The Total Synthesis of (±)-Ochotensine and Related Compounds

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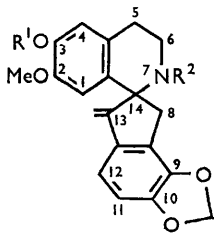
The total synthesis of racemic forms of ochotensine (I), ochotensimine (II), and analogous compounds (III) and (IV), which are isomeric with the respective alkaloids at the positions of the methylenedioxy-groups, is described.

VERY recently a preliminary communication on a total synthesis of (±)-ochotensimine (II), an alkaloid first isolated by Manske [1] together with ochotensine (I) and other alkaloids from *Corydalis ochotensis* Turcz., was published by McLean, Lin, and Whelan [2] who have also contributed to the elucidation [3] of the structures of these alkaloids. Since this type of alkaloid is the first example possessing a spiro-structure in the class of naturally occurring benzylisoquinoline alkaloids, we have been working independently for some time on a general synthesis. We now describe our work on the scope of the synthetic procedure for (±)-ochotensimine (II) and its isomer (III), which was complete prior to the publication of ref. 2. Although our synthetic pathway was in principle very similar to that of the Canadian authors, details including the conditions of the Pictet–Spengler cyclisation are remarkably different. In addition, we report the first total synthesis of (±)-ochotensine (I) and its isomer (IV).

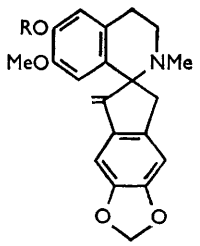
First we attempted to prepare a model compound (V) which contains two methoxy-groups in place of a methylenedioxy-group in the molecule of ochotensimine (II). The Pictet–Spengler condensation of 2,3-dimethoxyphenylpyruvic acid with 3,4-dihydroxyphenethylamine hydrochloride by keeping the aqueous mixture at 25° and pH 4·5 for 12 days and then at pH 7·4 overnight yielded the amino-acid (VI) in 49% yield. Methylation of this with an excess of diazomethane gave the *O*-methylated and the *ON*-methylated products (VII) and (VIII), which were separated by chromatography on alumina. An attempt was made to cyclise the *ON*-methylated compound (VIII) by the Friedel–Crafts reaction using as a condensing agent ethyl polyphosphate in boiling chloroform, or polyphosphoric acid at 100°, or anhydrous hydrofluoric acid at low temperature (−50° to −15°); unchanged starting material was recovered in each case. On the other hand, on heating compound (VIII) in polyphosphoric acid at 145° under forcing conditions, the methoxy-groups suffered extensive hydrolysis followed by lactonisation, to give a compound which exhibited absorption for an enolic δ-lactone at 1760 cm.$^{-1}$ in the infrared spectrum, and the parent peak at *m/e* 341 corresponding to $C_{19}H_{19}NO_5$ and a fragment peak at *m/e* 326 (M^+ − Me) in the mass spectrum. Based on these findings and the nature of the starting material, a partial structure (IX) is assigned. Since

[1] R. H. F. Manske, *Canad. J. Res.*, 1940, *B*, **18**, 75.
[2] S. McLean, M. S. Lin, and J. Whelan, *Tetrahedron Letters*, 1968, 2425.
[3] S. McLean, M. S. Lin, and R. H. F. Manske, *Canad. J. Chem.*, 1966, **44**, 2449; S. McLean, M. S. Lin, A. C. Macdonard, and J. Trotter, *Tetrahedron Letters*, 1966, 185.

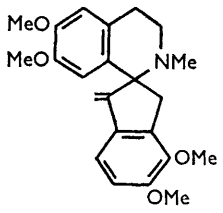
saponification of the tertiary carboxylic ester was thus shown to be difficult without cleavage of the *O*-methyl groups on benzene rings under our conditions, and the methylenedioxy-group which is contained in ochotensine and ochotensimine seemed less stable than the methoxy-



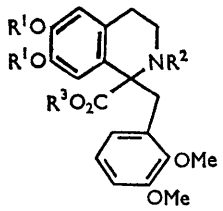
(I) $R^1 = H$, $R^2 = Me$
(II) $R^1 = R^2 = Me$
(XXIV) $R^1 = Me$, $R^2 = H$
(XXXII) $R^1 = CH_2{\cdot}OMe$, $R^2 = Me$



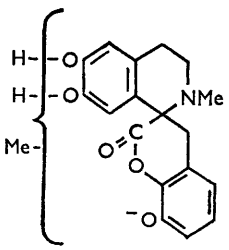
(III) R = Me
(IV) R = H
(XXIX) $R = CH_2{\cdot}OMe$



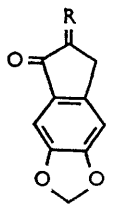
(V)



(VI) $R^1 = R^2 = R^3 = H$
(VII) $R^1 = R^3 = Me$, $R^2 = H$
(VIII) $R^1 = R^2 = R^3 = Me$



(IX)



(X) R = O
(XI) R = N·OH

group, it was thought that the use of a pyruvic acid derivative for one of the starting materials for our synthetic approach would not be promising.

