THALIPINE, A NEW APORPHINE-BENZYLISOQUINOLINE ALKALOID[1]

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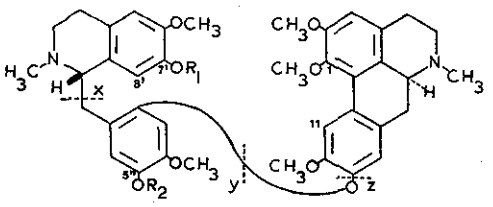
(+)-Thalipine (1) has been obtained from Thalictrum polygamum Muhl. Like most other alkaloids of this plant, it is derived biogenetically from (+)-reticuline without recourse to O-demethylation.

As part of an intensive study of the alkaloids of Thalictrum polygamum Muhl. (Ranunculaceae), we have isolated from 100 kg of the dried and powdered whole plant 20 mg of the new diphenolic aporphine-benzylisoquinoline dimer (+)-thalipine (1). The alkaloid was obtained as an amorphous powder, and in too small an amount to allow crystallization, $[\alpha]_D^{EtOH}$ +59° (c = 0.0048 g/ml), λ_{max}^{EtOH} 280, 289, 298 and 307 nm (log ε 4.06, 4.00, 3.93 and 3.86).

Mass spectroscopy showed an $(M - 2H)^+$ ion at m/e 666 for $C_{38}H_{42}N_2O_8$, so that the molecular formula for thalipine must be $C_{39}H_{44}N_2O_8$. The diagnostic peaks were at m/e 476 $(M - x)^+$, 340 $(M - y)^+$, 324 $(M - z)^+$, and 192 (x, base). One phenolic group must, therefore, be located on the bicyclic isoquinoline moiety, while the other is on the benzyl ring.[2,3]



1, $R_1 = R_2 = H$
2, $R_1 = H$, $R_2 = CH_3$
3, $R_1 = R_2 = CH_3$
4, $R_1 = H$, $R_2 = Ac$
5, $R_1 = R_2 = Ac$
6, $R_1 = CH_3$, $R_2 = Ac$
7, $R_1 = CH_3$, $R_2 = H$

The 60 MHz pmr spectrum showed singlets for two N-CH_3 (δ2.49 and 2.54), a C-1 CH_3O (δ3.70), a C-10 CH_3O (δ3.96), and three additional CH_3O (δ3.76 (2), and 3.90); and seven aromatic protons including a C-8' singlet (δ6.35), a C-11 singlet (δ8.09), and five other singlets (δ6.45, 6.51, 6.55, 6.71 and 6.76). The downfield position (δ6.35) of the C-8' proton signal, and the absence of a high field δ3.58 methoxyl signal locate one of the phenolic groups of thalipine at C-7'.[3]

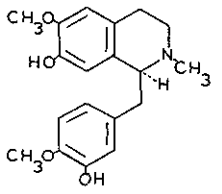
Short term diazomethane O-methylation of thalipine (1) afforded the known alkaloids (+)-thalmelatine (2)[4] and (+)-thalicarpine (3).[4] Similarly, controlled acetylation of 1 using acetic anhydride in chloroform at room temperature provided the amorphous monoacetate 4, $C_{41}H_{46}N_2O_9$, as well as the amorphous diacetate 5, $C_{43}H_{48}N_2O_{10}$, which were separated by tlc.

In order to prove conclusively the position of the phenolic function in the benzyl moiety of thalipine, the crude mixture of mono and diacetates from the acetic anhydride in chloroform treatment of 1 was O-methylated with diazomethane. Chromatographic separation of the products furnished, besides thalipine diacetate (5), the known compound (+)-pennsylvanine acetate (6), which was further saponified to (+)-pennsylvanine (7), identical with the natural product.[3]

