# Total Synthesis of (±)-Obaberine [Studies on the Syntheses of Heterocyclic Compounds. Part CCCXLIX (1)]

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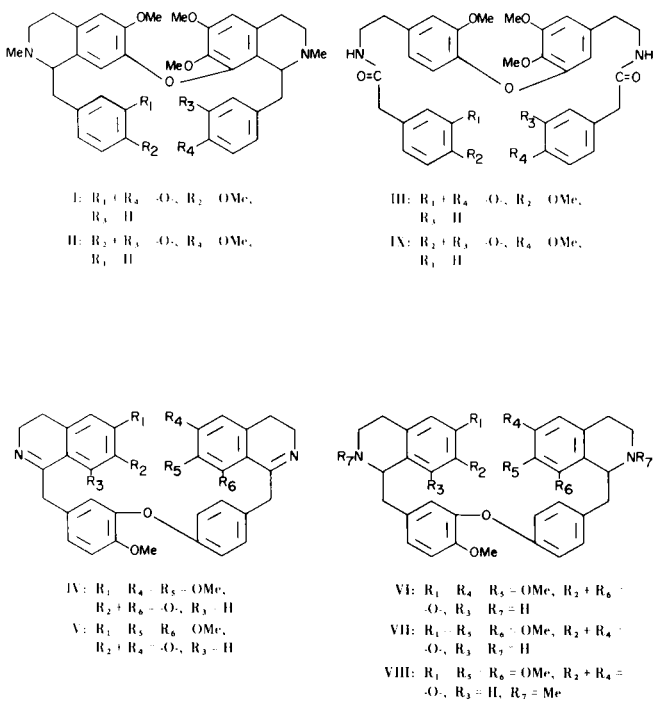
Cyclization of one of two cyclic bisamides (III and IX), followed by reduction and successive methylation, gave our expected bis-coclaurine derivatives, one of which was identical with *O*-methyloxyacanthine, namely natural obaberine (I).

Obaberine (I) (3) and tetrandrine (II) (4), whose plannar structures are related to the isomer having an antipodal diphenyl ether linkage, belong to non-phenolic bisbenzylisoquinoline alkaloids. One of the present authors (5) has reported on the synthesis of head-to-head coupled bisbenzylisoquinoline which has two biphenyl ether bonds in a molecule. The purpose of the present investigation was to study the synthesis of these two types of isomeric bisbenzylisoquinolines using a similar synthetic procedure as that for stebisimine (6).

CHART I



I: $R_1+R_4$ = -O-, $R_2$ = OMe, $R_3$ = H
II: $R_2+R_3$ = -O-, $R_4$ = OMe, $R_1$ = H
III: $R_1+R_4$ = -O-, $R_2$ = OMe, $R_3$ = H
IX: $R_2+R_3$ = -O-, $R_4$ = OMe, $R_1$ = H
IV: $R_1$ = $R_4$ = $R_5$ = OMe, $R_2+R_6$ = -O-, $R_3$ = H
V: $R_1$ = $R_5$ = $R_6$ = OMe, $R_2+R_4$ = -O-, $R_3$ = H
VI: $R_1$ = $R_4$ = $R_5$ = OMe, $R_2+R_6$ = -O-, $R_3$ = $R_7$ = H
VII: $R_1$ = $R_5$ = $R_6$ = OMe, $R_2+R_4$ = -O-, $R_3$ = $R_7$ = H
VIII: $R_1$ = $R_5$ = $R_6$ = OMe, $R_2+R_4$ = -O-, $R_3$ = H, $R_7$ = Me

Bischler-Napieralski reaction of the bisamide (III), which was obtained by a standard method (6), with phosphoryl chloride in chloroform gave a mixture of 3,4-dihydroisoquinoline derivatives (IV and V), which were reduced to the 1,2,3,4-tetrahydroisoquinoline derivatives (VI and VII) with sodium borohydride in chloroform-methanol solution. Methylation of compounds VI and VII with formalin and formic acid yielded dimeric 1,2,3,4-tetrahydro-2-methylisoquinoline derivatives (I and VIII) which were carefully chromatographed on silica gel using chloroform-methanol as solvent to give the base A (I or VIII), m.p. 189-190°, and the base B (I or VIII), m.p. 177-179°. The infrared spectrum in chloroform of the former compound (A) was identical with that of *O*-methyloxyacanthine, namely natural obaberine.

