Total Synthesis of Stebisimine

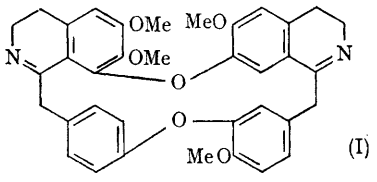
By T. KAMETANI,* O. KUSAMA, and K. FUKUMOTO

(*Pharmaceutical Institute, School of Medicine, Tohoku University, Kitayobancho, Sendai, Japan*)

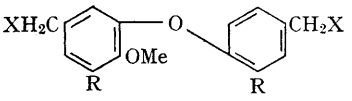
STEBISIMINE, an alkaloid isolated from *Stephania japonica*, was assigned the structure (I) by spectroscopic and chemical methods.[1] This is an interesting bisbenzylisoquinoline alkaloid since it has two 3,4-dihydroisoquinoline moieties. Here we report a total synthesis of stebisimine, which corroborates the suggested structure (I).

Schotten–Baumann reaction of 3,5′-bisaminoethyl-2,2′,3′-trimethoxydiphenyl ether (II)[2] with the diacid chloride (III) [prepared from 4,5′-dicarboxymethyl-2′-methoxydiphenyl ether (IV)[3] and thionyl chloride in the presence of pyridine at room temperature] in the presence of 5% potassium hydroxide solution in chloroform at

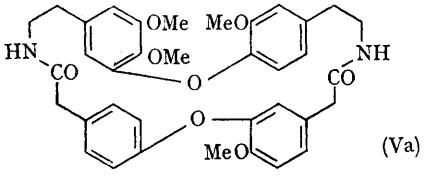
0–5° with stirring for 2 hr., gave a mixture of two bisamides (Va and Vb), which were separated by silicic acid chromatography. The first $CHCl_3$–MeOH (99 : 1) eluent afforded a bisamide (Va) as colourless prisms, m.p. 120—121°, ν_{max} 3355, 3265, 1644 (in KBr), n.m.r. (τ in $CDCl_3$) 7·15—7·7 (methylene protons), 6·4—6·7 (methylene protons), 6·29, 6·26, 6·20, 6·16 (aromatic OMe, singlets), 4·34—5·0 (NH), 2·8—3·9 (aromatic protons), R_F 0·45 [silica gel, 0·2 mm., $CHCl_3$–Me_2CO (5 : 4)], and further $CHCl_3$–MeOH (98 : 2) eluent gave the second bisamide (Vb) as pale yellow prisms, m.p. 138—140°, ν_{max} 3320, 3305, 1648 (in KBr), n.m.r. (τ in $CDCl_3$) 7·2—7·55, 6·35—6·75 (methylene protons), 6·29, 6·23, 6·19, 6·15 (aromatic OMe), 4·35—4·75 (NH), 2·9—4·0 (aromatic protons). The former bisamide (Va) was subjected to Bischler–Napieralski reaction with phosphoryl chloride in chloroform at 60—65° for 15 hr. and careful work-up involving silicic acid chromatography with $CHCl_3$–MeOH (99 : 1) as an eluent gave two 3,3′,4,4′-tetrahydroisoquinolines, which were separated on being triturated with ether. The ether-soluble part gave stebisimine (I), $C_{36}H_{34}O_6N_2,C_6H_{14},H_2O$, m.p. 105—106°, R_F 0·58 (silica gel, 0·2 mm., $CHCl_3$: Me_2CO : MeOH = 5 : 4 : 1), whose i.r. and u.v. spectra showed ν_{max} 1610 cm.$^{-1}$ (in $CHCl_3$) and λ_{max} 236, 277 mμ (in MeOH) and n.m.r. spectrum (τ in $CDCl_3$) revealed the expected *O*-methyl resonances at 6·77, 6·15, 6·13, and 6·07 as singlets, and aromatic protons at 4·09 (1H, J = ~1 c./sec.) as a doublet and at 2·8—3·8 corresponding to nine protons. In addition there are two broad resonances corresponding to fourteen protons, centred at 9·10 and 8·55, due to the hexane. The n.m.r. spectra of synthetic and natural stebisimine (sample kindly given by Professor D. H. R. Barton, whom we thank) were superimposable upon each other except in hexane region, and the i.r. spectra in chloroform were superimposable, but those in KBr differed a little in the region of



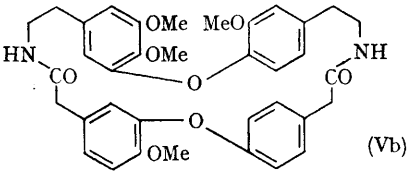
(I)



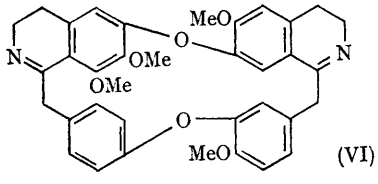
(II) X=CH_2·NH_2, R=OMe
(III) X=COCl, R=H
(IV) X=CO_2H, R=H



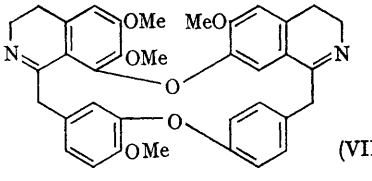
(Va)



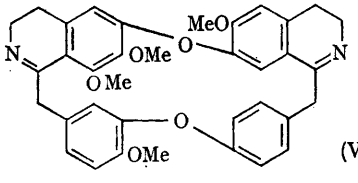
(Vb)



(VI)



(VIIa)



(VIIb)

1270—1280 and 820—840 cm.$^{-1}$ because of the presence of hexane.

On the other hand, another part insoluble in ether gave the second bisbenzylisoquinoline (VI), m.p. 203—210° (decomp.), which showed similar i.r. and u.v. spectra. However, there were some differences in the n.m.r. spectrum (τ in $CDCl_3$); thus it showed the *O*-methyl resonances at 6·38, 6·26, and 6·05, and aromatic protons at 2·8—3·7. Therefore, the second bisbenzylisoquinoline (VI) seemed to be the product which cyclized to a different position from stebisimine.[2,4,5]

The latter bisamide (Vb) was also treated with phosphoryl chloride in chloroform at 60—65° for 15 hr. to give two products (VIIa and VIIb), which were different from stebisimine on direct comparison of i.r. ($CHCl_3$ and KBr) and n.m.r. spectra and R_F-value. The transformations of stebisimine (I) and bisbenzylisoquinoline (VIIa) to obaberine and tetrandrine, respectively, are in progress.

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