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THALICTRUM ALKALOIDS VI: (-)-VERONAMINE, A GLYCOSIDIC BENZYLISOQUINOLINE[1]

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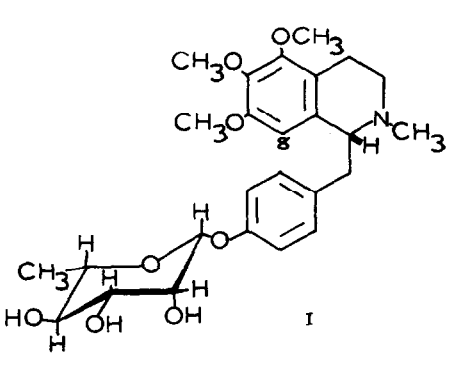
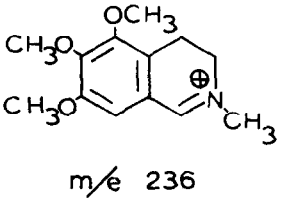
We wish to report the isolation, structural elucidation and synthesis of the new alkaloid (-)-veronamine (I) obtained from T. fendleri Engelm. To our knowledge, this is the first synthesis of a glycosidic isoquinoline alkaloid to have been carried out.[2]

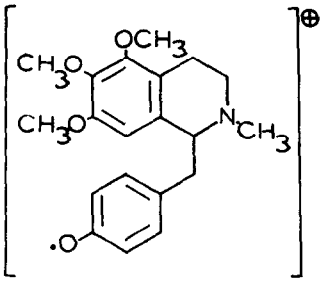
Column chromatography over cellulose powder of the crude tertiary alkaloid hydrochloride salts using methyl ethyl ketone-water as eluant gave as a middle fraction an oil which was further purified by preparative TLC over silica gel.[1,3] Amorphous (-)-veronamine (I) so obtained showed a very weak parent peak at m/e 489 for $C_{26}H_{35}O_8N$, a base peak at m/e 236, and a small but important peak at m/e 342:



I



m/e 236



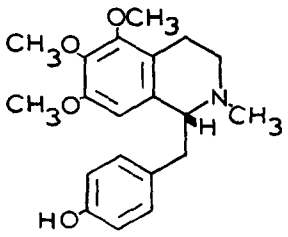
m/e 342

The UV spectrum exhibited λ_{max}^{EtOH} 275 and 282 mμ (log e 3.44 and 3.43). The NMR spectrum in $CDCl_3$ showed as distinct peaks a C-methyl doublet at δ 1.21 (J = 6.5 Hz), a singlet N-methyl group at δ 2.49, and three O-methyl groups (9 protons) as a singlet at δ 3.85. Additionally,

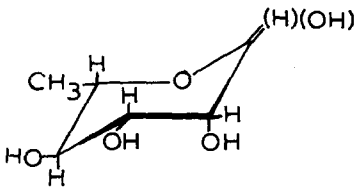
the anomeric proton appeared as a broad doublet at δ 5.42, while the C-8 aromatic proton absorption was situated characteristically upfield at δ 5.85 (singlet). The alkaloid also possessed $[\alpha]_D$ -155° (MeOH).

Hydrolysis of (-)-veronamine (I) with 3% H_2SO_4 over a steam bath yielded (-)-thalifendlerine (II), identical in its specific rotation and in every other respect with naturally occurring (-)-thalifendlerine (II) obtained previously from T. fendleri.[1,4] (-)-Thalifendlerine (II) shows a negative Cotton effect, indicating the molecule has the D (or R) configuration:[5,6] $[\alpha]_D$ -108° (MeOH); ORD (c 0.5 in MeOH) $[\alpha]_{289}$ -3200° (tr), $[\alpha]_{276}$ -1200° (pk).

The Ihl-Pechmann and Tauber benzidine spot tests pointed to the fact that the sugar moiety also obtained from the acid hydrolysis of (-)-veronamine is a hexose,[7] and comparative paper chromatography using the aniline-oxalate spray[8] eliminated all the common hexoses except L-(-)-rhamnose (III). It was then found that the diethyl dithioacetal derivative of the sugar obtained from the hydrolysis of (-)-veronamine was identical in its TLC behavior, mp, and mass spectrum with the diethyl dithioacetal (IV) of authentic L-(-)-rhamnose.[9] All of the data, therefore, pointed to expression I for (-)-veronamine, except that at this stage the exact stereochemistry at the anomeric center could not be defined.



II



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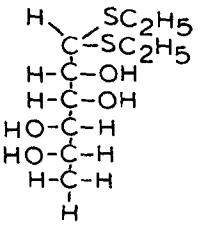
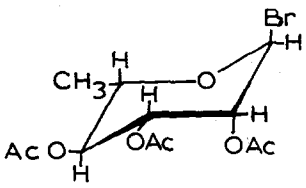
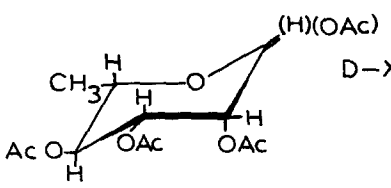


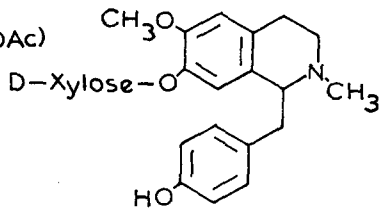
IV



V



VI



VII

The best method for synthesizing (-)-veronamine (I) appeared to be through the Koenigs-Knorr reaction.[10] This involved in the present case the condensation of 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide (V), prepared from tetraacetylated L-rhamnose (VI) by the method of Zemplén and Gerecs,[11] with (-)-thalifendlerine (II), followed by hydrolysis of the acetate functions. However, initial attempts to carry out the condensation using Ag_2CO_3 as the base under usual Koenigs-Knorr reaction conditions gave none of the desired product, possibly because of alkylation at the basic nitrogen atom of thalifendlerine (II).

The standard Koenigs-Knorr conditions were, therefore, modified so that the dry potassium salt of natural (-)-thalifendlerine was condensed in dry acetone with the triacetyl bromide V. Treatment of the crude reaction product with $NaOCH_3$ in methanol to cleave the acetate functions, followed by preparative TLC on silica gel afforded (-)-veronamine (I) as a white foam in 85% overall yield, identical by IR, UV, NMR, TLC and rotational comparisons with the naturally occuring base. The chemical shift for the anomeric protons was found to be identical in both instances. It follows, therefore, that the two materials must have the same configuration at the anomeric center.[12]

It is known that the Koenigs-Knorr reaction occurs with Walden inversion at the anomeric carbon when alkali is employed.[13] Since the triacetyl bromide V used in the condensation has the α configuration as indicated,[11] the resulting glycoside, namely (-)-veronamine (I) must have the β configuration.

(-)-Veronamine is actually the second glycosidic benzylisoquinoline to be isolated, the first being latericine (VII), in which the monosaccharide unit is D-(+)-xylose.[14] It is possible that glycosidic alkaloids are quite common in nature, but are not readily isolated because of the facile hydrolysis of the glycosidic bond under the acidic conditions used during isolation.[3]

The physiological activity of (-)-veronamine (I) will be reported in a separate paper.

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