Total Synthesis of (±)-Obaberine

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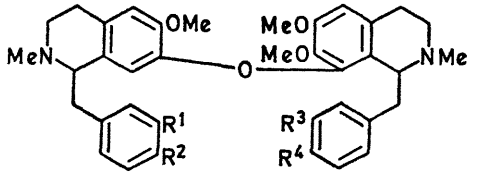
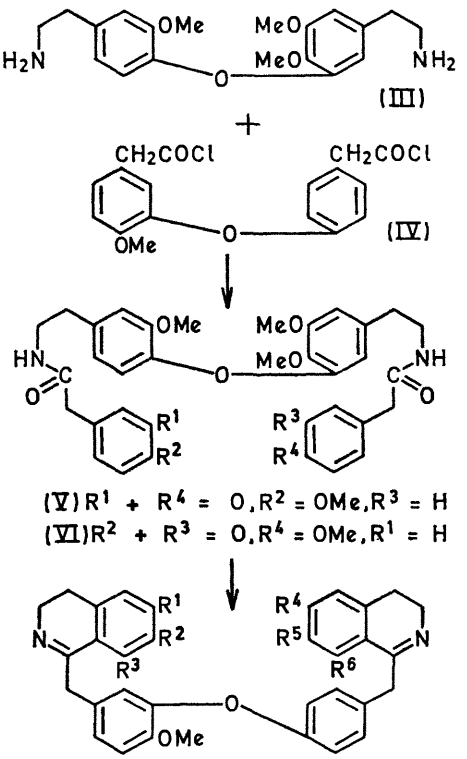
Summary Cyclization of one of two bisamides (V) and VI), followed by reduction and methylation, gave the expected biscoclaurine derivatives (one of which was identical with *O*-methyloxyacanthine) thus completing the total synthesis of obaberine (I).

OBABERINE (I)[1] and tetrandrine (II)[2] are non-phenolic bisbenzylisoquinoline alkaloids. One of us[3] has reported on the synthesis of head-to-head coupled bisbenzylisoquinolines which have two biphenyl ether bonds in a molecule. We have studied the synthesis of these two types of isomeric bisbenzylisoquinolines by the same synthetic procedure as that used for stebisimine.[4]



(I) $R^1 + R^4 = O$, $R^2 = OMe$, $R^3 = H$
(II) $R^2 + R^3 = O$, $R^4 = OMe$, $R^1 = H$

Two isomeric diamides (V and VI) were obtained by Schotten–Baumann reaction between the diamine (III) and dicarboxylic acid chloride (IV). In this case the amides were separated and their structures were elucidated by comparison with authentic samples.[4] Bischler–Napieralski reaction of the amide (V) with phosphoryl chloride in chloroform gave a mixture of 3,4-dihydroisoquinoline derivatives (VII and VIII), which were reduced to the 1,2,3,4-tetrahydroisoquinoline derivatives (XI and XII) with sodium borohydride in chloroform–methanol solution. Methylation of the resulting compounds (XI and XII) with formalin and formic acid yielded biscoclaurine derivatives (I and XV) which were carefully chromatographed on silica



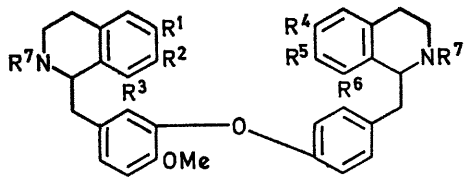
(V) $R^1 + R^4 = O$, $R^2 = OMe$, $R^3 = H$
(VI) $R^2 + R^3 = O$, $R^4 = OMe$, $R^1 = H$

(VII) $R^1 = R^4 = R^5 = OMe$, $R^2 + R^6 = O$, $R^3 = H$
(VIII) $R^1 = R^5 = R^6 = OMe$, $R^2 + R^4 = O$, $R^3 = H$
(IX) $R^1 = R^2 = R^4 = OMe$, $R^3 + R^5 = O$, $R^6 = H$
(X) $R^2 = R^3 = R^4 = OMe$, $R^1 + R^5 = O$, $R^6 = H$

gel using chloroform–methanol as solvent to give the base A (I or XV), m.p. 189—190°, R_F 0·64 (chloroform–methanol, 10 : 1), n.m.r. (τ): 6·0 (OCH_3), 6·12 (OCH_3), 6·18 ($OCH_3 \times 2$), 7·38 (NCH_3), and 7·60 (NCH_3); mass spectrum:†

† The mass spectral pattern of the product, which was obtained by reduction of stebisimine dimethiodide, was identical with that of the bases (A and B); D. H. R. Barton, G. W. Kirby, and A. Wiechers, *J. Chem. Soc.* (*C*), 1966, 2312.

(*m/e*) 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, and 174; and the base B (I or XV), m.p. 177—179°, R_F 0·48 (chloroform–methanol, 10 : 1), n.m.r. (τ): 6·01 (OCH_3), 6·16 (OCH_3), 6·37 ($OCH_3 \times 2$), and 7·42 ($NCH_3 \times 2$); mass spectrum: (*m/e*) 622, 621, 607, 591, 396, 395, 381, 379, 198, 190, 175, and 174. The i.r. spectrum (in $CHCl_3$) of the former compound (A) was identical with that of *O*-methyloxyacanthine, natural obaberine, kindly donated by Prof. M. Tomita.



(XI) $R^1=R^4=R^5=OMe$, $R^2+R^6=O$, $R^3=R^7=H$
(XII) $R^1=R^5=R^6=OMe$, $R^2+R^4=O$, $R^3=R^7=H$
(XIII) $R^1=R^3=R^4=OMe$, $R^3+R^5=O$, $R^6=R^7=H$
(XIV) $R^2=R^3=R^4=OMe$, $R^1+R^5=O$, $R^6=R^7=H$
(XV) $R^1=R^5=R^6=OMe$, $R^2+R^4=O$, $R^3=H$, $R^7=Me$
(XVI) $R^2=R^3=R^4=OMe$, $R^1+R^5=O$, $R^6=H$, $R^7=Me$

The second bisamide (VI) was also cyclized with phosphoryl chloride in chloroform to give the 3,4-dihydroisoquinoline derivatives (IX and X), which were reduced to the 1,2,3,4-tetrahydroisoquinoline derivatives (XIII and XIV). After *N*-methylation of the above compounds, a mixture of *N*-methyl derivatives (II and XVI) was subjected to silica gel chromatography, but they could not be separated by chromatography.

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[1] T. Kugo, M. Tanaka, and T. Sagae, *J. Pharm. Soc. Japan*, 1960, **80**, 1425.
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[3] T. Kametani, H. Iida, S. Kano, S. Tanaka, K. Fukumoto, S. Shibuya, and H. Yagi, *J. Heterocyclic Chem.*, 1967, **4**, 85.
[4] T. Kametani, O. Kusama, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1968, 1798.