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ALKALOIDS OF THALICTRUM. IX. ADIANTIFOLINE, A NEW DIMERIC BENZYLISOQUINOLINE-APORPHINE ALKALOID*

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There are three reported dimeric benzylisoquinoline-aporphine alkaloids, thalicarpine (I) (1), thalmelatine (II) (2) and dehydrothalicarpine (III) (3). They have been found almost exclusively in the genus Thalictrum, family Ranunculaceae except for thalicarpine which has also been isolated from Hernandia ovigera L. (4) (Hernandiaceae).

This communication concerns a new member of this group isolated from the nonphenolic tertiary alkaloid fraction of the roots and tops of Thalictrum minus L. var. adiantifolium Hort. and named adiantifoline (IV). The alkaloid crystallized from absolute ethanol as pale yellow needles, m.p. 143.5-144°, $[\alpha]_D^{28}$ + 90° (c 0.11, MeOH) and showed a UV spectrum, λ_{max}^{EtOH} 312 mμ (log ε 4.34), 302 (4.39), 283 (4.51) which was almost identical with that obtained for thalicarpine (I). The NMR spectrum in deuterochloroform at 60 MHz exhibited two N-methyl peaks at 2.44 and 2.47 δ, eight O-methyl groups at 3.59 (3H), 3.78 (9H), 3.82 (3H), 3.89 (3H), 3.94 (3H) and 3.96 δ (3H) and six aromatic protons at 6.24 (1H), 6.55 (2H), 6.60 (2H) and 8.08 δ (1H). An additional 14 protons (methylene and methine) were found as broad envelopes of peaks between 2.3 and 4.3 δ. The spectrum in general is very similar to thalicarpine except for the presence of an additional O-methyl group and the lack of an aromatic proton.

The first discernible peak with the highest mass in the mass spectrum of adiantifoline (IV) was found at m/e 519 (2.8%) but clearly was not the molecular ion as m/e 520 and 521 were of almost the same intensity. The mass spectrum of thalicarpine shows a very weak and easily missed molecular ion peak at m/e 696 (0.1%). The first sizeable peaks are found at m/e 490, 491 (largest) and 492. Elemental analysis of adiantifoline (IV) supported the formula $C_{42}H_{50}N_2O_9$ (M.W. 726); Calcd: C, 69.41; H, 6.88; N, 3.85, Found: C, 70.03; H, 7.01; N, 3.96. The difference in mass of 30 units between adiantifoline and thalicarpine at the highest mass fragments is equivalent to one methoxy group. A very intense peak at m/e 206 was present in the

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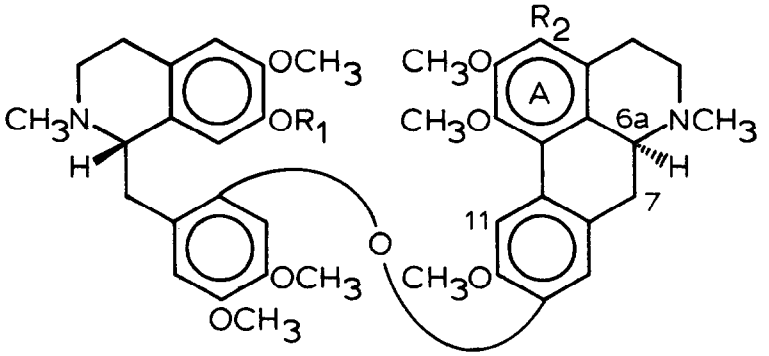
spectrum of both compounds I and IV and was assigned to the fragment V obtained from the benzyltetrahydroisoquinoline portion of the molecules. The extra methoxy group must therefore reside in either the aporphine or the benzyl part of the tetrahydroisoquinoline portion and is supported by the m/e 520 peak. Further evidence for this assignment was obtained by the preparation of compound VI by permanganate oxidation (5) of adiantifoline (IV). This substance, m.p. 230-231.5° as orange-red needles from acetone-methanol gave a UV spectrum, λ_{max}^{MeOH} 436 mμ (log ε 3.61), 314 (4.16), 274 (4.73) and an intense IR peak at ν_{KBr} 1680 cm^{-1}; consistent with the phenanthrene system and aromatic aldehyde structure. The mass spectrum showed a M^+ peak at m/e 533. The corresponding substance VII (5) prepared from thalicarpine (I) gave a very similar UV and IR spectrum.

