The Total Synthesis of the Thalictrum Alkaloid Adiantifoline

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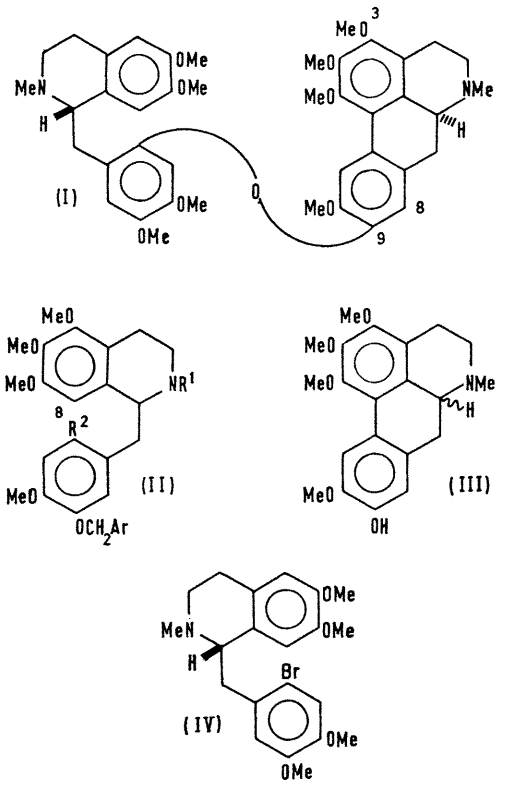
Summary A total synthesis of compound (I) was accomplished and the product shown to be identical with the Thalictrum alkaloid, adiantifoline.

ADIANTIFOLINE, a dimeric benzylisoquinoline–aporphine alkaloid from *Thalictrum minus* L. var. *adiantifolium* Hort., was assigned the structure (I).[1] Although the benzylisoquinoline portion was based on sound experimental evidence (isolation of 6′-hydroxylaudanosine on cleavage with Na–NH_3), the aporphine part could be satisfied by a number of possible structures. For example, the methoxy-group at C-3 could be moved to C-8 or the diphenyl ether bridge could be made to C-8 with and without the appropriate interchange of the relevant methoxy-group. We report here the synthesis of compound (I) and show its identity with the natural product.

Treatment of 2,3,4-trimethoxyphenethylamine[2] with the acid chloride of 3-benzyloxy-4-methoxyphenylacetic acid[3] under Schotten–Baumann conditions gave the corresponding amide, m.p. 104°, ν_{max} ($CHCl_3$) 3310 (N–H), 1635,

and 1580 cm.$^{-1}$ (sec. amide) which was cyclized by the Bischler–Napieralski reaction and the imine product immediately reduced with $NaBH_4$ to the amine (II; $R^1 = R^2 = H$), HCl salt, m.p. 118—119°. *N*-Methylation of this product by HCHO and $NaBH_4$ gave a substance (II; R^1 = Me, $R^2 = H$), HCl salt, m.p. 123—125° (dec.); τ ($CDCl_3$ 4·40 (1H singlet, 8-H); which was nitrated in the cold with HNO_3 in HOAc to the nitrobenzylisoquinoline (II; R^1 = Me, $R^2 = NO_2$), HCl salt m.p. 129—131°; τ ($CDCl_3$) 3·75 (1H singlet, 8-H), 3·43, and 2·47 (1H singlets, 2′-H and 5′-H); a Pschorr cyclization of the nitro-amine yielded a mixture which on silicic acid chromatography afforded the aporphine (III) (17%) m.p. 206—207°; λ_{max} (MeOH) 312 nm. (ϵ 12,100), 301 (13,600), 231 (14,100), and a bathochromic shift in base to 323 nm. (ϵ 18,800); τ ($CDCl_3$) 2·04 (1H singlet, 11-H) and 3·18 (1H singlet, 8-H). The aporphine product allows for the establishment of the nitration position in the starting material.† Resolution of substance (III) into optical isomers was achieved by di-*p*-toluoyl-(+)-tartaric acid to give (+)-(*S*)1,2,3,10-tetramethoxy-9-hydroxyaporphine, m.p. 186—187°, $[\alpha]_D$ + 108° (MeOH). The 9-methoxy-product (diazomethane) has the same physical constants as the alkaloid thalicsimidine from *Thalictrum simplex* L.[4]



An Ullmann condensation of (+)-(*S*)-6′-bromolaudanosine (IV)[5] with (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine afforded a mixture which, after chromatography on silicic acid, gave compound (I) (21%) as a microcrystalline powder, m.p. 107—108° (hexane) a polymorph of the originally reported natural product.[1] Compound (I) and adiantifoline gave the same i.r. ($CHCl_3$), n.m.r. ($CDCl_3$), and u.v. spectra (MeOH), identical c.d. curves (MeOH) and mobility in four t.l.c. (silica gel G) systems.

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† Nitration in the 6′-position was previously reported for a closely related substance by M. Shamma and W. A. Slusarchyk, *Tetrahedron*, 1967, **23**, 2563.

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