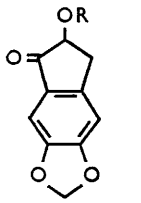
We therefore investigated indane-1,2-dione derivatives as starting materials. Prior to an approach to ochotensine (I) and its *O*-methyl ether, ochotensimine (II), it seemed preferable to prepare as a model compound an idomer (III) of ochotensimine in order to determine suitable conditions for the sequence of reactions, since 5,6-methylenedioxyindane-1,2-dione (X) is readily available from piperonal, while 4,5-methylenedioxyindane-1,2-dione (XXI) which is required for the synthesis of natural alkaloids has to be prepared in many steps from *o*-vanillin. The indane-1,2-dione (X) was prepared as described in the literature by hydrolysis of the corresponding 2-hydroxyiminoindan-1-one (XI). Although no mention was made of the reaction time in the published paper,[4] we ascertained that the best yield of the indanedione (X) was obtained by heating the α-hydroxyiminoindanone (XI) with formalin in concentrated hydrochloric acid for only 5—7 min. Longer periods of heating resulted in marked decrease in yields of the indanedione (X). During attempts to hydrolyse the α-hydroxyiminoindanone (XI) with pyruvic acid in place of formalin in acetic acid, we isolated unexpectedly the 2-hydroxyindan-1-one (XII) along with a small amount of its acetate (XIII). The acetate was smoothly hydrolysed to give the ketol (XII), which on oxidation afforded the indanedione (X). A Pictet–Spengler condensation of 5,6-methylenedioxyindane-1,2-dione (X) with 3,4-dihydroxyphenethylamine hydrobromide in refluxing absolute ethanol afforded a 60% yield of the spiroisoquinoline (XIV), whose spectral properties and analytical data confirmed the assigned structure. Treatment of this phenol (XIV) with an excess of diazomethane gave the di-*O*-methyl ether (XV) which on *N*-methylation with formaldehyde and formic acid furnished the compound (XVI) in good yield. 3,4-Dimethoxyphenethylamine hydrochloride underwent similarly the Pictet–Spengler cyclisation with 5,6-methylenedioxyindane-1,2-dione (X), to furnish the same product as (XV), though the yield was far lower than in the former case. The last step to the compound (III) involved the Wittig reaction with methylenetriphenylphosphorane in dimethyl sulphoxide.[5] The resulting oily product was shown to have the expected structure (III) by its mass spectrum, which had the parent peak at *m/e* 365 corresponding to $C_{22}H_{23}NO_4$, and by the n.m.r. spectrum, which exhibited four aromatic protons at τ 3·03, 3·30, 3·47, and 3·72 as singlets, two methylenedioxy-group protons at 4·02 as a singlet, two *exo*-methylene protons at 4·48 and 5·15 as singlets, six methoxy-group protons at 6·16 and 6·37 as singlets, and three *N*-methyl protons at 7·86 as a singlet. The compound was characterised as its crystalline perchlorate, m.p. 263—265°. Since the preparation of the model compound (III) was thus accomplished, we pursued the synthesis of ochotensimine (II) along similar lines. First, 4,5-methylenedioxyindan-1-one (XVII) was prepared in 29% yield by cyclisation in the presence of phosphorus pentoxide of 2,3-methylenedioxyhydrocinnamic acid, which in turn was obtained by hydrogenation of 2,3-methylenedioxycinnamic acid [6] over Raney nickel. As a by-product we obtained 3,4-dihydro-8-(2,3-methylenedioxyhydrocinnamoyl)oxycoumarin (XVIII), which showed the parent peak at *m/e* 340 in the mass spectrum and afforded on alkaline hydrolysis 2,3-methylenedioxyhydrocinnamic acid and 2,3-dihydroxyhydrocinnamic acid. The latter acid was converted into 3,4-dihydro-8-hydroxycoumarin (XIX) on sublimation *in vacuo*. The i.r. and n.m.r. spectra were also in accord with the assigned structure (XVIII) (see Experimental). Furthermore, the presence of 2,3-methylenedioxyhydrocinnamic anhydride in the reaction mixture

[4] W. H. Perkin, jun., W. M. Roberts, and R. Robinson, *J. Chem. Soc.*, 1914, 2405.

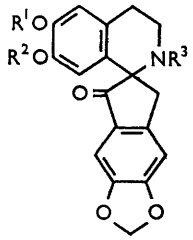
[5] R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 1963, **28**, 1128.

[6] W. H. Perkin, jun., and V. M. Trikojus, *J. Chem. Soc.*, 1926. 2925.

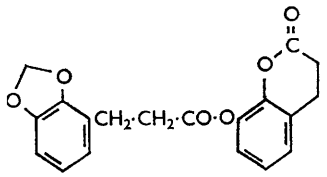
was indicated by the i.r. spectrum of a chromatographic fraction which exhibited bands at 1815 and 1750 cm.$^{-1}$. This indanone cyclisation could not be effected satisfactorily by treatment of the acid with phosphorus



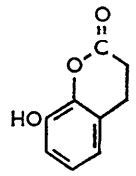
(XII) R = H
(XIII) R = Ac



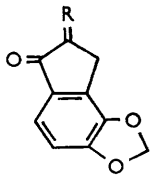
(XIV) $R^1 = R^2 = R^3 = H$
(XV) $R^1 = R^2 = Me$, $R^3 = H$
(XVI) $R^1 = R^2 = R^3 = Me$
(XXVI) $R^1 = R^3 = H$, $R^2 = Me$
(XXVII) $R^1 = H$, $R^2 = R^3 = Me$
(XXVIII) $R^1 = CH_2{\cdot}OMe$, $R^2 = R^3 = Me$



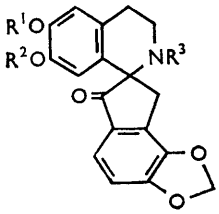
(XVIII)



(XIX)



(XVII) R = H_2
(XX) R = N·OH
(XXI) R = O



(XXII) $R^1 = R^2 = R^3 = H$
(XXIII) $R^1 = R^2 = Me$, $R^3 = H$
(XXV) $R^1 = H$, $R^2 = R^3 = Me$
(XXX) $R^1 = R^3 = H$, $R^2 = Me$
(XXXI) $R^1 = CH_2{\cdot}OMe$, $R^2 = R^3 = Me$

