839. *Syntheses Along Biosynthetic Pathways. Part I. Synthesis of (+)-Isothebaine*

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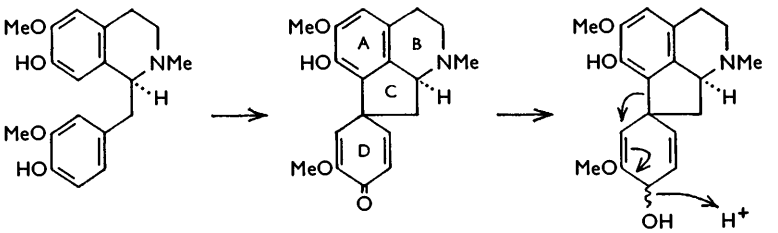
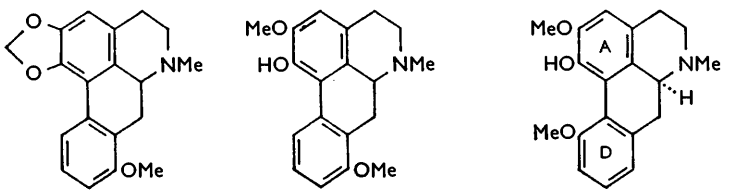
The aim of this Series of Papers is outlined.

(±)-Orientaline [as structure (I)], the suggested biosynthetic precursor of isothebaine (IV), is oxidised to afford racemic orientalinone [as structure (II)] and this is converted by reduction followed by dienol-benzene rearrangement into (±)-isothebaine. Orientaline is resolved, the absolute configurations of the enantiomers are determined, and they are used to establish the absolute stereochemistry of natural (+)-isothebaine. By employing (+)-orientaline (I) as the starting material for oxidation, (−)-orientalinone (II) and (+)-isothebaine (IV) are synthesised. A preliminary account of the work on racemic compounds has been published.[1]

The synthesis of natural products by routes which are based upon those used, or thought to be used, in nature has many attractions not the least being the simplicity of approach which is often possible. Robinson's famous tropinone synthesis [2] clearly illustrates this aspect and there have been many other examples which are discussed by van Tamelen.[3] More recently, several elegant syntheses of this type have been reported in the alkaloid field [3, 4a–c] and elsewhere.[4d–g]



(I) (II) (III)



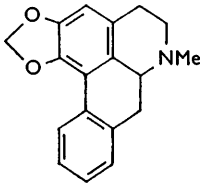
(VI) (V) (IV)

The work to be described in the present series of papers complements biosynthetic studies with tracers in living plants. As the detailed biosynthetic pathways are elucidated, or as plausible biosynthetic routes are proposed, so attempts to reproduce them in the laboratory can be initiated. It is not intended to restrict the synthetic methods to

[1] A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.
[2] R. Robinson, *J.*, 1917, **111**, 762.
[3] E. E. van Tamelen, " Progress in the Chemistry of Organic Natural Products," ed. L. Zechmeister, Springer-Verlag, Vienna, vol. 19, 1961, p. 242.
[4] (*a*) D. H. R. Barton and G. W. Kirby, *J.*, 1962, 806; (*b*) B. Frank, G. Blaschke, and G. Schlingloff, *Angew. Chem.*, 1963, **75**, 957; (*c*) D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 1963, 203; (*d*) T. A. Davidson and A. I. Scott, *ibid.*, 1960, 390; (*e*) C. J. Brown, D. E. Clark, W. D. Ollis, and P. L. Veal, *ibid.*, p. 393; (*f*) A. C. Day, J. Nabney, and A. I. Scott, *J.*, 1961, 4067; (*g*) C. H. Hassall and J. R. Lewis, *ibid.*, p. 2312.

extremely mild ones run under " physiological conditions "; reactions drawn from the full range of organic chemistry will be used as required.

