a model for an elimination with rearrangement leading to (XLVIII). This model is, however, unsuitable as bimolecular replacement of $-NH_3^+$ by $-O^-$ is impeded by the *neo*pentyl system, and owing to the absence of a β-hydrogen atom normal elimination is impossible; hence the abnormal reaction observed is the only easy reaction. In the methohydroxide of (XLIX), bimolecular replacement is not impeded and the product (L) is quite normal. This has been confirmed (cf. Rapoport and Lavigne, *loc. cit.*) by the failure to isolate acetic acid after the Kuhn–Roth oxidation of piperonylidene-β-thebenone and of 6-methoxythebentriene (LI).

The oxide rings in thebenol and thebenone are therefore differently constituted, but both are six-membered. The abnormal addition of the phenoxide ion to an olefin in the preparation of thebenol illustrates how a spatial probability factor can bring about an energetically unfavourable reaction.



(XLV) (XLVI) (XLVII) (XLVIII)



(XLIX) (L) (LI)

(LII) $Ph{\cdot}CH_2{\cdot}CMe_2{\cdot}CH_2{\cdot}NMe_3^+ \longrightarrow Ph{\cdot}CH{=}CMe{\cdot}CH_2Me$ (LIII)

Experimental

C-Methyl Determinations.—(i) Thebenol. Found: *C*-Me, 4·2, 6·5. Calc. for one *C*-Me, 5·6%. (ii) 6-Methoxythebentriene and piperonylidene-β-thebenone, no *C*-Me.

Diacetylmorphothebaine.—Morphothebaine (2 g.) was acetylated with acetic anhydride and pyridine at room temperature. The *diacetyl derivative* was purified by chromatography on alumina, 1 : 1 benzene–light petroleum (b. p. 40—60°) being used for elution. The base crystallised from light petroleum (b. p. 60—80°) in pale yellow rods, m. p. 125—128° (Found: C, 69·6; H, 5·9; N, 4·0. $C_{22}H_{23}O_5N$ requires C, 69·4; H, 6·0; N, 3·7%).

Metathebainone Methine Hydrobromide.—The *hydrobromide* was precipitated when metathebainone methine was dissolved in alcoholic hydrobromic acid and recrystallised from 96% ethanol as yellow prisms, m. p. 236—237° (decomp.) (Found: C, 57·1, 57·0; H, 6·1, 6·1; N, 3·3; loss at 120°/vac., 0. $C_{19}H_{23}O_3N,HBr,\frac{1}{4}H_2O$ requires C, 57·6; H, 6·2%). Schöpf and Borkowsky (*loc. cit.*) found for their material prepared from 14-hydroxydihydrothebainone methine, m. p. 230—231° and, after drying at 100°/*in vacuo*, C, 57·1; H, 6·2%.

O-Phenylglyoxylyldihydrocodeine.—Dihydrocodeine (5 g.) and phenylglyoxylyl chloride (3 g.) were kept in pyridine (15 ml.) at room temperature overnight. The mixture was diluted with aqueous sodium carbonate and extracted four times with benzene, and the benzene extracts were repeatedly washed with water, dried (Na_2SO_4), and evaporated. Recrystallisation twice from 1 : 1 benzene–light petroleum (b. p. 100—120°) gave *phenylglyoxylyldihydrocodeine* as colourless prisms, m. p. 171° (Found: C, 72·1; H, 6·3. $C_{26}H_{27}O_5N$ requires C, 72·0; H, 6·2%).

Reaction of Phenylglyoxylyldihydrocodeine with Methylmagnesium Iodide.—A solution of the ester (5 g.) in dry benzene (100 ml.) and dry ether (30 ml.) was slowly added to one of methylmagnesium iodide (4 mols.; from 1·15 g. of magnesium) in ether–benzene. The mixture was left for 3 hr. at room temperature, then boiled under reflux for 3 hr. and decomposed with ammonium chloride solution, the benzene–ether layer separated, and the aqueous layer extracted with chloroform. The organic layers were separately dried and evaporated. The residual oil was boiled under reflux with 5% methanolic potassium hydroxide for 5 hr., and the solution evaporated to small bulk, diluted with water, filtered, extracted with ether, acidified with hydrochloric acid, and extracted five times with ether. The latter extracts were then dried and evaporated leaving a black oil. This was repeatedly extracted with small quantities of boiling light petroleum (b. p. 100—120°); a violet solution was obtained. The combined petroleum extracts, on cooling, deposited 283 mg. of atrolactic acid as colourless needles, $[\alpha]_D^{18}$ −5·73° (*c* 1·4 in EtOH).

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