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THALICTROPINE AND THALICTROGAMINE, TWO NEW DIMERIC ISOQUINOLINE ALKALOIDS[1]

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In the course of our continuing study of Thalictrum polygamum (Muhl.) (Ranunculaceae),[2a,b] we have isolated two new dimeric isoquinoline alkaloids, thalictropine (1) and thalictrogamine (2).

Thalictropine (1), $C_{40}H_{46}O_8N_2$, a major alkaloid in the plant, crystallized as white needles, mp 167° (MeOH), $[\alpha]_D^{25}$ +120° (c 0.3, MeOH). The ir spectrum ($CHCl_3$) contained a peak at 3500 cm^{-1} due to phenolic hydroxyl absorption. The uv absorption, λ_{max}^{MeOH} 225, 278, 298sh and 310 sh nm (log ε 4.46, 4.12, 3.88 and 3.70) showed a bathochromic shift in base to 281, 300sh and 340 nm.[3] The mass spectrum m/e 682 (M^+), 476 (M - a), 326 (M - b), 310 (M - c) and 206 (a, base) indicated that thalictropine was an aporphine-benzylisoquinoline dimer with a phenolic function located on the aporphine moiety.[4a,b]

The nmr spectrum ($CDCl_3$) of 1 contained singlets for two N-methyl groups (δ2.47 and 2.50), six O-methyls (δ3.58, 3.78 (2), 3.82, 3 88 and 3 92), a shielded C-8' aromatic proton (δ6.20), five aromatic protons (δ6.55 (3), 6 59 and 6.67), and a deshielded C-11 aromatic proton (δ8.18).[4a,b]

The alkaloid was very susceptible to aerial oxidation, so that for characterization purposes it was treated with acetic anhydride in pyridine to afford thalictropine acetate (4), $C_{42}H_{48}O_9N_2$, mp 182-183° (MeOH). The most significant feature in the nmr spectrum of 4 was a singlet at δ2.34 (3H) for the acetate methyl, and another singlet (1H) due to the C-11 proton at δ7 60, considerably upfield from its position in the nmr spectrum of 1. This upfield shift of the C-11 proton denotes a C-1 acetoxy function,[5] and indeed the nmr spectrum of thalictropine (1) and that of a sample of synthetic 1-O-demethylthalicarpine[6] were superimposable.

The second alkaloid, thalictrogamine (2), $C_{39}H_{44}O_8N_2$, amorphous base, $[\alpha]_D^{25}$ +135° (c 0.2, MeOH), exhibited hydroxyl absorption in the ir spectrum at 3520 cm^{-1}. The uv spectrum, λ_{max}^{EtOH}

230sh, 277, 298sh and 307sh nm (log 4.39, 4.11, 3.98 and 3.82) showed a bathochromic shift in base to 280, 300sh and 340 nm. Comparison of the mass spectrum of 2, m/e 668 (M^+), 476 (M - a), 326 (M - b), 309 (M - c - 1) and 192 (a, base) with those of 1 and 3, indicated that thalictrogamine is a diphenolic aporphine-benzylisoquinoline base with one phenolic function on the isoquinoline B ring and another on the aporphine moiety.

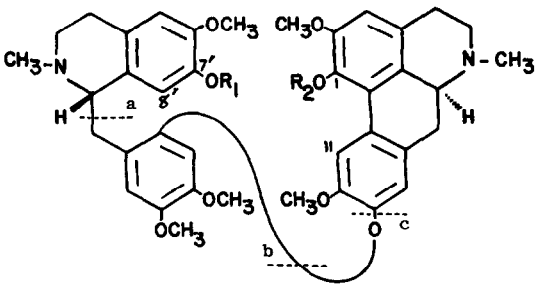
The nmr spectrum of 2 contained singlets for two N-methyl groups at δ2.49 and 2.53, five aromatic methoxyls at δ3.79, 3.82 (2), 3.92 and 3.95, one C-8' proton at δ6.40, five other aromatic protons at δ6.51, 6.57 (3) and 6.78, and a C-11 proton at δ8.18. The most salient features of this spectrum were (a) the downfield position (δ6.40) of the C-8' proton signal as also observed for thalmelatine (5) (δ6.40), but not for thalicarpine (3) (δ6.25) or thalictropine (1) (δ6.20), and (b) the absence of a high field (δ3.58) singlet resonance characteristic of the C-7' methoxyl in thalicarpine (3), thalictropine (1), and other C-7' methoxylated aporphine-benzylisoquinolines.[7]