Isothebaine (IV) occurs in the oriental poppy,[5] *Papaver orientale*, and its structure has been firmly established.[6] We reasoned (see below) that this alkaloid should be a favourable case for attack by synthesis and it was therefore selected as the first objective. The structural relationship of the aporphine alkaloids, of which isothebaine is a member, to the 1-benzyltetrahydroisoquinolines has long been recognised [7,8] and Barton and Cohen proposed [9] that the bond between rings A and D in this series of alkaloids [see structure (IV)] is generated by phenol oxidation. In the case of isothebaine (IV), however, such a coupling cannot be straightforward because of the necessity to account for the unusual oxygenation pattern in ring D. A similar problem is presented by the structure of stephanine (VI), found in *Stephania japonica*.[10] The formation of both isothebaine and stephanine can be explained, however, by the proposed biosynthetic pathway [11] which starts from the 1-benzylisoquinoline (I), named [12] orientaline. Phenol oxidation [9,13] of this base could generate the dienone (II) and reduction to form the dienol(s) (III) provides a suitable system for dienol–benzene rearrangement; if this occurs as shown, isothebaine (IV) would be formed. No stereochemistry is specified for the allylic hydroxyl group in structure (III) but it seems probable that in nature the reduction is a stereospecific one. The dienol–benzene rearrangement is now well established in several systems [14,15] and, importantly, for the conversion of prephenic acid into phenylpyruvic acid; [14] moreover, it was postulated [9] for the biosynthesis of alkaloids related to roemerine (VII) before it was recognised experimentally. Only one direction of dienol–benzene rearrangement is shown in structure (III). Three others are theoretically open to the two dienols (III) and one such change could afford the base (V) which is closely related to stephanine (VI).



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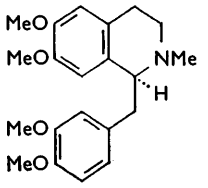

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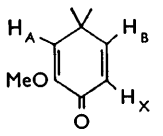


(IX)

Intramolecular phenol coupling of orientaline (I) could in principle generate four products, the dienone (II) and the bases of structure (X), (XI), and (XII) without regard to stereochemistry. Of these, compounds (X) and (XI) are sterically impossible and the bis-dienone is a very improbable product in that it is a highly strained system. Experiments on the oxidation of orientaline were thus undertaken with the encouraging knowledge that the desired dienone (II) was the only expected product of intramolecular coupling.

(±)-Orientaline [as structure (I)] was prepared by standard methods [12,16] and was

[5] W. Klee, *Arch. Pharm.*, 1914, **252**, 211; D. Neubauer and K. Mothes, *Planta Medica*, 1961, **4**, 466.
[6] K. W. Bentley and S. F. Dyke, *J. Org. Chem.*, 1957, **22**, 429, and references cited therein.
[7] Sir R. Robinson, " The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.
[8] R. H. F. Manske, *J.*, 1954, 2987.
[9] D. H. R. Barton and T. Cohen, " Festschrift A. Stoll," Birkhauser, Basle, 1957, p. 117.
[10] H. Kondo and T. Sanada, *J. Pharm. Soc. Japan*, 1928, **48**, 163.
[11] A. R. Battersby, Tilden Lecture, *Proc. Chem. Soc.*, 1963, 189.
[12] A. R. Battersby, D. M. Foulkes, and R. Binks, *J.*, 1965, 3323.
[13] H. Erdtman and C. A. Wachtmeister, " *Festschift A. Stoll*," Birkhauser, Basle, 1957, p. 144.
[14] H. Plieninger, *Angew. Chem. Internat. Edn.*, 1962, **1**, 367, and refs. therein.
[15] M. J. Gentles, J. B. Moss, H. L. Herzog, and E. B. Herschberg, *J. Amer. Chem. Soc.*, 1958, **80**, 3702.
[16] J. Kunimoto, *Yakugaku Zasshi*, 1961, **81**, 1253.

