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THALICTRUM ALKALOIDS II.[1] THALIDASTINE

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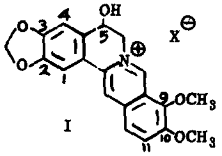
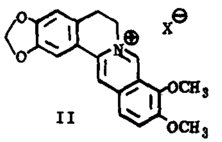
In 1963, Nijland reported the isolation from Hydrastis canadensis of berberastine (I), the first protoberberine found to be hydroxylated at C-5.[2] This alkaloid was actually present in the plant in very small amounts, to the extent of about one part to every two hundred of the accompanying berberine (II), the most abundant quaternary alkaloid present.

A subsequent biosynthetic study clearly showed that berberastine is not derived from oxidation of berberine, but could not determine whether berberastine is the product of a normal pathway or an aberrant biosynthesis.[3] Very recently, the hypothesis has been advanced that berberastine could prove to be the first representative of a larger group of natural compounds which are related to 4-hydroxynorlaudanosoline.[4]

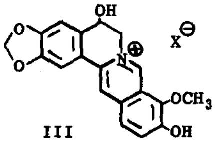
We have now found that Thalictrum fendleri produces an alkaloid, thalidastine (III), which is a 5-hydroxylated protoberberine, and is thus the second compound related to 4-hydroxynorlaudanosoline. Interestingly enough, thalidastine (III) is present in relatively large amounts, to the extent of 0.7 g. for every 1 g. of the accompanying berberine (II). Thalidastine (III) is thus one of the major alkaloids of T. fendleri, and must be a product of one of the principal biosynthetic pathways of this plant



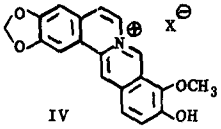
I



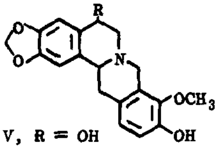
II



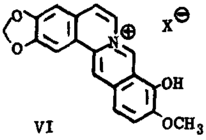
III



IV



V, R = OH
VII, R = H



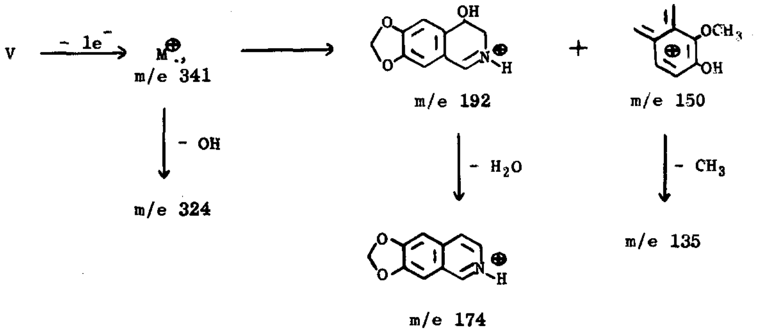
VI

Thalidastine chloride (III), $C_{19}H_{16}O_5N^{\oplus}\ Cl^{\ominus}$, was obtained as yellow-brown crystals darkening above 230° (decomp.), $[\alpha]_D^{25}$ 138° (MeOH). The uv spectrum resembled that of berberine chloride and showed λ_{max}^{EtOH} 348, 269, and 233 mμ (log e 4.10, 4.16, and 4.17). The phenolic character of the alkaloid was indicated by the change to a deep red color, as well as by a bathochromic shift in the uv, upon the addition of base. Dehydration of III to yellow-brown deoxythalidastine chloride (IV), $C_{19}H_{14}O_4N^{\oplus}\ Cl^{\ominus}$, which darkens $>$210° (decomp.), occurred upon heating to 85° in vacuo, or on standing at room temperature for a few weeks, or preferably upon heating at 100° in 2N HCl for 15 minutes.[5]

The nmr spectrum of deoxythalidastine chloride (IV) in trifluoroacetic acid with TMS as an internal standard exhibited one methoxy group at 4.32 p.p.m., one methylenedioxy function at 6.34 p.p.m., and eight aromatic protons, six of which appeared as singlets at 7.43, 8.03, 8.09, 8.22, 9.37, and 9.88 p.p.m. The remaining two aromatic protons were found as two poorly defined doublets centered at 7.92 and 8.69 p.p.m. (J = 7.2 c.p.s.).

The uv spectrum of deoxythalidastine chloride (IV) was substantially different from that of thalidastine chloride (III), and showed λ_{max}^{EtOH} 463, 348, 308, 278, 270, and 247 mμ (log e 3.68, 3.71, 4.08, 4.18, 4.18, and 4.24). It is possible to distinguish between 2,3,9,10 and 2,3,10,11 substituted dehydroberberinium salts of type IV on the basis of their uv spectra. Thus all 2,3,9,10 substituted dehydroberberinium salts have maxima in the regions of 348-358 and 460-490 mμ, whereas their 10,11 counterparts exhibit maxima at 322-332 and 413-422 mμ.[6] Deoxythalidastine chloride (IV) must, therefore, be 2,3,9,10 substituted.

Reduction of thalidastine chloride (III) with Adams catalyst in ethanol gave tetrahydrothalidastine (V) as colorless needles, m.p. 201-202°. The mass spectrum of V exhibited a molecular ion peak at m/e 341, in conformity with the formula $C_{19}H_{19}O_5N$, and other intense peaks at m/e 324, 192 (base), 174, 150 and 135, pointing to the following fragmentation pattern:



Deoxythalidastine bromide (IV), which darkens > 220°, was clearly different from a sample of dehydroberberrubinium bromide (VI).[6] Additionally, hydrogenation of deoxythalidastine chloride (IV) with Adams catalyst for 72 hrs. gave the known tetrahydrothalifendine[1] (VII), m.p. 210-211°, identical with an authentic sample in our possession in terms of mixture melting points and TLC R_f values.

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References

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2. M.M. Nijland, Pharm. Weekblad, 98, 301 (1963).
3. I. Monkovic and I.D. Spencer, J. Am. Chem. Soc., 87, 1137 (1965).
4. I. Monkovic and I.D. Spencer, Can. J. Chem., 43, 2017 (1965).
5. Thalidastine should, therefore, always be stored in its red form to avoid dehydration.
6. C.K. Bradsher and N.L. Dutta, J. Am. Chem. Soc., 82, 1145 (1960); J. Org. Chem., 26, 2231 (1961); and J. Org. Chem., 27, 2213 (1962).