In order to obtain another type of biscoclaurines, *e.g.*, tetrandrine, the second bisamide (IX) was subjected to the Bischler-Napieralski reaction, followed by reduction and *N*-methylation in a similar manner as in the case of the bisamide III, but no pure compounds could be separated by chromatography. Thus a total synthesis of (±)-obaberine (I) has been accomplished.

## EXPERIMENTAL (7)

Tlc was carried out on silica gel (thickness 0.25 mm). Ir spectra were taken with a HITACHI EPI-$S_2$ spectrophotometer, and nmr spectra were measured on a HITACHI H-60 spectrometer with tetramethylsilane as an internal standard in deuteriochloroform. Mass spectra were determined with a HITACHI RMU-7 mass spectrometer equipped with a direct inlet system; chamber voltage 80eV; total emission 80 $\mu$A; ion chamber temperature 200°.

### Bischler-Napieralski Reaction of the Bisamide (III) [Total Synthesis of (±)-Obaberine (1)]

A mixture of 2.0 g. of the bisamide (III) (6), 12 ml. of phosphoryl chloride, and 60 ml. of dry chloroform was allowed to stand overnight at room temperature, and then the mixture was heated mildly at 65° for 3 hours. After the reaction, the excess solvent and reagent was evaporated *in vacuo* under a current of nitrogen to give a syrup, whose methanolic solution was reduced with 8.0 g. of sodium borohydride for 1 hour. After the above mixture had been heated on a water-bath for 30 minutes, removal of the solvent gave a residue which was extracted with ether. The ex-

tract was washed with water, dried over sodium sulfate, and evaporated to give 1.6 g. of a pale yellow syrup, which was mixed with 20 ml. of 37% formalin (20 ml.) and 20 ml. of 98% formic acid. The resulting mixture was heated on a water bath for 5 hours and the solvent was then distilled off under reduced pressure to leave a brown syrup, which was basified with 10% ammonium hydroxide solution and extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give 1.3 g. of a pale brown amorphous substance which was chromatographed on 30 g. of silica gel using chloroform and chloroform-methanol as eluant.

Evaporation of chloroform-methanol (100:1) eluate gave a pale yellow syrup, which solidified on triturating with ether. Recrystallization from ether-petroleum ether afforded 15 mg. of a colourless powder (base A), m.p. 189-190°; $R_f$ 0.64 (chloroform-methanol, 10:1), nmr ($\tau$), 6.01 ($OCH_3$) 6.12 ($OCH_3$), 6.18 ($OCH_3$ x 2), 7.38 ($NCH_3$), 7.60 ($NCH_3$), mass (m/e) (8), 622 ($M^+$), 621 ($M^+$-1), 607 ($M^+$-$CH_3$), 591 ($M^+$-$OCH_3$), 396, 395 (base peak), 381, 379, 365, 349, 335, 198 (isotope peak 198.5), 190, 175, 174. The ir spectrum in chloroform of the base (A) was identical with that of natural obaberine, namely, *O*-methyloxyacanthine, which was derived from natural oxyacanthine.

*Anal.* Calcd. for $C_{38}H_{42}N_2O_6.1/2H_2O$ (10); C, 72.23; H, 6.86. Found: C, 71.77; H, 7.30.

Furthermore, removal of the chloroform-methanol [(100:2) and (100:3)] eluate gave a pale yellow syrup, whose recrystallization from chloroform-*n*-hexane or ether-petroleum ether gave a colorless powder (base B), m.p. 177-179°, $R_f$ 0.48 (chloroform-methanol, 10:1); nmr ($\tau$), 6.01 ($OCH_3$), 6.16 ($OCH_3$), 6.37 ($OCH_3$ x 2), 7.42 ($NCH_3$ x 2); mass (m/e) (8), 622, 621, 607, 591 396, 395, 381, 379, 198, 190, 175, 174.

*Anal.* Calcd. for $C_{38}H_{42}N_2O_6.1H_2O$ (10): C, 71.23; H, 6.92. Found: C, 71.37; H, 6.95.

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(6) T. Kametani, O. Kusama, and K. Fukumoto, *J. Chem. Soc. (C)*, 1789 (1968).

(7) All the melting points were uncorrected.

(8) The mass spectral pattern (9) of the product, which was obtained by reduction of stebisimine dimethiodide, was identical with that of the bases (A and B).

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(10) These samples were dried over phosphorus pentoxide at 50° for three days. In this case when they were dreid at higher temperature, coloration was observed. Furthermore, since the mass spectrum revealed the real molecular formula, the presence of water of crystallization was confirmed.

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