characterised as its crystalline perchlorate. The best conditions found for phenol oxidation of this substance involved a two-phase system of chloroform and aqueous ferricyanide with ammonium acetate buffer. By this method, the desired material [as structure (II)], $C_{19}H_{21}NO_4$, now named (±)-orientalinone, was obtained and it could be prepared consistently in the crystalline state in 2·5—3·5% yield. Structure (II) in fact represents two substances, one having the methoxyl group of ring D below the general plane of rings A, B, and C and the other having ring D reversed so that its methoxyl group lies above this plane. Future investigations will show which of these stereoisomers corresponds to orientalinone. The structure assigned to the oxidation product was supported by its infrared spectrum which showed typical dienone absorptions at 1665, 1630, and 1605 cm.$^{-1}$. Further, its nuclear magnetic resonance spectrum showed the expected *O*-methyl (τ 6·23, 3H) and (τ 6·40, 3H) and *N*-methyl (τ 7·62, 3H) resonances and a singlet at τ 3·46 assigned to the lone proton of ring A. In addition, the spectrum showed a doublet at τ 4·08 corresponding to one proton and this signal is assigned to H_A of the dienone system (see formula (IX)]; transannular coupling (J_{AB} = 2·5 c./sec.) occurs with H_B. A further doublet, equivalent to one proton and centred at τ 3·67, corresponds to H_X with J_{BX} = 10 c./sec. and a quartet centred at τ 3·21 (one proton) is assigned to H_B. The signal for H_B is split by coupling to both H_A and H_X. This interpretation is based upon the assignments for simple cyclohexadienone systems [17] and for the closely related systems of pronuciferine [18] (XIV) * and crotonosine [19] (XV). The signal for H_A in orientalinone [(IX) and (II)] appears *ca.* 1 p.p.m. upfield from the signals given by the corresponding protons in the bases (XIV) and (XV); this is in keeping with the known shielding effect of oxygen on the β-proton of an enol ether system.[20]

Reduction of (±)-orientalinone [as structure (II)] with borohydride afforded a mixture of two dienols, (±)-orientalinol-I and (±)-orientalinol-II [as structure (III)], which could be separated chromatographically. The former was obtained crystalline but the latter has remained amorphous. Initially, however, the dienol-benzene rearrangement [as structure (III)] ⟶ [as structure (IV)] was carried out by treatment of the mixture of orientalinols with aqueous acid. This afforded a mixture of products from which (±)-isothebaine was isolated in 36% yield based upon the starting (±)-orientalinone; the crystalline synthetic product was identified by direct comparison with natural isothebaine (IV). Micro-quantities of pure orientalinol-I and orientalinol-II were also rearranged in this way and thin-layer chromatography of the products showed that (±)-isothebaine is formed from both isomers. This behaviour can be compared with the formation of thebaine from both salutaridinols.[4c,21]

The success with racemic materials opened the way to a synthesis of the naturally occurring (±)-isothebaine (IV) but a knowledge of its absolute configuration is a prerequisite. No direct determination has been made but the sign of rotation of natural isothebaine at 589 mμ has been interpreted [22] in favour of the stereochemistry of formula (IV).

As a first step towards a rigid determination of the absolute configuration of (+)-isothebaine, (±)-*OO'*-dibenzylorientaline [as structure (I; OH ⟶ OCH_2Ph)] was resolved

* The synthesis of pronuciferine, not along the biosynthetic route, has recently been reported, K. Bernauer, *Experientia*, 1964, **20**, 380.

[17] W. von Philipsborn, *Helv. Chim. Acta*, 1965, **48**, in the press.

[18] K. Bernauer, *Helv. Chim. Acta*, 1963, **46**, 1783; 1964, **47**, 2122; see also M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffauf, and I. A. Weisbach, *Chem. and Ind.*, 1964, 282.

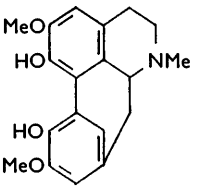
[19] L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *Proc. Chem. Soc.*, 1963, 280; 1964, 261; see also B. Gilbert, M. E. A. Gilbert, M. M. de Oliveira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 694.

[20] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 62.

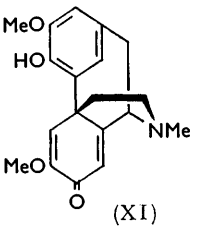
[21] D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J.*, 1965, 2423.