pentachloride followed by stannic chloride owing to extensive cleavage of the methylenedioxy-group during the reaction, the yield of the desired product (XVII) being less than 5%. Treatment of the indanone (XVII) with isopentyl nitrite in methanol afforded the α-hydroxyiminoindanone (XX), which on hydrolysis in boiling hydrochloric acid in the presence of formalin for a short time gave the desired indane-1,2-dione (XXI) in 66% yield, although McLean, Lin, and Whelan [2] reported the unsuccessful hydrolysis of this α-hydroxyimino-ketone (XX). Cyclisation of this diketone (XXI) with 3,4-dihydroxyphenethylamine hydrobromide under the same conditions as described for (XIV) gave the spiroisoquinoline (XXII). The spectral properties of this base (XXII) were very similar to those of the spiroisoquinoline (XIV) mentioned above, confirming its structure. Treatment of this base (XXII) with an excess of diazomethane in ether–tetrahydrofuran–methanol for 2 days at room temperature gave, unexpectedly, in contrast to the isomeric base (XIV), no more than a trace of the desired dimethoxyisoquinoline (XXIII), the main product being neutral. Only when the reaction was carried out in ether–tetrahydrofuran under otherwise the same conditions, was a small amount of the dimethoxyisoquinoline (XXIII) isolated along with a predominant amount of the above neutral product. The structure of this neutral product remains to be elucidated. The dimethoxyisoquinoline (XXIII) was also obtained by direct condensation of 3,4-dimethoxyphenethylamine hydrochloride with 4,5-methylenedioxyindane-1,2-dione (XXI), though the yield was far from satisfactory. The crude dimethoxyisoquinoline (XXIII) was, without further purification, submitted to the Wittig reaction with methylenetriphenylphosphorane in dimethyl sulphoxide, to give (±)-norochotensimine (XXIV), which showed in the n.m.r. spectrum peaks at τ 2·91 and 3·24 as an AB-type quartet (J_{AB} 8 c./sec.) due to protons at positions 11 and 12, at 3·43 and 3·54 as singlets due to protons at positions 1 and 4, at 4·01 as a singlet due to the methylenedioxy-group protons, and at 4·52 and 5·32 as singlets due to the *exo*-methylene protons. Treatment of this compound (XXIV) with formaldehyde followed by sodium borohydride afforded (±)-ochotensimine (II) as an oil which was characterized as its crystalline perchlorate, m.p. 235—238°. The identity of this synthetic compound with an authentic sample of (+)-ochotensimine was proved by comparison of their n.m.r., i.r. (in chloroform), and mass spectra, and t.l.c.

The development of serviceable routes to (±)-ochotensimine (II) and its analogue (III) prompted an investigation of the synthesis of ochotensine (I) by the analogous pathway. Since, however, ochotensine contains a phenolic hydroxy-group, the phenolic function in the intermediate (XXV) must be protected in advance of the Wittig reaction by a suitable group which is stable toward strong alkali and can be removed easily after the reaction is complete. Preliminary experiments by use of the hydroxy-keto-base (XXVI), which is isomeric with the key intermediate (XXV) for the synthesis of ochotensine with respect to the position of a methylenedioxy-group, revealed that methoxymethyl was a preferable protecting group for a phenolic hydroxy-group in the Wittig reaction.[7] It is stable enough in dimethyl sulphoxide, and can be cleaved readily by dilute hydrochloric acid. Other usual protecting groups such as acetyl, tetrahydropyranyl, and t-butyl were unsuitable under the Wittig conditions. The intermediate (XXVII) for the preparation of the analogue (IV) of ochotensine (I) was prepared in a similar way to that mentioned above, by condensation of 3-hydroxy-4-methoxyphenethylamine hydrochloride with 5,6-methylenedioxyindane-1,2-dione (X) in 50% yield followed by *N*-methylation by the Eschweiler–Clark method. Methoxymethylation of this hydroxyketo-base (XXVII) was carried out by treatment of its dry sodium salt with chloromethyl methyl ether in chloroform. The resulting methoxymethyl derivative

[7] M. A. Abdel-Rahman, H. W. Elliott, R. Binks, W. Küng, and H. Rapoport, *J. Medicin. Chem.*, 1966, **9**, 1.

(XXVIII) was treated with methylenetriphenylphosphorane in dimethyl sulphoxide as usual, to give the methoxymethyl-*exo*-methylene base (XXIX) which was hydrolysed with dilute hydrochloric acid, affording an isomer (IV) of ochotensine (I). Since the overall yield of these procedures was fairly good, we then carried out the synthesis of ochotensine in a similar manner. Condensation of 3-hydroxy-4-methoxyphenethylamine hydrochloride with 4,5-methylenedioxyindane-1,2-dione (XXI) gave a 42% yield of the key intermediate, the spiro-keto-isoquinoline (XXX) which was *N*-methylated, then *O*-methoxymethylated, and finally converted into the *exo*-methylene derivative (XXXII) in the same manner as above. Hydrolysis of the methoxymethyl-*exo*-methylene derivative (XXXII) in dilute hydrochloric acid furnished (±)-ochotensine (I), m.p. 241—243·5°, identical with an authentic sample in mass spectrum and t.l.c. The synthetic as well as the natural ochotensine are only slightly soluble in solvents such as chloroform and carbon tetrachloride usually employed for measurement of i.r. spectra, and direct comparison of the respective i.r. spectra in solution could not be made. However, the synthetic racemic ochotensine exhibited in the i.r. spectrum in KBr bands identical with those of (+)-ochotensine from natural sources. Also, the melting point of the synthetic sample was not depressed on admixture with optically active ochotensine. These facts indicate that the synthetic ochotensine is a racemic micture (conglomerate) rather than a racemic compound. Resolution of the racemate is under investigation.

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were measured in chloroform, u.v. spectra in 99% ethanol, and n.m.r. spectra in deuteriochloroform at 60 Mc./sec. with tetramethylsilane as internal reference. Mass spectra were determined with a Hitachi RMU-6D mass spectromer with a direct heated-inlet system. Light petroleum refers to the fraction of b.p. 30—70°.

1,2,3,4-*Tetrahydro*-6,7-*dihydroxy*-1-(2,3-*dimethoxybenzyl*)-*isoquinoline*-1-*carboxylic Acid* (VI).—3,4-Dihydroxyphenethylamine hydrochloride (190 mg.) in water was added to a solution of 2,3-dimethoxyphenylpyruvic acid [8] (220 mg.) in aqueous ammonia (2 ml.). The solution was adjusted to pH 4·5 by adding dilute hydrochloric acid, set aside at 25° for 12 days, adjusted to pH 7·4 with aqueous ammonia, and kept at the same temperature for a further 1 day. The deposited crystals were collected on a filter and washed with methanol, to give the *product* (VI) (175 mg.), m.p. 190—200°, which was used without further purification.