Sodium and liquid ammonia cleavage of adiantifoline (IV) gave a mixture of products (tlc) which were separated into phenolic and nonphenolic fractions. The phenolic fraction yielded a crystalline hydroiodide salt from acetone, m.p. 194-196° (d) after darkening at 185-187°, UV spectrum λ_{max}^{MeOH} 239 mμ (log ε 4.03) and IR spectrum superimposable with that of the hydroiodide salt of the compound VIII (6'-hydroxylaudanosine) obtained from thalicarpine (I). The point of connection of the benzyltetrahydroisoquinoline to the aporphine is thus at the 6' position and the extra methoxy group must therefore be in the aporphine part. The nonphenolic cleavage fraction yielded a crystalline compound, m.p. 166-169.5° from ether, λ_{max}^{MeOH} 287.5 mμ (log ε 3.42). 280 (3.44) and having a carbonyl absorption at 1715 cm^{-1} in the infrared. A high resolution mass spectrum showed a molecular ion at m/e 285.1730 which calculated at 285.1729 for $C_{18}H_{23}O_2N$. This product was also obtained from thalicarpine (I) and assigned structure IX (6).

Product IX fixed the positions of two of the oxygens on the aporphine side of adiantifoline. Assuming that the oxygen bridge is at C-9 as in thalicarpine and that the C-1 methoxy is lost during sodium and liquid ammonia cleavage leaves only the assignment of the position for one methoxy group. The C-11 position can be excluded as the NMR spectrum exhibits a peak at 8.08 (singlet, 1H) characteristic for such a proton (7). Of the two remaining open positions C-3 is favored over C-8 because the genus Thalictrum has yielded a number of benzylisoquinoline derived alkaloids with a trioxygenated ring A. These include ocoteine (8), preocoteine (9), takatonine (10), thalifendlerine (11), hernandezine (12), thalidezine (9) and thalidasine (13) to mention a few. The added steric hindrance introduced about the diphenyl ether linkage if position C-8 contained the methoxy group also makes it a less attractive possibility, especially from biosynthetic considerations which require the bridge oxygen to originate from the aporphine part.

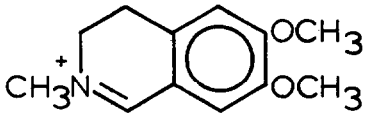


I, R_1=CH_3; R_2=H

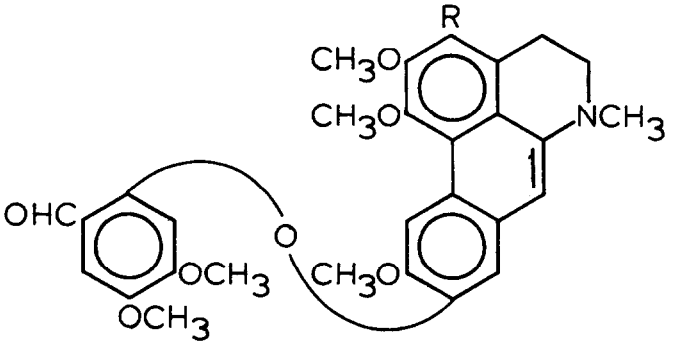
II, R_1=R_2=H

III, 6a,7-dehydro-I

IV, R_1=CH_3; R_2=OCH_3

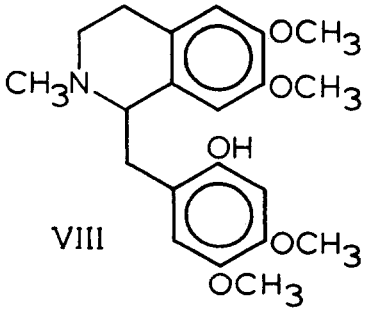


V m/e 206

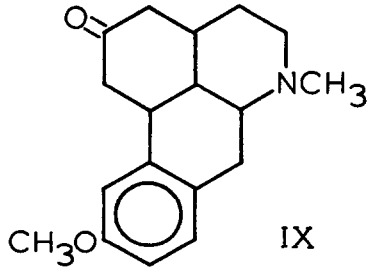


VI, R=OCH_3

VII, R=H



VIII



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The lack of sufficient amounts of adiantifoline precluded the isolation of the products in low yield from the sodium and liquid ammonia cleavage to assign the stereochemistry to the two asymmetric centers and to gain further information on the total oxygenation pattern. A comparison of the ORD and CD curves for adiantifoline (IV) and thalicarpine (I) suggests they have the same stereochemistry. Both exhibit three clearly defined Cotton effect curves (two negative and one positive) in the CD; adiantifoline with molecular ellipticities $[\theta]_{305}$ - 33,800, $[\theta]_{275}$ - 31,200 and $[\theta]_{241}$ + 234,000 and thalicarpine with $[\theta]_{306}$ - 16,300, $[\theta]_{275}$ - 18,000 and $[\theta]_{239}$ + 242,000.

Synthetic studies are now in progress for final proof of the structure and stereochemistry of adiantifoline based on the findings reported here.

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