[22] C. Djerassi, K. Mislow, and M. Shamma, *Experientia*, 1962, **18**, 53.

through the *OO'*-dibenzoyltartaric acid salts. Both enantiomers of the base were obtained crystalline and each was debenzylated catalytically to afford (+)- and (−)-orientalines. Methylation of (+)-orientaline afforded (+)-laudanosine (VIII) which is of firmly established absolute configuration by chemical correlation with the natural amino-acids.[23] (+)-Orientaline thus has the absolute configuration (I) and (−)-orientaline is represented by structure (XIII). Samples of the enantiomeric orientalines were labelled with tritium at the free positions of the aromatic rings by acid-catalysed exchange [24] in tritiated water. It was demonstrated by nuclear magnetic resonance that when acidified deuterium oxide



(X)



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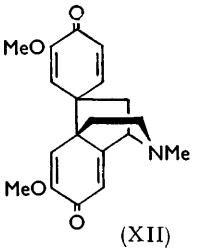

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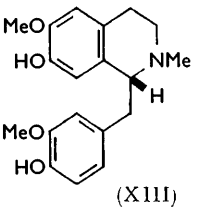

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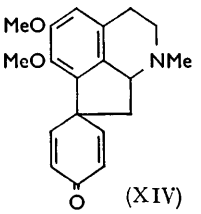

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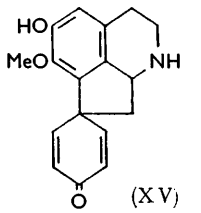

(XV)

was used under the same conditions, quantitative replacement of the aromatic protons by deuterium occurred.

Small quantities of (+)-3*H*-orientaline and (−)-3*H*-orientaline were taken separately through the reaction sequence used above for the synthesis of (±)-isothebaine and so were obtained two reaction products. One must contain (+)-isothebaine identical with the natural alkaloid and the other will contain its enantiomer. Dilution of each product with a large excess of natural (+)-isothebaine and repeated crystallisation of the two specimens gave a clear result. That derived from (+)-orientaline rapidly reached constant activity whereas that from (−)-orientaline lost activity steadily until it became almost radioinactive. It follows that (+)-orientaline (I) is the correct precursor of (+)-isothebaine which in turn is proved to have the absolute stereochemistry shown in formula (IV). A synthesis of the natural alkaloid could now be undertaken with confidence and large quantities of (+)- and (−)-orientalines were prepared for the following experiments.

Oxidation of (−)-orientaline (XIII) in the way described above afforded (+)-orientalinone [enantiomer of compound (II)]. Similarly, (+)-orientaline (I) gave (−)-orientalinone (II) which was reduced by borohydride to produce a mixture of the orientalinols (III). These were rearranged without separation in a solution of hydrogen chloride in anhydrous methanol–ether when (+)-isothebaine (IV) crystallised from the reaction mixture as its hydrochloride; these conditions are superior to aqueous acid for the dienol-benzene rearrangement in this case. The synthetic (+)-isothebaine was identified with natural isothebaine by rigorous comparison (see p. 4556) and the first synthesis of (+)-isothebaine was thus complete. These experiments establish that the suggested biosynthetic pathway to isothebaine [11] is a chemically feasible one and it is pleasing that recent tracer

[23] H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, 1956, **39**, 889.
[24] G. W. Kirby and L. Ogunkoya, quoted in ref. 21; A. Murray and D. L. Williams, "Organic Syntheses with Isotopes," Part II, Interscience Publishers, New York, 1962, p. 91.

experiments on *P. orientale* plants [25] provide powerful evidence that this route is followed in the living plant.

Experimental

Melting points were determined on a Kofler hot-stage apparatus. Unless specified to the contrary values for $[\alpha]_D$ refer to $CHCl_3$ solutions. Evaporations were carried out under reduced pressure at $<40°$. Radioactivity measurements were made by solution scintillation counting on a Packard " Tricarb " Liquid Scintillation Spectrometer (model 3003) as previously described.[12]

(±)-*Orientaline Perchlorate.*—*OO'*-Dibenzylorientaline [12,16] (1 g.) was debenzylated by hot concentrated hydrochloric acid [12] or by hydrogenolysis of the benzyl groups at atmospheric pressure over 10% palladised charcoal (0·15 g.) in methanol (35 ml.) containing concentrated hydrochloric acid (0·3 ml.).

