A Total Synthesis of (±)-Capaurimine

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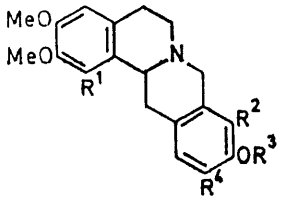
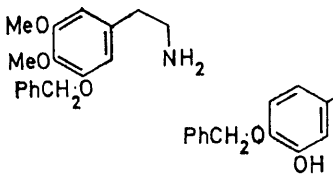
Capaurimine (2) was synthesised by a Mannich reaction of 8-benzyloxy-1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (16), followed by methylation of the Mannich base (6) and debenzylation of the resulting compound (9). The intramolecular Mannich reaction occurred preferentially at the position *ortho* to the hydroxy-group.

The isolation of (±)-capaurimine together with (±)-kikemanine (4) and (±)-tetrahydropalmatine (5) from a quaternary basic fraction of *Corydalis pallida var. tenuis* (Yatabe) is also described.

CAPAURIMINE, which is found in various plants of the *Corydalis* species [1,2,3a] together with the corresponding quaternary base,[3b] was assigned structure (1) by Manske [4] on the basis of degradative evidence. However, it was later found [5] that the characteristics of the synthetic compound (1) were different from those of natural

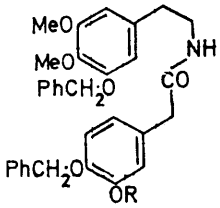


(1) $R^1 = R^2 = OH$, $R^3 = Me$, $R^4 = H$
(2) $R^1 = OH$, $R^2 = OMe$, $R^3 = R^4 = H$
(3) $R^1 = OH$, $R^2 = OMe$, $R^3 = CO{\cdot}C_6H_4Br\text{-}p$, $R^4 = H$
(4) $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
(5) $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = Me$
(6) $R^1 = O{\cdot}CH_2Ph$, $R^2 = OH$, $R^3 = CH_2Ph$, $R^4 = H$
(7) $R^1 = O{\cdot}CH_2Ph$, $R^2 = H$, $R^3 = CH_2Ph$, $R^4 = OH$
(8) $R^1 = R^2 = H$, $R^3 = CH_2Ph$, $R^4 = OH$
(9) $R^1 = O{\cdot}CH_2Ph$, $R^2 = OMe$, $R^3 = CH_2Ph$, $R^4 = H$

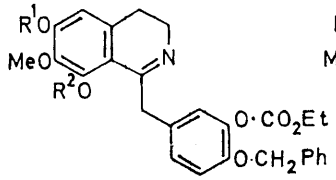


(10)

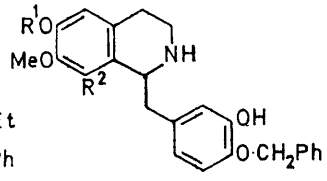
(11)



(12) R = H
(13) R = CO_2Et



(14) $R^1 = Me$, $R^2 = CH_2Ph$
(15) $R^1 = CH_2Ph$, $R^2 = Me$



(16) $R^1 = Me$, $R^2 = O{\cdot}CH_2Ph$
(17) $R^1 = CH_2Ph$, $R^2 = OMe$
(18) $R^1 = Me$, $R^2 = H$

capaurimine. Chemical and spectroscopic studies and reinvestigation of the oxidative degradation of capaurimine revealed it to be 5,6,13,13a-tetrahydro-2,3,9-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizine-1,10-diol (2).[6] An *X*-ray analysis of capaurimine mono-*p*-bromobenzoate (3) [7] supported this assignment. In the course of this work [6-8] it was found that capaurimine derivatives assume the *cis*-quinolizidine conformation because of interaction between the C-1 oxygen atom and the protons at C-13. In preliminary experiments related to capaurimine (2), we have already synthesised (±)-kikemanine (4),[9] the laevorotatory isomer of which was isolated together with capaurimine from *C. pallida var. tenuis* (Yatabe) [2] and possessed the same pattern of substituents in ring D. (±)-Capaurimine has now been synthesised by application of the same method. As well as the details of this synthesis, we report the isolation of (±)-capaurimine (2), (±)-kikemanine (4), and (±)-tetrahydropalmatine (5) from *C. pallida var. tenuis*.