Treatment of the Acid (VI) *with Diazomethane*.—The foregoing isoquinoline (VI) (0·4 g.) in methanol (50 ml.) was treated with an excess of ethereal diazomethane for 2 days at room temperature. Working up in the usual manner gave an oil (300 mg.) which was chromatographed in benzene on alumina. Benzene eluate gave the *tetramethoxy*-N-*methylisoquinolinecarboxylate* (VIII) (130 mg.), m.p. 104—105° (from ether–light petroleum) (Found: C, 66·7; H, 7·1; N, 3·3. $C_{23}H_{29}NO_6$ requires C, 66·5; H, 7·0; N, 3·4%), $\nu_{max.}$ 1720 cm.$^{-1}$ (CO), τ 6·20 (s, 2 OCH_3), 6·24 (s, 1 OCH_3), 6·30 (s, 2 OCH_3), and 7·50 (s, NCH_3). Further elution with the same solvent gave the *tetramethoxyisoquinolinecarboxylate* (VII) (120 mg.), m.p. 116—118° (Found: C, 65·6; H, 6·5; N, 3·6. $C_{22}H_{27}NO_6$ requires C, 65·8; H, 6·8; N, 3·5%), $\nu_{max.}$ 1720 cm.$^{-1}$ (CO), τ 6·08 (s, 1 OCH_3), 6·16 (s, 2 OCH_3), 6·20 (s, 1 OCH_3), and 6·28 (s, 1 OCH_3).

Treatment of the Tetramethoxy-N-*methylisoquinolinecarboxylate* (VIII) *with Polyphosphoric Acid*.—The isoquinolinecarboxylate (VIII) (30 mg.) in polyphosphoric acid (0·2 ml.) was heated on an oil-bath at 145° for 1·5 hr. After cooling, crushed ice was carefully added, and the aqueous solution was basified with aqueous ammonia and extracted with ether. The extract was washed with water, dried, and evaporated, to leave a solid (5 mg.) which crystallised from ether to give the *phenolic lactone* (IX), m.p. 156—159·5°, $\nu_{max.}$ 1760 cm.$^{-1}$ (CO). The mass spectrum showed the parent peak at *m/e* 341 ($C_{19}H_{19}NO_5$ requires *M*, 341) and a fragment peak (M^+ − 15) at *m/e* 326.

Reaction of the α-*Hydroxyimino-ketone* (XI) *with Pyruvic Acid*.—The α-hydroxyimino-ketone (XI)[9] (500 mg.) and pyruvic acid (7 ml.) were heated under reflux in acetic acid (50 ml.) and water (20 ml.) for 8 hr., and the mixture was concentrated under reduced pressure, to leave an oil which was taken up in ether. The organic layer was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to dryness, and the residue (318 mg.) was chromatographed in chloroform on silica gel. The initial chloroform eluate gave the α-*acetoxyindanone* (XIII) (38 mg.), m.p. 119—121° (from ethanol–ether) (Found: C, 61·7; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%), $\nu_{max.}$ 1740 (OAc), 1712 (CO), and 1612 cm.$^{-1}$ (Ph). Further elution with chloroform gave the α-*hydroxy-ketone* (XII) (205 mg.), m.p. 155—160° (from ethanol–ether) (Found: C, 62·8; H, 4·4. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%), $\nu_{max.}$ 3400 (OH), 1705 (CO), and 1612 (Ph) cm.$^{-1}$.

Hydrolysis of the α-*Acetoxyindanone* (XIII).—The α-acetoxyindanone (XIII) (10 mg.) in methanol (2 ml.) and concentrated hydrochloric acid (0·3 ml.) was refluxed on a water-bath for 7 min., and the mixture was concentrated to dryness, to give the α-*hydroxyindanone* (XII) (5 mg.), identical with the sample mentioned above.

Oxidation of the α-*Hydroxyindanone* (XII).—The α-hydroxyindanone (XII) (40 mg.) was treated with the Jones reagent in the usual manner, to give the indanedione (X) (22 mg.), m.p. 160—165° (from benzene), identical with the sample obtained by treatment of the α-hydroxyiminoketone (XI) with formalin and concentrated hydrochloric acid as described below.

5,6-*Methylenedioxyindane*-1,2-*dione* (X).—The α-Hydroxyiminoketone (XI) (2 g.), 37% formalin (8 ml.), and concentrated hydrochloric acid (2 ml.) were stirred for 5 min. at 100°. After cooling, water was added to the mixture, and the deposited crystals were collected and crystallised from benzene, to give the *product* (X) (1·5 g.), m.p. 160—165° (lit.,[4] 166° after softening at 140°).

Spiro-[5,6-*methylenedioxyindan*-1-*one*-2,1′-1′,2′,3′,4′-*tetrahydro*-6′,7′-*dihydroxyisoquinoline*] (XIV).—5,6-Methylenedioxyindane-1,2-dione (X) (1·5 g.) and 3,4-dihydroxyphenethylamine hydrobromide (2·1 g.) were refluxed in absolute

[8] S. Chakravarti and M. Swaminathan, *J. Indian Chem. Soc.*, 1934, **11**, 107.

[9] W. H. Perkin, jun., and R. Robinson, *J. Chem. Soc.*, 1907, 1081.

ethanol (50 ml.) for 5 hr. The mixture was concentrated under reduced pressure, the residue dissolved in water and filtered, and the filtrate neutralised with aqueous ammonia. The precipitate which formed was crystallised from methanol–tetrahydrofuran, to give the *product* (XIV) as prisms (1·5 g.), m.p. 256—259° (Found: C, 66·2; H, 4·8; N, 4·2. $C_{18}H_{15}NO_5$ requires C, 66·5; H, 4·7; N, 4·3%), $\lambda_{max.}$ 236, 272, 298, and 324 mμ (log ε 4·27, 3·88, 3·77, and 3·94), $\nu_{max.}$ (Nujol) 1682 cm.$^{-1}$, τ [$CDON(CD_3)_2$] 2·92 (s, 2 ar. CH), 3·45 (s, 1 ar. CH), 3·83 (s, 1 ar. CH), and 3·73 (br s, OCH_2O).

Spiro-[5,6-*methylenedioxyindan*-1-*one*-2,1′-1′,2′,3′,4′-*tetrahydro*-6′,7′-*dimethoxyisoquinoline*] (XV).—(*a*) The foregoing dihydroxy-compound (XIV) (0·5 g.) in tetrahydrofuran (150 ml.) and methanol (25 ml.) was treated with an excess of ethereal diazomethane at room temperature overnight. After working up in the usual manner, the *non-phenolic base* (XV) (0·25 g.) was obtained as prisms (from methanol), m.p. 178—181·5° [Found: C, 67·1; H, 5·5; N, 3·8%; *M* (mass spectrum), 353. $C_{20}H_{19}NO_5,\frac{1}{4}H_2O$ requires C, 67·1; H, 5·5; N, 3·9%; *M*, 353]. The n.m.r. spectrum showed methoxy-group proton singlets at τ 6·14 and 6·38.

