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THE STRUCTURE OF FETIDINE

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The alkaloid (+)-fetidine, isolated from *Thalictrum foetidum*, belongs to the small family of benzyltetrahydroisoquinoline-aporphine dimers.[1,2] The structure proposed in the literature (1) is in accord with its oxidation to 1-oxo-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2) and its reductive cleavage by sodium in ammonia to give (+)-isoboldine (3), (+)-laudanosine (4), and (+)-laudanidine (5), the latter being a secondary cleavage product derived from (4).[3] As pointed out by Schiff and Doskotch, the above evidence actually gives no proof for the assigned terminus of the diphenyl ether linkage onto the benzyl portion of the laudanosine unit.[4]

In our hands, isolation and separation (countercurrent and tlc) of the bases of *T. foetidum* afforded two major constituents, thalicarpine (6) and fetidine, m.p. 125-126° (lit.[3] m.p. 132-135°); the identity of the latter was confirmed by sodium in ammonia cleavage to the reported products (3), (4) and (5). Since we felt that fetidine might actually be the desmethylthalicarpine (7), the latter was synthesized by Ullmann condensation (K_2CO_3 and CuO in pyridine) of (+)-isoboldine (3) and (+)-6'-bromolaudanosine (8).[5] Although base (7) proved to be different (uv, nmr) from fetidine, neither fetidine nor (7) showed uv absorption in basic solution characteristic of a 9-hydroxyaporphine,[6] thus ruling out the possibility that the ether bridge of either might originate at C-1 of the isoboldine unit.

The 100 MHz nmr spectrum of fetidine has been reported to show, in the aromatic region, a singlet at δ 8.07 (1 H) and a band at 6.05 - 6.73 (6 H).[7] We have found that the seven aromatic protons are completely resolved at 220 MHz, as follows: δ 6.14 (s, 1 H), 6.42 (s, 1 H), 6.52 (s, 2 H), 8.12 (s, 1 H) and an AB quartet (J = 8.5 Hz) centered at 6.75 (1 H) and 6.81 (1 H). Since the observed quartet requires a pair of adjacent aromatic hydrogens, fetidine must be represented as structure (9). Fetidine is thus the first example of a bisbenzylisoquinoline alkaloid to contain a 2,3,4-trioxygenated benzyl unit.

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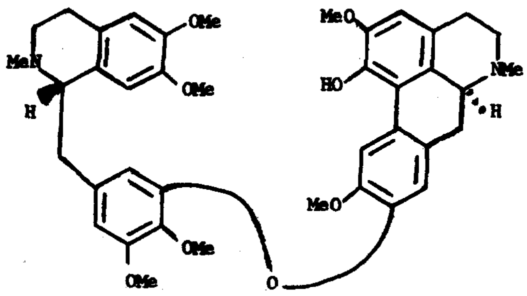
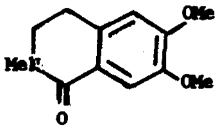
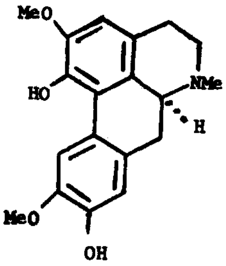


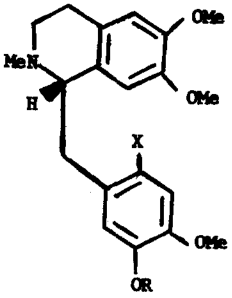
(1)



(2)



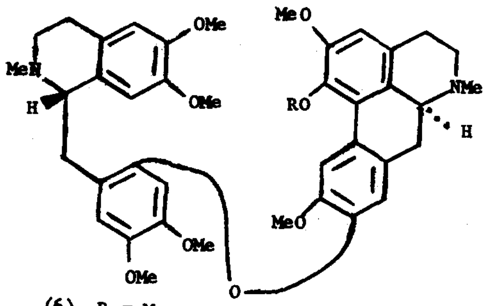
(3)



(4) R = Me; X = H

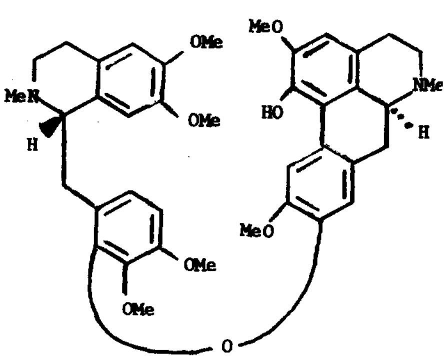
(5) R = X = H

(8) R = Me; X = Br



(6) R = Me

(7) R = H



(9)

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