Condensation of 3-benzyloxy-4,5-dimethoxyphenethylamine (10) [10] and 4-benzyloxy-3-hydroxyphenylacetic acid (11),[9] followed by *O*-ethoxycarbonylation of the resulting amide (12), gave the ester (13). A Bischler–Napieralski reaction with phosphoryl chloride then afforded a mixture of the 3,4-dihydroisoquinolines (14) and (15), which was reduced with sodium borohydride and then hydrolysed to give a mixture of tetrahydroisoquinolines (16) and (17). At this stage chromatographic separation on silica gel, followed by careful recrystallisation, afforded crystals and a syrup. The n.m.r. spectrum of the crystals showed one O·CH_2Ph signal as a pair of doublets (J 11 Hz) at δ 5·25 and 4·88 p.p.m. Since this indicated that the *O*-benzyl group was hindered, this compound was identified as 8-benzyloxy-1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (16). An intramolecular Mannich reaction of this base (16) with formalin gave a mixture of the protoberberines (6) and (7). In the case of the synthesis of kikemanine (4),[9] the analogous condensation, with the hydrochloride of the starting

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[6] T. Kametani, M. Ihara, and T. Honda, *J. Chem. Soc.* (*C*), 1969, 2342.
[7] T. Kametani, M. Ihara, Y. Kitahara, C. Kabuto, H. Shimanouchi, and Y. Sasada, *Chem. Comm.*, 1970, 1241.
[8] H. Shimanouchi, Y. Sasada, M. Ihara, and T. Kametani, *Acta Cryst.*, 1969, *B***25**, 1310; H. Shimanouchi, Y. Sasada, K. Wakisaka, T. Kametani, and M. Ihara, *ibid.*, 1970, *B***26**, 607.
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tetrahydroisoquinoline (18), gave only a product (8) cyclised at the position *para* to the hydroxy-group. In this case, whether the Mannich reaction was carried out at pH 6·4 or whether the hydrochloride of the tetrahydroisoquinoline (12) was used without pH adjustment, the cyclisation occurred preferentially at the position *ortho* to the hydroxy-group to give the 1,2,3,9,10-pentasubstituted protoberberine (6). The n.m.r. spectrum of this product showed signals for the *ortho*-coupled C-11 and C-12 protons (J 8 Hz) at δ 6·44 and 6·69 p.p.m. Methylation of the Mannich base (6) with diazomethane, followed by debenzylation of the product (9), gave (±)-capaurimine (2), whose i.r. ($CHCl_3$), n.m.r., and mass spectra were identical with those of natural material. A mixed m.p. test with (±)-capaurimine (2) isolated as follows showed no depression.

Sodium borohydride reduction of the chloride of the quaternary basic fraction of *C. pallida var. tenuis* [2] gave a mixture of tertiary bases, which were separated by chromatography on silica gel to afford (±)-capaurimine (2), (±)-kikemanine (4),[11] and (±)-tetrahydropalmatine (5).

EXPERIMENTAL

M.p.s were determined with a Yanagimoto Micro apparatus (MP-S2). I.r. spectra were taken with a type EPI-3 Hitachi recording spectrometer. The mass spectrum was measured with a Hitachi RMU-7 spectrometer. N.m.r. spectra were measured with a Hitachi H-60 instrument for solutions in deuteriochloroform with tetramethylsilane as internal standard. The pH was measured with a Metrohm potentiograph E-336.

N-(3-Benzyloxy-4,5-dimethoxyphenethyl)-4-benzyloxy-3-hydroxyphenylacetamide (12).—A mixture of 3-benzyloxy-4,5-dimethoxyphenethylamine (10) [10] (9 g) and 4-benzyloxy-3-hydroxyphenylacetic acid (11) [9] (8·3 g) was heated in an oil-bath at 170—180° for 5 h under a current of nitrogen. The cooled mixture was dissolved in chloroform, washed with 5% hydrochloric acid solution, water, 5% ammonia, and water, and dried (Na_2SO_4). Evaporation left the *amide* (16 g), which was chromatographed on silica gel to give a syrup (Found: C, 73·1; H, 6·35; N, 2·9. $C_{32}H_{33}NO_6$ requires C, 72·85; H, 6·3; N, 2·65%), $\nu_{max.}$ ($CHCl_3$) 3500 (OH), 3400 (NH), and 1658 cm^{-1} (C=O), δ 3·35 (2H, s, CO·CH_2Ph), 3·75 and 3·79 (each 3H, s, OMe), and 5·00 p.p.m. (4H, s, 2 × O·CH_2Ph).