(*b*) 5,6-Methylenedioxyindane-1,2-dione (X) (190 mg.) and 3,4-dimethoxyphenethylamine hydrochloride (223 mg.) were refluxed in absolute ethanol (10 ml.) for 5 hr. The mixture was evaporated under reduced pressure, and the residue taken up in water. The insoluble material was filtered off, and the filtrate basified with aqueous ammonia and extracted with ethyl acetate. The organic layer was extracted with dilute hydrochloric acid, and the acid layer again made alkaline with aqueous ammonia and extracted with ethyl acetate. Evaporation of the extract left an oil (75 mg.) which was chromatographed in benzene on alumina. The initial benzene eluate was discarded. Further elution with benzene–chloroform (99 : 1) gave the *product* (XV) (10 mg.) as prisms, m.p. 178—181° (from methanol), identical in m.p., mixed m.p., and i.r. spectrum with the compound obtained in (*a*).

Spiro-[5,6-*methylenedioxyindan*-1-*one*-2,1′-1′,2′,3′,4′-*tetrahydro*-6′,7′-*dimethoxy*-2′-*methylisoquinoline*] (XVI).—The above base (XV) (0·15 g.) was heated with 99% formic acid (1 ml.) and 37% formalin (1 ml.) on a water-bath for 2·5 hr. The mixture was concentrated under reduced pressure, and the residue taken up in ether after basification with dilute aqueous sodium hydroxide. The ethereal extract was extracted with dilute hydrochloric acid, and the acid layer again basified with aqueous ammonia, and extracted with ether. The extract was washed with water, dried, and evaporated, to give the N-*methyl derivative* (XVI) as needles (from methanol–ether), m.p. 116—118° [Found: *M* (mass spectrum), 367. $C_{21}H_{21}NO_5$ requires *M*, 367], τ 2·83, 3·12, 3·40, and 3·87 (s, 4 aromatic CH), 3·89 (s, OCH_2O), 6·17 and 6·42 (s, 2 OCH_3), and 7·70 (s, NCH_3).

Spiro-[1-*methylene*-5,6-*methylenedioxyindane*-2,1′-1′,2′,3′,4′-*tetrahydro*-6′,7′-*dimethoxy*-2′-*methylisoquinoline*] (III).—The foregoing base (77 mg.) in dimethyl sulphoxide (3 ml.) was treated with 0·5M-methylenetriphenylphosphorane [5] in dimethyl sulphoxide (1·2 ml.) at 52° for 20 hr. Water was added to the mixture, and the whole was extracted with pentane which was shaken with 10% hydrochloric acid. The acid layer was basified with aqueous ammonia and extracted with ether. The ether extract was washed with water, dried, and evaporated, to give a residue which was chromatographed in benzene on alumina (0·5 g.). The initial benzene eluate gave the base (III) as an oil [Found: *M* (mass spectrum), 365. $C_{22}H_{23}NO_4$ requires *M*, 365], τ 3·03, 3·30, 3·47, and 3·72 (s, 4 aromatic CH), 4·02 (s, OCH_2O), 4·48 and 5·15 (s, $=CH_2$), 6·16 and 6·37 (s, 2 OCH_3), and 7·86 (s, NCH_3). The *perchlorate* formed prisms, m.p. 263—265° (decomp.) (from ethanol) (Found: C, 56·3; H, 5·7. $C_{22}H_{23}NO_4,HClO_4,C_2H_5OH$ requires C, 56·3; H, 5·9%).

2,3-*Methylenedioxybenzaldehyde*.—2,3-Methylenedioxybenzyl alcohol [10] (21 g.) was heated under reflux with activated manganese dioxide (200 g.) in chloroform (2 l.) for 2·5 hr. After cooling, the manganese dioxide was collected on a filter, boiled with chloroform for 10 min., and again filtered off, and the combined filtrates were concentrated under reduced pressure, to give the *product* (17·5 g.), m.p. 33—34° (from ether–light petroleum) (lit.,[6] 34°).

2,3-*Methylenedioxyhydrocinnamic Acid*.—2,3-Methylenedioxycinnamic acid (16·4 g.), m.p. 194—196·5°, prepared from the above aldehyde by the literature [6] method was dissolved in an aqueous sodium hydroxide (3·42 g.) solution (50 ml.) and hydrogenated over Raney nickel (5 g.) at 45 atmos. and 125° for 2 hr. The catalyst was filtered off and the filtrate was acidified with hydrochloric acid and extracted with ether. The ethereal extract was dried and evaporated, to give the *product* which crystallised from ether–light petroleum as needles (16 g.), m.p. 78—79° [Found: C, 61·6; H, 5·2%; *M* (mass spectrum), 194. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%; *M*, 194].

Friedel–Crafts Cyclisation of 2,3-*Methylenedioxyhydrocinnamic Acid with Phosphorus Pentoxide*.—2,3-Methylenedioxyhydrocinnamic acid (1·4 g.), phosphorus pentoxide (6 g.), and benzene (45 ml.) were heated for 3 hr. on a water-bath, then cooled. Crushed ice was carefully added to the mixture to destroy the excess of the reagent, and the aqueous layer was extracted with benzene. The combined benzene layers were washed with aqueous sodium carbonate and water, dried, and concentrated to dryness, to give a residue (950 mg.) which was chromatographed in chloroform on silica gel. The initial chloroform eluate gave a mixture of 2,3-methylenedioxyhydrocinnamic anhydride and the ester-lactone (XVIII) as a colourless oil (250 mg.), $\nu_{max.}$ 1815 (CO) and 1750br (CO) cm.$^{-1}$, which, after saponification with aqueous potassium carbonate, gave 2,3-methylenedioxyhydrocinnamic acid (130 mg.). Further elution with the same solvent gave the *ester-lactone* (XVIII) (195 mg.) m.p. 71—73° (from ethanol) [Found: C, 67·1; H, 4·6%; *M* (mass spectrum), 340. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·8%; *M*, 340], $\nu_{max.}$ 1765 cm.$^{-1}$ (CO), τ 2·86—3·36 (m, 6 aromatic CH), 4·06 (s, OCH_2O), and 6·80—7·43 (m, 4 CH_2). The subsequent chloroform eluate gave the *indanone* (XVII) (220 mg.), m.p. 164—167° (from ethanol–ether) (lit.,[2] 165—168°), $\nu_{max.}$ 1700 (CO) cm.$^{-1}$ (Found: C, 68·4; H, 4·6. $C_{10}H_8O_3$ requires C, 68·2; H, 4·5%), τ 2·71 and 3·07 (AB-type quartet, *J* 8 c./sec. 2 ar. CH), and 3·83 (s, OCH_2O). Final elution with chloroform–ethanol (100 : 1) gave an oily brown residue (30 mg.) which was not investigated further. Work-up of the sodium carbonate washing in the usual manner gave the starting acid (70 mg.). In the second run, 2,3-methylenedioxyhydrocinnamic acid (11·2 g.) was cyclised in boiling benzene (250 ml.) in the presence of phosphorus pentoxide (55 g.) under otherwise the same conditions as above, to yield the *indanone* (XVII) (3 g.) (29%).