A solution of the orientaline hydrochloride (0·1 g.) so obtained, in water (0·8 ml.) was treated with sodium perchlorate (0·12 g.) in water (0·4 ml.). The precipitate was washed with water and recrystallised from ethanol to give *orientaline perchlorate* (80 mg.), m. p. 127° (Found: C, 51·1; H, 5·9; N, 3·0. $C_{19}H_{26}NO_9Cl$ requires C, 50·9; H, 5·9; N, 3·1%).

(±)-*Orientalinone.*—(±)-*OO'*-Dibenzylorientaline (1 g.) was debenzylated as above and the resultant (±)-orientaline hydrochloride was dissolved in a solution of ammonium acetate (16 g.) in water (200 ml.). The solution was distributed evenly among four flasks and after the addition of chloroform (50 ml.) to each, the flasks were shaken vigorously for 10 min. A solution of potassium ferricyanide (0·3 g.) in aqueous ammonium acetate (8% by wt., 20 ml.) was then added to each sample and the flasks were shaken vigorously for 3 hr. before their contents were combined. The aqueous layer was basified with ammonia and extracted with chloroform (4 × 200 ml.) which afforded a gum (646 mg.). This was fractionated on neutral alumina (35 g., activity III) in 1 : 1 (by vol.) benzene–chloroform with control by thin-layer chromatography. Evaporation of the appropriate fractions gave a gum (21—28 mg.) which crystallised from chloroform–benzene to afford *orientalinone* (15—21 mg.), m. p. 203° (decomp.) (Found: C, 69·4; H, 6·5; *M*, mass spectrum, 327), $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·4%; *M*, 327.)

(±)-*Orientalinol*-I *and* (±)-*Orientalinol*-II.—Sodium borohydride (0·25 g.) was added portionwise during 1 hr. to a solution of (±)-orientalinone (45 mg.) in methanol (2·5 ml.). After a further 1 hr., the methanol was evaporated, water was added to the residue, and the products (45 mg.) were extracted into chloroform. These were fractionated on alumina (activity III) in chloroform–benzene (1 : 3 by vol.) to give *orientalinol*-I (14 mg.) which crystallised from benzene, m. p. 190° (decomp.) (Found: *M*, mass spectrum, 329. $C_{19}H_{23}NO_4$ requires *M*, 329). This was followed by a mixture of orientalinol-I and -II (15 mg.) and finally orientalinol-II (8 mg.) was eluted (Found: *M*, mass spectrum, 329; the spectrum was almost identical with that given by orientalinol-I).

(±)-*Isothebaine.*—The mixture of orientalinol-I and orientalinol-II (21·5 mg.) was dissolved in the minimum volume of methanol and aqueous N-hydrochloric acid (4 ml.) was added. After being kept at room temperature overnight, the solution was basified with sodium carbonate and extracted with chloroform to afford a gum (20 mg.). This was chromatographed on alumina (activity III) in benzene–chloroform (3 : 1 by vol.) and the fractions containing (±)-isothebaine were combined and evaporated to a gum (8·0 mg.) which was homogeneous and indistinguishable from natural (±)-isothebaine by thin-layer chromatography using alkaline potassium permanganate, concentrated nitric acid, alkaline diazotised sulphanilic acid, and Dragendorff's reagent. This material crystallised from ethanol–ether and had m. p. 164—166°; the infrared spectrum ($CHCl_3$) was identical with that of natural (+)-isothebaine.

(+)- *and* (−)-*Dibenzylorientaline.*—A solution of (±)-*OO'*-dibenzylorientaline (13·2 g.) and (−)-*OO'*-dibenzoyltartaric acid [26] (9·3 g.) in ethyl acetate (150 ml.) was kept at 4° for 2 hr. The crystals were collected and recrystallised thrice from ethyl acetate to yield (+)-*dibenzylorientaline* (−)-OO'-*dibenzoyltartrate* (4·6 g.), m. p. 109—110°, $[\alpha]_D^{21}$ +16·5° (*c* 1·08) (Found: C, 70·4; H, 5·6; N, 1·8. $C_{51}H_{49}NO_{12}$ requires C, 70·5; H, 5·8; N, 1·6%).