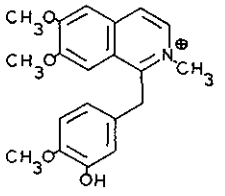
The positive optical rotation of thalipine (1), as well as its CD curve (c = 0.068 mg/ml, MeOH) $[\theta]_{305} = -5.9\times10^3$, $[\theta]_{289} = +2.9\times10^3$, $[\theta]_{274} = -3.9\times10^3$, $[\theta]_{240} = +1.1\times10^5$, and $[\theta]_{208} = -3.7\times10^4$, further confirm that the configuration of the two chiral centers must be similar to those of (+)-thalicarpine (3) and related alkaloids.[2-4]

The importance of thalipine lies primarily in the message it conveys and emphasizes concerning the biogenetic processes occurring in T. polygamum, viz. the tetrahydrobenzylisoquinoline (+)-reticuline is one of the main alkaloidal building blocks in T. polygamum, and O-demethylation is not a favored process in that plant. A (+)-reticuline unit and a (+)-aporphine derived from (+)-reticuline condense together to form dimers of the (+)-thalicarpine series. With the advent of (+)-thalipine, there remains one obvious aporphine-benzylisoquinoline dimer to be isolated from T. polygamum, namely the C-1, C-7', C-5", triphenol analog of thalicarpine (3).

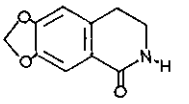
The alkaloids of T. polygamum which can be considered to be biogenetically derived from (+)-reticuline include:



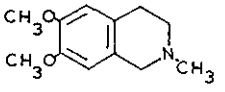
(+)-Reticuline[5]



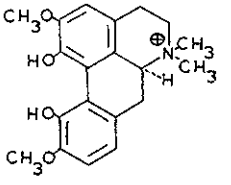
N-Methylpalaudinium cation[6]



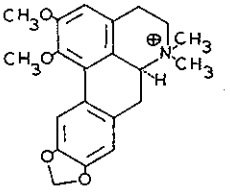
Noroxyhydrastinine[5,7]



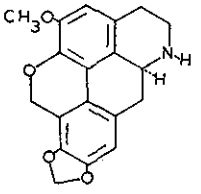
O-Methylcorypalline[5,8]



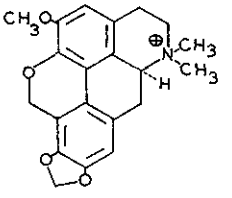
(+)-Magnoflorine[6,13]



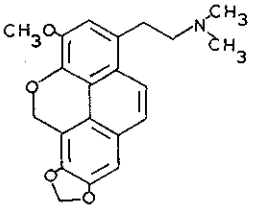
(+)-Nantenine N-metho salt[9]



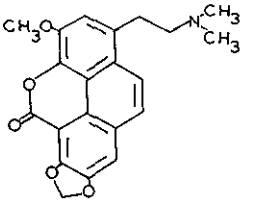
(+)-Bisnorthalphenine[10]



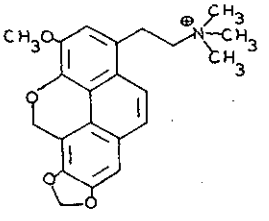
(+)-Thalphenine[11]



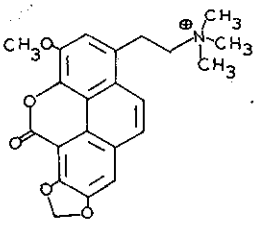
Thaliglucine[11,12]



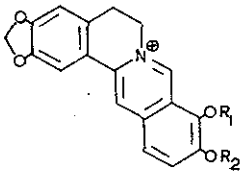
Thaliglucinone[3,12,13]



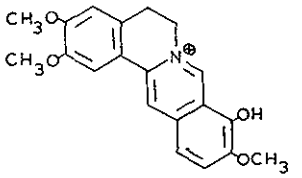
Thaliglucine N-metho salt[10]



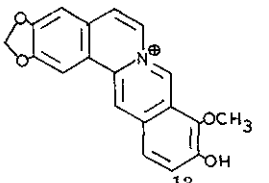
Thaliglucinone N-metho salt[10]