Alkaline Hydrolysis of the Ester-lactone (XVIII).—The

[10] T. R. Govindachari, K. Nagarajan, S. Rajadurai, and U. R. Rao, *Chem. Ber.*, 1958, **91**, 36.

foregoing ester-lactone (XVIII) (92 mg.), potassium carbonate (50 mg.), methanol (5 ml.), and water (1 ml.) were heated on a water-bath for 2 hr. and the mixture was diluted with water. The aqueous solution was washed with ether, acidified with concentrated hydrochloric acid, and extracted with ether. The extract was washed with water, dried, and evaporated, to leave a residue (55 mg.) which was chromatographed in chloroform on silica gel. The chloroform eluate gave 2,3-methylenedixoyhydrocinnamic acid (35 mg.) (mixed m.p. and i.r. comparison). The chloroform–ethanol (100 : 3) eluate gave 2,3-dihydroxyphenylhydrocinnamic acid (13 mg.), m.p. 125—127°, $\nu_{max.}$ (KBr) 1721 (CO) and 1689 cm.$^{-1}$ (CO), $\nu_{max.}$ (THF) 1730 cm.$^{-1}$ (CO). Distillation of the acid at 127° (bath)/0·07 mm. gave *8-hydroxy-3,4-dihydrocoumarin* (XIX), m.p. 72—74° (from n-hexane–ether) (Found: C, 66·1; H, 5·2. $C_8H_8O_3$ requires C, 65·9; H, 4·9%), $\nu_{max.}$ 3495 (OH) and 1770 cm.$^{-1}$ (CO).

2-Hydroxyimino-4,5-methylenedioxyindan-1-one (XX).—To a solution of the indanone (XVII) (4·4 g.) in hot methanol (200 ml.) was added isopentyl nitrite (6·75 g.) and then concentrated hydrochloric acid (2·25 ml.) in portions. The precipitate which soon separated out was collected and crystallised from ethanol, to give the *product* (XX) as orange-brown needles (4·1 g.), m.p. 245—250° [Found: C, 58·6; H, 3·6; N, 6·8%; *M* (mass spectrum), 205. $C_{10}H_7NO_4$ requires C, 58·5; H, 3·4; N, 6·8%; *M*, 205], $\nu_{max.}$ (Nujol) 1700 cm.$^{-1}$ (CO).

4,5-Methylenedioxyindane-1,2-dione (XXI).—The α-hydroxyiminoindanone (XX) (1·3 g.), 37% formalin (5 ml.), and concentrated hydrochloric acid (1·25 ml.) were stirred at 100° for 6 min. then cooled. Water was added and the precipitated solid was collected and crystallised from benzene to give the *product* (XXI) as golden yellow needles (0·8 g.), m.p. 171—178° (lit.,[2] 158—168°) [Found: C, 63·4; H, 3·4%; *M* (mass spectrum), 190. $C_{10}H_6O_4$ requires C, 63·2; H, 3·2%; *M*, 190], $\nu_{max.}$ (Nujol) 1762 (CO) and 1702 cm.$^{-1}$ (CO), τ (CD_3COCD_3) 2·47 and 2·94 (AB-type quartet, *J* 8·5 c./sec., 2 ar. CH), 3·71 (s, OCH_2O), and 6·43, (s, benzylic CH_2).

Spiro-[4,5-methylenedioxyindan-1-one-2,1′-1′,2′,3′,4′-tetrahydro-6′,7′-dihydroxyisoquinoline] (XXII).—The indanedione (XXI) (0·8 g.) and 3,4-dihydroxyphenethylamine hydrobromide (1·08 g.) in absolute ethanol (30 ml.) were heated under reflux for 5 hr. After working up, the *product* (XXII) was crystallised from methanol–ethyl acetate, to give prisms (0·59 g.), m.p. 227—230° and 240—243° [Found: C, 65·5; H, 4·8%; *M* (mass spectrum), 325. $C_{18}H_{15}NO_5,\frac{1}{3}H_2O$ requires C, 65·3; H, 4·8%; *M* (anhydrous), 325], $\lambda_{max.}$ 236·5, 292, and 316sh mμ (log ε 4·45, 4·04, and 3·69), $\nu_{max.}$ (Nujol) 1682 cm.$^{-1}$ (CO), τ [$CDON(CD_3)_2$] 2·61 and 2·94 (AB-type quartet, *J* 8 c./sec., 2 ar. CH), 3·43 and 3·81 (s, 2 ar. CH), and 3·73 (s, OCH_2O).