The base was recovered from this salt (4·5 g.) as usual into chloroform and the product was crystallised from ethanol to give (+)-OO'-*dibenzylorientaline* (2·25 g.), m. p. 85—87°, $[\alpha]_D^{21}$ +58·6° (*c* 1·15) (Found: C, 77·8; H, 6·9; N, 2·8. $C_{33}H_{35}NO_4$ requires C, 77·8; H, 6·9; N, 2·8%).

The mother-liquors from the (+)-dibenzylorientaline (−)-*OO'*-dibenzoyltartrate were worked

[25] A. R. Battersby, R. T. Brown, T. H. Brown, and G. Iverach, unpublished work.
[26] C. L. Butler and L. H. Cretcher, *J. Amer. Chem. Soc.*, 1933, **55**, 2605.

for base which was dissolved in ethanol when (±)-*OO'*-dibenzylorientaline separated (7·5 g.). Concentration of the ethanolic mother-liquor yielded partly resolved (−)-base (2·0 g.), $[\alpha]_D^{21}$ −50·4° (*c* 0·96). This was treated with (+)-*OO'*-dibenzoyltartaric acid (1·4 g.) as above and the salt was recrystallised twice from ethyl acetate to give (−)-OO'-*dibenzylorientaline* (+)-OO'-*dibenzoyltartrate* (2·2 g.), m. p. 110—111°, $[\alpha]_D^{21}$ −18·0° (*c* 1·14) (Found: C, 70·3; H, 5·6; N, 1·8%).

(−)-OO'-*Dibenzylorientaline* was recovered from the foregoing salt and crystallised as for the (+)-enantiomer; it showed m. p. 84—86°, $[\alpha]_D^{21}$ −60·6° (*c*, 0·99) (Found: C, 78·0; H, 6·8; N, 2·8%).

(+)- *and* (−)-*Orientaline.*—(+)-*OO'*-Dibenzylorientaline was debenzylated by catalytic hydrogenation as above to give (+)-orientaline hydrochloride $[\alpha]_D^{21}$ +53·5° (*c* 1·28 in water). This was converted as above into (+)-*orientaline perchlorate*, which, crystallised from ethanol, had m. p. 128—130° (Found: C, 50·7; H, 5·7; N, 3·2. $C_{19}H_{26}ClNO_9$ requires C, 50·9; H, 5·9; N, 3·1%).

Similarly the (−)-*OO'*-dibenzyl ether afforded (−)-orientaline hydrochloride, $[\alpha]_D^{21}$ −53·4° (*c* 1·26 in water). (−)-*Orientaline perchlorate* crystallised from ethanol and had m. p. 124—125° (Found: C, 50·6; H, 5·7; N, 3·1%).

Methylation of (+)-*Orientaline.*—The base recovered from (+)-orientaline hydrochloride (50 mg.) was methylated in methanol (10 ml.) with ethereal diazomethane (50 ml., 3%) for 3 days. Chromatography of the products on neutral alumina (activity I) in 1 : 1 benzene–chloroform yielded (+)-laudanosine (18 mg.), m. p. 87—89°, $[\alpha]_D^{23}$ +54·2° (*c* 0·99 in $CHCl_3$), identified by infrared comparison with authentic material.

(+)- *and* (−)-*Orientalinone.*—(−)-*OO'*-Dibenzylorientaline (1·0 g.) was debenzylated and oxidised as above to yield (+)-*orientalinone* (19 mg.), m. p. 184—186° (decomp.), $[\alpha]_D^{21}$ +62·3° (*c* 0·74).

(+)-*OO'*-Dibenzylorientaline (4 g.) similarly gave (−)-*orientalinone* (58 mg.), m. p. 183—184° (decomp.), $[\alpha]_D^{21}$ −62·6° (*c* 0·84). The infrared spectra and mass spectra of these two enantiomers by direct inlet were identical with those of (±)-orientalinone (Found: *M*, 327 in both cases. $C_{19}H_{21}NO_4$ requires *M*, 327).