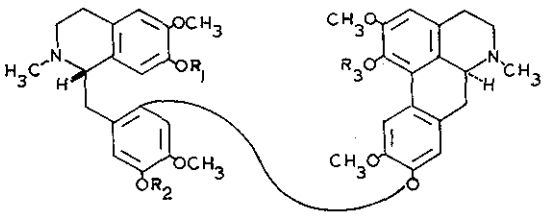
Berberine, $R_1 = R_2 = CH_3$[6,13]
Berberrubine, $R_1 = H$, $R_2 = CH_3$[13]
Thalifendine, $R_1 = CH_3$, $R_2 = H$[6,13]



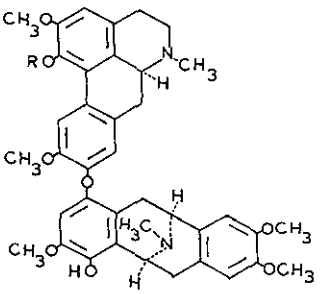
Palmatrubine[5,14]



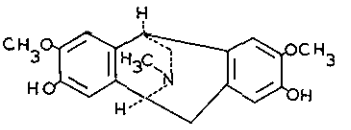
Deoxythalidastine[13]



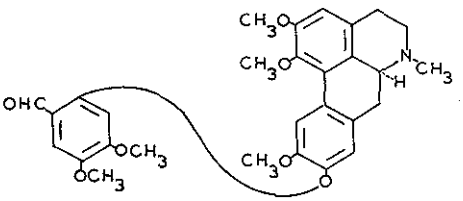
(+)-Thalicarpine, $R_1 = R_2 = R_3 = CH_3$[2,4,13]
(+)-Thalmelatine, $R_1 = H$, $R_2 = R_3 = CH_3$[3,4]
(+)-Thalictropine, $R_1 = R_2 = CH_3$, $R_3 = H$[2]
(+)-Thalictrogamine, $R_1 = R_3 = H$, $R_2 = CH_3$[2]
(+)-Pennsylvanine, $R_1 = R_3 = CH_3$, $R_2 = H$[3]
(+)-Pennsylvanamine, $R_1 = CH_3$, $R_2 = R_3 = H$[3]
(+)-Thalipine, $R_1 = R_2 = H$, $R_3 = CH_3$



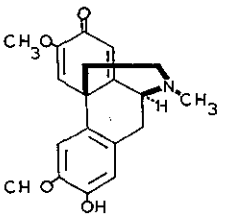
(-)-Pennsylpavine, $R = CH_3$[16]
(-)-Pennsylpavoline, $R = H$[16]



(-)-Thalidine[5,17]



(+)-Hernandaline[3,15]



(-)-Pallidine[5,18]

Twenty-seven of the above twenty-nine alkaloids must be derived biogenetically from (+)-reticuline without resort to O-demethylation; while only two, namely thalifendine and deoxythalidastine, suffered O-demethylation at some stage in their formation.

References

1. This project was supported by NIH research grant CA-11450, awarded by the National Cancer Institute, PHS/DHEW. Elemental analyses were by high and low resolution mass spectroscopy. All pmr spectra were obtained at 60 MHz with TMS as internal standard. TLC was on Merck Silica Gel G, F-254.
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3. M. Shamma and J.L. Moniot, Tetrahedron Lett., 1974, 2291.
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5. This is the first reported isolation of this known alkaloid from T. polygamum.
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19. In a private communication, Profs. J.L. Beal and R.W. Doskotch have indicated their independent isolation of (+)-thalipine from T. revolutum.

20. Known coclaurine derived alkaloids also found in T. polygamum include the bis-benzylisoquinolines (+)-thalrugosine,[21] (+)-hernandezine,[5] (+)-homoaromoline,[3] (-)-O-methylrepandine,[3] and (-)-thalidasine.[3] The known phenanthrene alkaloid thalflavidine, which must originally be derived from a C-5 oxygenated (+)-reticuline unit is also present in T. polygamum.[5]

21. M. Shamma and S.Y. Yao, Experientia, 1973, 29, 517.

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