The Total Synthesis of (±)-Capaurine [Studies on the Syntheses of Heterocyclic Compounds. CCCXLVIII (1)]

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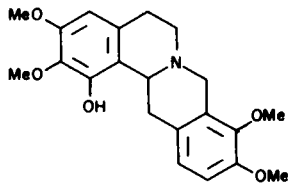
The total synthesis of (±)-capaurine (I) confirmed the suggested structure of I.

Capaurine (3) has been isolated as the (−)- and (±)-form (4) of an alkaloid, $C_{21}H_{25}O_5N$, from *Corydalis aurea* (5), *C. Micrantha* (6), *C. Montana* (7), and *C. Pallida* (8). The structure of this alkaloid was assigned to I by Manske (9) as a consequence of various chemical degradations. Furthermore, X-ray analysis of natural capaurine as its hydrobromide was carried out (10) and showed the structure of capaurine to be correct and to have the *cis*-conformation in its crystalline state. Since (±)-capaurine and (−)-capaurine have not yet been synthesized, we have synthesized the racemate I by application of earlier methods (11,12,13) and have found that its IR (chloroform) and NMR (deuteriochloroform) spectra were superimposable with those of natural (−)-capaurine. We now wish to report these results.

CHART 1

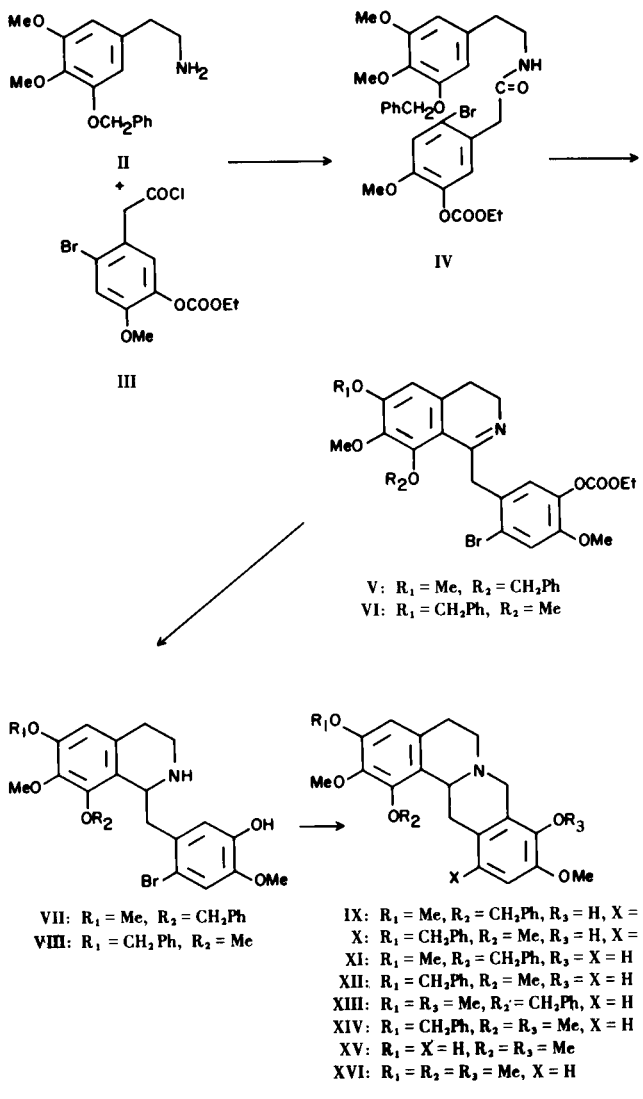


I

Schotten-Baumann reaction of 3-benzyloxy-4,5-dimethoxyphenethylamine (II) (14) with 2-bromo-5-ethoxycarbonyloxy-4-methoxyphenacetyl chloride (III) prepared from the phenylacetic acid (15) gave the crystalline amide IV. Bischler-Napieralski reaction of IV afforded a mixture of the 3,4-dihydroisoquinolines (V and VI). Reduction of this mixture with sodium borohydride was accompanied by hydrolysis of the ethoxycarbonyl function and afforded a mixture of two phenolic 1,2,3,4-tetrahydroisoquinolines (VII and VIII), which could not be separated and purified, but showed the characteristic IR spectral data.

Cyclization of the above mixture (VII and VIII) with 37% formalin and acetic acid, followed by debromination of IX and X with zinc powder and 50% acetic acid, afforded a mixture of XI and XII, which was methylated with diazomethane to give a mixture of XIII and XIV. Starting with the cyclization and continuing until the preparation of I, attempted separation of the two isomers was unsuccessful.