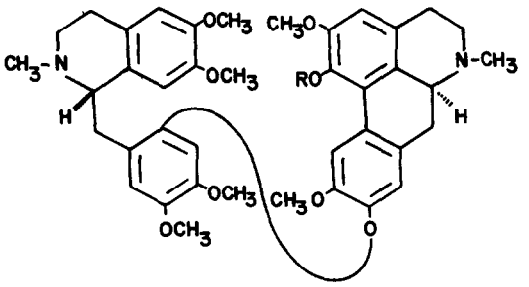
Thalictrogamine (2) was even more susceptible to aerial oxidation than 1, both alkaloids tending to turn green upon standing. The mass spectrum of thalictrogamine diacetate, 6, $C_{43}H_{48}O_{10}N_2$ mp 147-148° (Et_2O), m/e 752 (M^+), 518 (M - a), 368 (M - b), and 234 (a, base), further confirmed the relative locations of the phenolic functions in the alkaloid, i.e. one on the isoquinoline B ring, and the other on the aporphine moiety.

The nmr spectrum of 6 contained, in addition to singlets at δ2.19 and 2.34 for the acetate methyl groups, a singlet at δ6.43 due to the C-8' proton and consistent with the downfield shift observed for aromatic protons ortho to acetate functions,[8] and a singlet at δ7.60 due to the C-11 proton thus confirming the presence of a phenolic function at C-1 in the dimer 2. The low-field aromatic proton at δ6.78 in thalictrogamine (2) was also shifted to slightly higher field, δ6.64, in the diacetate 6.

Diazomethane O-methylation of thalictrogamine (2) afforded thalictropine (1) and thalicarpine (3).[9] Samples of thalicarpine and O,O-dimethylthalictrogamine showed identical tlc R_f values, uv, ir and mass spectra, and ord curves. O-Methylthalictrogamine was identical with thalictropine, thus establishing the absolute configuration of 1 and 2

Space-filling molecular models indicate that for aporphine-benzylisoquinoline dimers of the thalicarpine series, the presence of a C-7' phenolic group results in a conformational change in the molecule due to hydrogen bonding of the hydroxyl hydrogen with such electron-rich centers as the C-1 oxygen (see expression 7) or the aporphine nitrogen (as in 8). The net result is that





1 $R_1 = CH_3$, $R_2 = H$

2. $R_1 = R_2 = H$

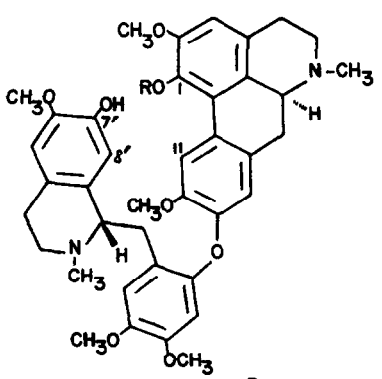
4. $R_1 = CH_3$, $R_2 = CH_3CO$

6. $R_1 = R_2 = CH_3CO$

3 $R = CH_3$

5 $R = H$

the C-8' aromatic proton in the nmr spectrum will be located further downfield, near δ6 4 rather than in the more usual δ6.2 range. It follows that C-8' aromatic proton absorption near δ6.4 is diagnostic of the presence of a C-7' hydroxyl group Furthermore, O-acetylation removes this capability for hydrogen bonding, and the configuration is altered such that the C-8' proton is again shielded as in thalicarpine (3) and thalictropine (1).



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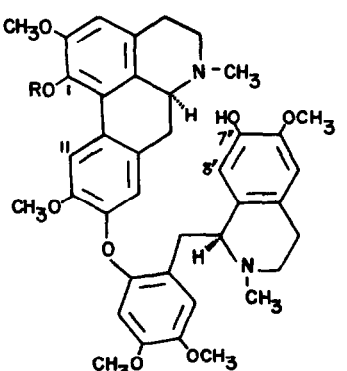

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1 This work was supported by research grant HF-12971 from the National Institutes of Health Elemental analyses were by high resolution mass spectroscopy.

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9. Thalicarpine was isolated in this laboratory from T. polygamum. The plant was collected in the immediate vicinity of University Park, Pa.