Spiro-[4,5-methylenedioxyindan-1-one-2,1′-1′,2′,3′,4′-tetrahydro-6′,7′-dimethoxyisoquinoline] (XXIII).—(*a*) The above dihydroxyketoisoquinoline (XXII) (0·35 g.) in tetrahydrofuran (70 ml.) was treated with an excess of diazomethane [prepared from nitrosomethylurea (2 g.)] in ether (20 ml.) overnight at room temperature. The excess of diazomethane was destroyed with a few drops of acetic acid. The reaction mixture was evaporated under reduced pressure, to leave a residue which was taken up in ether and extracted with dilute hydrochloric acid. The ether layer was dried and evaporated, to give an oil (73 mg.) which on chromatography in chloroform on alumina and elution with the same solvent gave crystals, m.p. 212—215° (from ethanol) (Found: C, 64·0; H, 5·6; N, 6·8%), $\lambda_{max.}$ 284 mμ, $\nu_{max.}$ 1685 cm.$^{-1}$ (CO), τ 2·97 and 3·20 (q, J_{AB} 8 c./sec.), 3·43 and 3·45 (s), 4·02 and 4·04 (AB-type quartet, *J* 1 c./sec.), 6·16 and 6·34 (s), 6·62 (s), and 7·18 (s). This compound is under investigation. The acidic aqueous layer was basified with aqueous ammonia and extracted with ether. The extract was washed with aqueous sodium hydroxide, dried, and evaporated to dryness, to give the *product* (XXIII) as an oil (30 mg.). This crude base was used directly in the Wittig reaction. The aqueous sodium hydroxide layer was made alkaline by adding ammonium chloride ,and extracted with ether. The ether extract was dried and evaporated, to give a mixture (60 mg.) of phenolic amines.

(*b*) 4,5-Methylenedioxyindane-1,2-dione (XXI) (190 mg.) and 3,4-dimethoxyphenethylamine hydrochloride (223 mg.) were heated under reflux in absolute ethanol (10 ml.) for 5 hr. Work-up as described above yielded an oil which was chromatographed in benzene on alumina. The benzene eluate gave an oil which was converted into its picrate (5 mg.), m.p. 142—145° (from methanol). The picrate was chromatographed in acetone on alumina. The acetone eluate gave the free *base* (XXIII), m.p. 172—175° (from methanol–ether) (lit.,[2] 176—179°) [Found: *M* (mass spectrum), 353. $C_{20}H_{19}NO_5$ requires *M*, 353].

Wittig Reaction with the Dimethoxyspiroisoquinoline (XXIII).—The foregoing crude base (XXIII) (60 mg.) was subjected to a Wittig reaction in the same manner as (XVI), and purified by chromatography in benzene on alumina to give the exo-*methylenespiroisoquinoline* (XXIV) (6 mg.), τ 2·91, 3·24 (AB-type quartet, *J* 8 c./sec., 2 ar. CH), 3·43, 3·54 (s, 2 ar. CH), 4·01 (s, OCH_2O), 4·52, 5·32 (s, CH_2=), 6·13 (s, 1 OCH_3), and 6·28 (s, 1 OCH_3).

(±)-*Ochotensimine* (II).—The foregoing *N*-nor-base (XXIV) (6 mg.) and 37% formalin (0·5 ml.) were kept at room temperature for 30 min. Sodium borohydride (150 mg.) was then added and the mixture stirred at room temperature for 1 hr. After evaporation of the solvent under reduced pressure, the residue was taken up in dilute hydrochloric acid. The aqueous solution was washed with ether, basified with aqueous ammonia, and extracted with ether. The ether layer was washed with water, dried, and evaporated to dryness, to leave a residue (5 mg.) which was chromatographed in benzene on alumina. The benzene eluate gave (±)-*ochotensimine* (II) (3 mg.) [Found: *M* (mass spectrum), 365. $C_{22}H_{23}NO_4$ requires *M*, 365], τ 2·88, 3·22 (AB-type quartet, *J* 8 c./sec., 2 ar. CH), 3·47, 3·70 (s, 2 ar. CH), 4·02 (s, OCH_2O), 4·37, 5·10 (s, CH_2=), 6·16, 6·37 (s, 2 OCH_3), and 7·86 (s, NCH_3). The synthetic compound was shown to be identical with an authentic sample of (+)-ochotensimine by comparison of their n.m.r., i.r. (in chloroform), and mass spectra, and t.l.c.

Spiro-[5,6-methylenedioxyindan-1-one-2,1′-1′,2′,3′,4′-tetrahydro-6′-hydroxy-7′-methoxyisoquinoline] (XXVI).—5,6-Methylenedioxyindane-1,2-dione (X) (760 mg.) and 3-hydroxy-4-methoxyphenethylamine hydrochloride[11] (890 mg.) were heated in ethanol (30 ml.) on a water-bath for 5 hr. Working up in the same manner as for (XIV) gave the *product* (XXVI) (635 mg.) as prisms, m.p. 206·5—208·5° (from ethanol) (Found: C, 67·3; H, 5·1; N, 4·4. $C_{19}H_{17}NO_5$ requires C, 67·3; H, 5·1; N, 4·1%), $\nu_{max.}$ 3500 (OH) and 1700 cm.$^{-1}$ (CO).

N-Methylation of the Monohydroxyspiroisoquinoline (XXVI).—The monohydroxyspiroisoquinoline (XXVI) (0·5

[11] K. E. Hamlin and F. E. Fischer, *J. Amer. Chem. Soc.*, 1953, **75**, 5119.

g.) was heated with 37% formalin (5 ml.) and 99% formic acid (5 ml.) on a water-bath for 4 hr. The mixture was evaporated under reduced pressure, to give a residue which was dissolved in 10% aqueous sodium hydroxide. The aqueous solution was washed with ether, made alkaline by adding ammonium chloride, and extracted with ethyl acetate. The organic layer was extracted with dilute hydrochloric acid. The acidic layer was again basified with aqueous ammonia and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to dryness, to leave the N-*methylmonohydroxyspiroisoquinoline* (XXVII) as prisms, m.p. 212—215° (from methanol) (Found: C, 67·7; H, 5·5; N, 4·2. $C_{20}H_{19}NO_5$ requires C, 68·0; H, 5·4; N, 4·0%).