CHART 2



Debenzylation of XIII and XIV with ethanolic hydrochloric acid solution gave a mixture of I and XV, whose TLC (16) showed two spots, namely R_f 0.74 (I) and R_f 0.48 (XV). This mixture was chromatographed on a silica gel column using chloroform as eluant as described in the experimental section. Recrystallization of the first eluate (R_f 0.74) from methanol gave (±)-capaurine (I), m.p. 205-207°, whose IR (chloroform) and NMR (deuteriochloroform) spectra were superimposable with those of natural (-)-capaurine donated by Dr. R. H. F. Manske. Evaporation of the second eluate gave the isomeric compound (XV) showing R_f 0.48 which could not be crystallized. Methylation of I and XV with diazomethane gave a non-phenolic base (XVI), m.p. 140-142° (17).

Thus, total synthesis of (±)-capaurine has been accomplished.

EXPERIMENTAL

N-(3-Benzyloxy-4,5-dimethoxyphenethyl)-2-(2-bromo-5-ethoxycarbonyloxy-4-methoxyphenyl)acetamide (IV).

To a cooled and stirred solution of 7.5 g. of 3-benzyloxy-4,5-dimethoxyphenethylamine (II) in 300 ml. of ether was added dropwise a solution of acid chloride, which was prepared as usual from 8 g. of 2-bromo-5-ethoxycarbonyloxy-4-methoxyphenylacetic acid (III), in 100 ml. of dry ether. The reaction mixture was kept alkaline by simultaneous addition of saturated sodium bicarbonate solution within 45 minutes. After the stirring had been continued at room temperature for 1.5 hours, the reaction mixture was extracted with ethyl acetate. The extract was washed with water, 5% hydrochloric acid solution, and water, dried over sodium sulfate, and evaporated to give crystals, which on recrystallization from chloroform-ether afforded 9 g. of colorless needles, m.p. 95-96°, ν max cm^{-1} (chloroform), 3500 (NH), 1760 (C=O), 1670 (C=O).

Anal. Calcd. for $C_{29}H_{32}BrNO_8$: C, 57.81; H, 5.35; N, 2.32. Found: C, 58.04; H, 5.17; N, 2.32.

Mixture of 8-Benzyloxy-6,7-dimethoxy-(V) and 6-Benzyloxy-7,8-dimethoxy-1-(2-bromo-5-ethoxycarbonyloxy-4-methoxybenzyl)-3,5-dihydroisoquinoline (VI).

A mixture of 8 g. of IV, 50 ml. of dry benzene, and 20 ml. of phosphoryl chloride was refluxed on a water-bath for 3 hours. Excess hexane was added to the reaction mixture, which was set aside overnight. The precipitated mixture of the hydrochlorides of V and VI [ν max cm^{-1} (chloroform) 1650 (C=N)] was separated by decantation and washed with hexane.

Mixture of 8-Benzyloxy-6,7-dimethoxy-(VII) and 6-Benzyloxy-7,8-dimethoxy-1-(2-bromo-5-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (VIII).

To a solution of 8 g. of the above mixture of V and VI in 250 ml. of methanol was added in small portions 5 g. of sodium borohydride at room temperature and the mixture was then refluxed for 1 hour. After removal of the solvent under reduced pressure, the residue was treated with 5% sodium hydroxide solution. An insoluble substance was removed by extraction with ether. The alkaline layer was saturated with an excess of crystalline ammonium chloride and extracted with chloroform. The extract was washed with water, dried over potassium carbonate, and evaporated to give 7 g. of a syrup, ν max cm^{-1} (potassium bromide), 3500 (OH), which was used in the next reaction without separation or purification.

Mixture of 1-Benzyloxy-2,3,10-trimethoxy-(IX) and 3-Benzyloxy-1,2,10-trimethoxy-12-bromo-9-hydroxy-5,6-13,13a-tetrahydro-8*H*-dibenz[*a*,*g*]quinolizine (X).

To a solution of 5 g. of the above mixture of VII and VIII in 40 ml. of acetic acid was added 40 ml. of 37% formalin, and the solution was refluxed in an oil-bath for 3 hours. After cooling, the reaction mixture was basified with ammonia and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give 4.8 g. of a mixture of IX and X as a pale yellowish syrup, ν max cm^{-1} (chloroform), 3500 (OH), τ (deuteriochloroform), 6.22-6.02 (18H, 6 x OCH_3), 4.92 (2H, singlet, OCH_2Ph), 4.85 (2H, doublet, J 2.5 cps, OCH_2Ph), 3.53 (1H, singlet, aromatic proton), 3.50 (1H, singlet, aromatic proton), 3.08 (1H, singlet, aromatic proton) and 3.06 (1H, singlet, aromatic proton).