N-(3-Benzyloxy-4,5-dimethoxyphenethyl)-4-benzyloxy-3-ethoxycarbonyloxyphenylacetamide (13).—To a solution of the phenolic amide (12) (15 g) and triethylamine (3·6 g) in benzene (300 ml), ethyl chloroformate (4 g) was added drop by drop with stirring at room temperature. After 2 h stirring, the benzene layer was washed with water, dried (Na_2SO_4), and evaporated to give a powder, which afforded the non-phenolic *amide* (13) (16 g) as needles, m.p. 89—90° (from ethanol) (Found: C, 69·8; H, 6·3; N, 2·0. $C_{35}H_{37}NO_8$ requires C, 70·1; H, 6·2; N, 2·35%), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (C=O), and 1660 (C=O) cm^{-1}, δ 1·26 (3H, t, J 7 Hz, O·CH_2·CH_3), 3·36 (2H, s, CO·CH_2Ph), 3·73 and 3·80 (each 3H, s, OMe), 4·18 (2H, q, J 7 Hz, O·CH_2·CH_3), and 4·99 p.p.m. (4H, s, O·CH_2Ph).

Mixture of 8-Benzyloxy-6,7-dimethoxy- (14) *and 6-Benzyloxy-7,8-dimethoxy-1-(4-benzyloxy-3-ethoxycarbonyloxybenzyl)-3,4-dihydroisoquinoline* (15).—A mixture of the non-phenolic amide (13) (15 g), phosphoryl chloride (15 ml), and dry benzene (200 ml) was refluxed for 3 h. The cooled mixture was poured into an excess of n-hexane and set aside overnight. The precipitate, $\nu_{max.}$ ($CHCl_3$) 1760 (C=O), 1640 (C=N^+), and 1590 (C=C) cm^{-1}, was used immediately because of difficulty in purification.

8-Benzyloxy-6,7-dimethoxy- (16) *and 6-Benzyloxy-7,8-dimethoxy-1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline* (17).—To a solution of the mixture of the dihydroisoquinolines (14) and (15) in methanol (300 ml), sodium borohydride (10 g) was added in portions at room temperature with stirring. After stirring for a further 30 min at room temperature, followed by addition of 10% sodium hydroxide solution (20 ml), the mixture was refluxed for 2 h. It was then cooled, evaporated, and diluted with water, and ammonium chloride was added. The mixture was extracted with chloroform; the extract was washed, dried (K_2CO_3), and evaporated to give a syrup (11 g), which was purified by column chromatography on silica gel (200 g). Elutions with chloroform–methanol (99 : 1 v/v) gave a yellowish syrup (4·5 g), which on trituration with methanol afforded the *8-benzyloxy-6,7-dimethoxyisoquinoline* (16) (1·5 g) as needles, m.p. 185—187° (from chloroform–hexane) (Found: C, 73·45; H, 6·2; N, 3·0. $C_{32}H_{33}NO_5$,0·66H_2O requires C, 73·4; H, 6·4; N, 2·7%), $\nu_{max.}$ ($CHCl_3$) 3500 (OH) cm^{-1}, δ 3·78 and 3·81 (each 3H, s, OMe), 4·88 and 5·25 (each 1H, d, J 11 Hz, O·CH_2Ph), 4·97 (2H, s, O·CH_2Ph), 6·35 (1H, s, 5-H), 6·34 (1H, q, J 2 and 7·5 Hz, 6-H), 6·52 (1H, d, J 2 Hz, 2′-H), and 6·66 p.p.m. (1H, d, J 7·5 Hz, 5′-H).

The base (16) was converted into the *hydrochloride*, needles, m.p. 192—193° (from methanol–ether) (Found: C, 70·45; H, 6·05; N, 2·9. $C_{32}H_{34}ClNO_5$ requires C, 70·1; H, 6·25; N, 2·55%).

Material from the methanolic mother liquor (from the trituration) was purified as the hydrochloride to give the *6-benzyloxy-7,8-dimethoxyisoquinoline* (17) *hydrochloride* (600 mg), needles, m.p. 172—174° (Found: C, 69·95; H, 6·2; N, 2·65%). Treatment with ammonia gave a pale reddish syrup (17), $\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1} (OH), δ 3·77 and 3·87 (each 3H, s, OMe), 4·90 and 4·94 (each 2H, s, 2 × O·CH_2Ph), 6·32 (1H, s, 5-H), and 6·50—6·80 p.p.m. (3H, ArH).

1,10-Dibenzyloxy-5,6,13,13a-tetrahydro-9-hydroxy-2,3-dimethoxy-8H-dibenzo[a,g]quinolizine (6).—(a) *Reaction at pH* 6·4. A solution of the hydrochloride of the tetrahydroisoquinoline (16) (600 mg) in methanol (60 ml) and water (50 ml) was adjusted to pH 6·4 with aqueous 5% sodium hydrogen carbonate. Then 37% formalin (25 ml) was added and the pH was readjusted to 6·4. After 18 h at room temperature the solvent was evaporated, the residue was basified with sodium hydrogen carbonate, and extracted with chloroform The extract was washed with water, dried (K_2CO_3), and evaporated to give a pale yellowish gum (600 mg), which was chromatographed on silica gel (25 g). Elution with chloroform gave the protoberberine (6) as a pale yellowish syrup (250 mg), $\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1} (OH), δ 3·80 and 3·81 (each 3H, s, OMe), 5·02 (4H, s, 2 × O·CH_2Ph), 6·40 (1H, s, 4-H), and 6·44 and 6·69 p.p.m. (each 1H, d, J 8 Hz, 11- and 12-H).