Methoxymethylation of the N-*Methylmonohydroxyspiroisoquinoline* (XXVII).—*N*-Methylmonohydroxyspiroisoquinoline (XXVII) (210 mg.) was added to 0·1N-methanolic sodium methoxide (6 ml.), and the mixture was evaporated to dryness under reduced pressure, to leave a residue which was taken up in chloroform (6 ml.). Chloromethyl methyl ether (48 mg.) in chloroform (1 ml.) was added with stirring to the above chloroform solution in an ice-bath under nitrogen. Stirring was continued overnight at room temperature, and the mixture was diluted with chloroform (50 ml.), washed with 5% aqueous sodium hydroxide and water, dried, and evaporated to dryness, to leave an oil which was chromatographed in benzene on alumina. The initial benzene eluate gave a trace of an oil which was not investigated further. Further elution with the same solvent gave the *methoxymethyl derivative* (XXVIII) (100 mg.) which crystallised from ethanol as prisms, m.p. 141—144° [Found: *M* (mass spectrum), 397. $C_{22}H_{23}NO_6$ requires *M*, 397]. From the aqueous sodium hydroxide washings was recovered the starting material (25 mg.).

Wittig Reaction of the Methoxymethylspiroisoquinoline (XXVIII).—The foregoing isoquinoline (XXVIII) (220 mg.) was treated with methylenetriphenylphosphorane in dimethyl sulphoxide as described for (III), to give the *exo*-methylenespiroisoquinoline (XXIX) (79 mg.) as an oil, τ 3·03, 3·20, 3·31, 3·70 (s, 4 ar. CH), 4·03 (s, OCH_2O), 4·48, 5·14 (s, CH_2=), 4·82 (s, CH_3OCH_2), 6·38, 6·49 (s, 2 OCH_3), and 7·86 (s, NCH_3).

Spiro-[1-*methylene*-5,6-*methylenedioxyindane*-2,1′-1′,2′,3′,4′-*tetrahydro*-6′-*hydroxy*-7′-*methoxy*-2′-*methylisoquinoline*] (IV).—The methoxymethylspiroisoquinoline (XXIX) (70 mg.) in 5% hydrochloric acid (10 ml.) was heated at 70° for 1 hr. The solution was cooled, basified with aqueous ammonia, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated, to leave the *product* (IV) (36 mg.) which crystallised from ethanol as plates, m.p. 167—169° (Found: C, 71·5; H, 6·0; N, 3·8. $C_{21}H_{21}NO_4$ requires C, 71·8; H, 6·0; N, 4·0%), $\nu_{max.}$ 3500 cm.$^{-1}$ (OH), τ 3·01, 3·30, 3·40, 3·72 (s, 4 ar. CH), 4·01 (s, OCH_2O), 4·45, 5·12 (s, CH_2=), 6·35 (s, OCH_3), and 7·84 (s, NCH_3).

Spiro-[4,5-*methylenedioxyindan*-1-*one*-2,1′-1′,2′,3′,4′-*tetrahydro*-6′-*hydroxy*-7′-*methoxyisoquinoline*] (XXX).—4,5-Methylenedioxyindane-1,2-dione (XXI) (190 mg.) and 3-hydroxy-4-methoxyphenethylamine hydrochloride (220 mg.) were heated in ethanol (10 ml.) on a water-bath for 5 hr. After work-up in the same manner as for (XXVI), the *product* (XXX) (140 mg.) crystallised from ethanol as prisms, m.p. 194—196·5° (Found: C, 67·2; H, 5·0; N, 4·3. $C_{19}H_{17}NO_5$ requires C, 67·3; H, 5·1; N, 4·1%), $\nu_{max.}$ 3500 (OH) and 1710 cm.$^{-1}$ (CO). Although McLean *et al.*[2] gave a far lower m.p. 104—107° for this compound, we were unable to find out the reason for this discrepancy, since they do not mention the solvent used for crystallisation.

N-*Methylation of the Hydroxyspiroisoquinoline* (XXX).—The above hydroxyspiroisoquinoline (XXX) (200 mg.) was treated with 37% formalin (3 ml.) and 99% formic acid (3 ml.) as mentioned for (XXVII), to give N-*methylspiroisoquinoline* (XXV) (150 mg.) as an oil which was converted into its *picrate*, m.p. 213—217° (from acetone–methanol) (Found: C, 53·8; H, 4·0; N, 9·4. $C_{20}H_{19}NO_5,C_6H_3N_3O_7$ requires C, 53·6; H, 3·8; N, 9·6%), τ (CD_3COCD_3) 6·88 (s, NCH_3) and 6·44 (s, 1 OCH_3). The *free base* regenerated from the picrate crystallised from benzene as prisms, m.p. 101—103° (Found: C, 72·9; H, 5·7. $C_{20}H_{19}NO_5,C_6H_6$ requires C, 72·4; H, 5·8%).

Methoxymethylation of the N-*Methylmonohydroxyspiroisoquinoline* (XXV).—The *N*-methyl phenolic base (XXV) (100 mg.) was methoxymethylated in the same way as (XXVIII), to yield the methoxymethyl derivative (XXXI) (70 mg.) as an oil, $\nu_{max.}$ 1705 cm.$^{-1}$ (CO).

Wittig Reaction of the Methoxymethylspiroisoquinoline (XXXI).—The methoxymethylspiroisoquinoline (XXXI) was subjected to the Wittig reaction in the same manner as (XVI), to give (±)-O-*methoxymethylochotensine* (XXXII) (30 mg.), τ 2·88, 3·23 (AB-type quartet, *J* 8·5 c./sec., 2 ar. CH), 3·20, 3·69 (s, 2 ar. CH), 4·01 (s, OCH_2O), 4·36, 5·09 (s, CH_2=), 4·80 (s, CH_3OCH_2O), 6·37, 6·48 (s, 2 OCH_3), and 7·85 (s, NCH_3).

(±)-*Ochotensine* (I).—The methoxymethylspiroisoquinoline (XXXII) (25 mg.) was hydrolysed with 5% hydrochloric acid (4 ml.) as mentioned for (XXIX), to give (±)-*ochotensine* (18 mg.) which crystallised from pyridine–ethanol as prisms, m.p. 241—243·5° [Found: C, 71·3; H, 5·9; N, 4·0%; *M* (mass spectrum), 351. $C_{21}H_{21}NO_4$ requires C, 71·8; H, 6·0; N, 4·0%; *M*, 351]. The synthetic sample was shown to be identical with an authentic sample of (+)-ochotensine from natural sources by comparison of their mass spectra and t.l.c. The i.r. spectrum in KBr of the synthetic sample was superimposable upon that of natural ochotensine. The m.p. of synthetic (±)-ochotensine was not depressed on admixture with a sample of (+)-ochotensine.

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