Mixture of 1-Benzyloxy-9-hydroxy-2,3,10-trimethoxy-(XI) and 3-Benzyloxy-9-hydroxy-1,2,10-trimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenz[*a*,*g*]quinolizine (XII).

To a solution of 4 g. of the above mixture of IX and X in 40 ml. of 50% acetic acid was added 4 g. of zinc powder and the mixture was refluxed in an oil-bath for 6 hours. After cooling an insoluble substance was removed by filtration, and the resultant filtrate was basified with ammonia and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give 2.6 g. of a mixture of XI and XII as a syrup, ν max cm^{-1} (chloroform) 3500 (OH), τ (deuteriochloroform), 3.50 (1H, singlet, aromatic proton), 3.48 (1H, singlet, aromatic proton), 3.38 (2H, doublet, J 8 cps, aromatic protons) and 3.25 (2H, doublet, J 8 cps, aromatic protons).

Mixture of 1-Benzyloxy-2,3,9,10-tetramethoxy-(XIII) and 3-Benzyloxy-1,2,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenz-[*a*,*g*]quinolizine (XIV).

To a solution of 2 g. of the above mixture of XI and XII in 100 ml. of methanol was added 200 ml. of an ethereal solution of diazomethane [prepared from 5 g. of nitrosomethylurea] and the resultant mixture was set aside at room temperature for 2 days. After removal of the solvent, the residue was chromatographed on alumina and eluted with benzene to give 1.6 g. of a mixture of the two non-phenolic bases XIII and XIV, τ (deuteriochloroform), 3.53 (1H, singlet, aromatic proton), 3.50 (1H, singlet, aromatic proton) and 3.20 (4H, singlet, aromatic protons).

(±)-Capaurine (I).

A solution of 1.5 g. of the above mixture of XIII and XIV in 40 ml. of concentrated hydrochloric acid-ethanol (1:1) was refluxed for 1.5 hours. After the solvent had been distilled off, the residue was dissolved in a small amount of methanol and then poured into cooled 5% ammonia. The oil which separated was extracted with chloroform. The extract was washed with water, dried over potassium carbonate, and evaporated to give 800 mg. of a syrup, which showed two spots on TLC (16). Column chromatography was carried out on silica gel (15 g.) and elution with chloroform as follows. Fractions 1-6 (each 25 ml.) gave 300 mg. of (±)-capaurine (I) showing R_f 0.74 and fractions 10-15 (each 25 ml.) gave 300 mg. of the isomer XV showing R_f 0.48.

Recrystallization of the former compound (I) from methanol gave the (±)-capaurine as colorless needles, m.p. 205-207°, τ (deu-

teriochloroform), 6.17 (9H, singlet, 3 x OCH_3), 6.12 (3H, singlet, OCH_3), 3.75 (1H, singlet, C_4-H), 3.20 (2H, singlet, C_{11}-H and C_{12}-H), whose IR (chloroform) and NMR spectra were superimposable with those of natural (−)-capaurine.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.56; H, 6.79; N, 3.74.

Attempted crystallization of the other compound, R_f 0.48, was unsuccessful. The NMR data, τ (deuteriochloroform), 6.16 (9H, singlet, 3 x OCH_3), 6.12 (3H, singlet, OCH_3), 3.52 (1H, singlet, C_4-H), 3.20 (2H, singlet, C_{11}-H and C_{12}-H), are compatible with 5,6,13,13a-tetrahydro-3-hydroxy-1,2,9,10-tetramethoxy-8*H*-dibenz[*a*,*g*]quinolizine (XV).

(±)-*O*-Methylcapaurine (XVI).

To a solution of 50 mg. of (±)-capaurine (I) in 10 ml. of methanol was added 100 ml. of an ethereal solution of diazomethane [prepared from 3 g. of nitrosomethylurea], and the resultant mixture was set aside at room temperature for 2 days. After removal of the solvent, the resultant residue was chromatographed on alumina. Removal of the benzene eluant gave 50 mg. of a nonphenolic base, which was recrystallized from methanol to give (±)-*O*-methylcapaurine (XVI) as colorless needles, m.p. 140-142° [lit. (17), m.p. 142°].

The NMR spectrum of the above specimen was superimposable with that of an authentic sample, τ (deuteriochloroform), 3.21 (2H, singlet, C_{11}-H and C_{12}-H), 3.57 (1H, singlet, C_4-H), 6.13 (3H, singlet, OCH_3), 6.16 (12H, singlet, 4 x OCH_3). The same treatment of XV with diazomethane also gave XVI, identical with the above sample by NMR spectral comparison.

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