(+)-[^{3}H]*Orientaline and* (−)-[^{3}H]*Orientaline and Their Conversion into* (+)-[^{3}H]*Isothebaine and* (−)-[^{3}H]*Isothebaine.*—(+)-Orientaline hydrochloride (49 mg.) was heated for 24 hr. in a sealed tube at 100° with concentrated hydrochloric acid (AnalaR, 64 mg.) and tritiated water-methanol (1 : 4 by vol.) of specific activity 1 c./ml. (0·1 ml.). The solution was evaporated to dryness and the residue was dissolved in methanol (5 ml.) which was then evaporated; the treatment with methanol and evaporation were repeated a further eight times. The final gum was converted into the perchlorate as above to yield (+)-[^{3}H]orientaline perchlorate (specific activity 0·08 mc./mg.).

In a similar way, (−)-[^{3}H]orientaline was prepared (specific activity 0·029 mc./mg.).

(+)-[^{3}H]Orientaline perchlorate (2·3 mg.) was mixed with (+)-orientaline hydrochloride (49 mg.) in water and the solution was basified under nitrogen with sodium hydrogen carbonate. Chloroform extraction afforded the free base which was dissolved in methanol, the solution was treated with an excess of methanolic hydrogen chloride and then evaporated. The residual orientaline hydrochloride (51 mg.) was oxidised with potassium ferricyanide as described earlier and the basic products were fractionated on thick silica gel plates in methanol-chloroform (1 : 6 by vol.). The sections corresponding to (−)-orientalinone were eluted and the gum so obtained was reduced with borohydride as above to a mixture of the 3*H*-orientalinols-I and -II. These were rearranged with acid and the product was diluted with natural isothebaine (0·1 g.). Crystallisation from ethanol gave the following weights (mg.) and activities (c./100 sec./mg.): 78; 7400: 56; 6670: 40; 6500: 23; 6480. Conversion of the final base into the hydrochloride and recrystallisation from methanol–ether caused no change in the specific activity.

The foregoing sequence was repeated with (−)-[^{3}H]orientaline perchlorate (5·0 mg.) mixed with (−)-orientaline hydrochloride (47·3 mg.). The weights (mg.) and activities (c./100 sec./mg.) found on recrystallisation of isothebaine were: 75; 1635: 53; 549: 28; 425: 24; 375. Conversion of the final base into isothebaine hydrochloride and recrystallisation twice from methanol–ether caused a further fall to 240 c./100 sec./mg.

Conversion of (−)-*Orientalinone into* (+)-*Isothebaine.*—Sodium borohydride (0·25 g.) was added portionwise to a solution of (−)-orientalinone (50 mg.) in methanol (5 ml.) and the solution was stirred at room temperature for 1 hr. The residue from evaporation of the methanol

was partitioned between water (10 ml.) and chloroform (4 × 10 ml.) and the washed chloroformic solutions were evaporated to a gum (50 mg.). This was dissolved in absolute methanol (1 ml.) and treated with a saturated solution of hydrogen chloride in anhydrous ether (2·5 ml.). After the solution had been kept at room temperature for 15 hr., the crystals of (+)-isothebaine hydrochloride (7·2 mg.) were collected, m. p. and mixed m. p. identical with that of natural material 202—206° (decomp.); this product was further examined below. The base (40 mg.) present in the mother-liquor from these crystals was recovered and shown to be rich in (+)-isothebaine by thin-layer chromatography. This base was fractionated on alumina (activity III) in benzene–chloroform (3 : 1 by vol.) and the fractions containing (+)-isothebaine were combined and the product crystallised as the hydrochloride to yield a further 9·0 mg. of this salt. The base recovered from the hydrochloride was indistinguishable by thin-layer chromatography from natural (+)-isothebaine; the natural and synthetic materials behaved identically towards different spray reagents and under ultraviolet light. The infrared and ultraviolet, nuclear magnetic resonance ($CDCl_3$), and mass spectra of the synthetic and natural materials were identical. Synthetic (+)-isothebaine showed $[\alpha]_D^{21}$ +261° ± 10° (*c* 0·61 in $CHCl_3$) and natural (+)-isothebaine showed $[\alpha]_D^{21}$ +281° ± 10° (*c* 1·11 in $CHCl_3$).

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