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The *picrate* formed yellowish-brown needles, m.p. 169—170° (ethanol) (Found: C, 61·95; H, 4·6. $C_{39}H_{36}N_4O_{12}$ requires C, 62·25r H, 4·8%).

(b) *From the hydrochloride of the tetrahydroisoquinoline* (16). A mixture of the hydrochloride (50 mg), 16% formalin (3·5 ml), and ethanol (2 ml) was refluxed for 3 h. The mixture was evaporated, the residue was basified with ammonia, and extracted with chloroform. The same work-up as in (a) gave the protoberberine (6) (35 mg), identified by i.r. and n.m.r. spectra. In both experiments, attempts to obtain the isomer (7) in pure form were unsuccessful.

1,10-*Dibenzyloxy*-5,6,13,13a-*tetrahydro*-2,3,9-*trimethoxy*-8H-*dibenzo*[a,g]*quinolizine* (9).—To a solution of the protoberberine (6) (200 mg) in a little methanol was added an ethereal solution of diazomethane, prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (10 g). The mixture was set aside for 2 days. Removal of the solvent left a residue (200 mg) which was chromatographed on alumina (6 g). Elution with benzene gave the non-phenolic base (9) (150 mg) as a yellowish syrup, treatment of which with methyl iodide gave the *methiodide* as fine needles, m.p. 196—200° (from methanol–ether) (Found: C, 61·75; H, 5·7. $C_{35}H_{39}INO_5$ requires C, 61·7; H, 5·6%).

(±)-*Capaurimine* (2).—A mixture of *OO*-dibenzylcapaurimine (9) (100 mg), concentrated hydrochloric acid (10 ml), and ethanol (20 ml) was refluxed on a water-bath for 1·5 h, then evaporated. The residue was basified with dilute aqueous ammonia and extracted with ethyl acetate. The extract was washed with water, dried (K_2CO_3), and evaporated to give a brown gum (60 mg). Chromatography on silica gel (3 g) in chloroform–methanol (99 : 1 v/v) gave (±)-capaurimine (2) (30 mg) as prisms, m.p. 210—212° (from methanol) (lit.,[3b] 212°), identical (i.r., n.m.r., and mass spectra, mixed m.p., and t.l.c.) with the racemic natural product.

Separation of the Quaternary Bases from Corydalis pallida var. tenuis (*Yatabe*).—The ammoniacal solution [2] obtained from the methanolic extract of the dried plant (3 kg) and treated as usual in order to remove the tertiary bases and the neutral and acidic compounds was adjusted with hydrochloric acid to about pH 5. To one third of this solution, saturated ammonium 'reineckate' solution at 60° was added until no more precipitate formed. Then the mixture was set aside overnight. The product (25 g) was filtered off, dried, and dissolved in acetone (*ca.* 500 ml). The solution was filtered and a slight excess of hot saturated silver sulphate solution was added. The mixture was again filtered, and barium chloride was added to the filtrate. After filtration again and concentration, sodium borohydride (12 g) was added in portions to the resulting solution, which was refluxed for 1 h and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a brown gum (160 mg) which was chromatographed on silica gel (20 g) with chloroform [fractions (30 ml) 1—10], chloroform–methanol (99 : 1 v/v; fractions 11—25), and chloroform–methanol (98 : 2 v/v; fractions 26—35) as eluants.

Fractions 7—13 gave (±)-tetrahydropalmatine (5) (6 mg) as scales, m.p. 151° (from methanol) (lit.,[12] 151°), identical (i.r. and n.m.r. spectra, mixed m.p., and t.l.c.) with an authentic sample.[12] Fractions 14—17 gave (±)-kikemanine (4) (12 mg) as prisms, m.p. 185° (from methanol) (lit.,[9] 185—187°), identical (i.r. and n.m.r. spectra, mixed m.p., and t.l.c.) with an authentic sample.[9] Fractions 18—26 gave (±)-capaurimine (2) (20 mg) as prisms, m.p. 212°, whose i.r. and n.m.r. spectra and t.l.c. behaviour were identical with those of (−)-capaurimine.[2]

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