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THALISTYLINE, A HYPOTENSIVE MONOQUATERNARY BISBENZYLISOQUINOLINE ALKALOID FROM *THALICTRUM*[1]

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The quaternary alkaloid fraction, as well as the chloroform-soluble tertiary alkaloid fraction, of *Thalictrum longistylum* D.C. and *T. podocarpum* Humb., roots from Colombia, South America, yielded after column chromatography on silicic acid and alumina, and precipitation from chloroform-diethyl ether, thalistyline chloride (**1**, X = Cl), a monoquaternary bisbenzyltetrahydroisoquinoline alkaloid. The alkaloid exhibited very strong hypotensive activity at 0.1 mg/kg in normotensive dog and rabbit.[2]

Thalistyline chloride (**1**, X = Cl^-), mp 150-153°; $[\alpha]_D^{25}$ +146° (c = 0.1, MeOH); uv (MeOH) λ_{max} 283 nm (log ϵ 3.84), 276 (3.86); showed a molecular ion at *m/e* 697.3513 (0.8%) corresponding to $C_{41}H_{49}N_2O_8$ (calc'd 697.3449) and two major fragment ions, *a* at *m/e* 236.1130 (100%), $C_{13}H_{18}NO_3$ (calc'd 236.1287) and *b* at *m/e* 220.0855 (88%), $C_{12}H_{14}NO_3$ (calc'd 220.0974). The 60 MHz proton NMR spectrum ($CDCl_3$, TMS) showed one tertiary N-methyl peak at δ 2.48, two quaternary N-methyls at δ 3.45, five O-methyls at δ 3.63, 3.77, 3.80 (double intensity) and 3.85, a methylenedioxy at δ 5.89 (confirmed by a positive Labat and chromatropic acid tests) and nine aromatic protons two of which were at δ 5.70 and 5.77 for H-8 and H-8'. An AA'BB' quartet (*J* 8 Hz) was located at δ 6.63 and 6.98. Crystalline thalistyline iodide (**1**, X = $I^{\ominus}$), mp 220-223° (d) and thalistyline methodiiodide, mp 266-268° (d) salts were prepared. The latter compound showed NMR peaks at δ (CF_3COOH, TMS) 3.27 and 3.53 for two quaternary N-methyls each and five methoxyls at δ 3.63, 3.73, 3.98, 4.03, and 4.06.

Sodium-liquid ammonia cleavage of thalistyline formed an optically inactive (by CD) non-phenolic base **2**, an oil with formula $C_{22}H_{31}NO_4$, molecular ion at *m/e* 373 (28%), base peak at *m/e* 58 ($Me_2\overset{+}{N} = \overset{\cdot}{C}H_2$), and fragments *c* and *d* at *m/e* 252 (6%) and 121 (36%), respectively. The proton NMR spectrum ($CDCl_3$) showed an AA'BB' quartet pattern centered at δ 7.10 and 6.81, four methoxyls at 3.89, 3.85, and 3.78 (double intensity), four benzylic protons as a singlet at

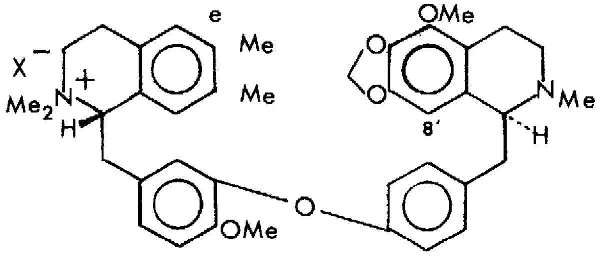
δ 2.83, two N-methyls at 2.33 and an A_2B_2 pattern between 2.2-3.0. In addition, two single peaks at δ 6.43 and 6.33 in a ratio of 2:1 but together integrating for one proton were assigned to the aromatic hydrogen of the pentasubstituted ring and reflected the presence of two conformers. The dimethylaminoethyl portion had its origin in the quaternary nitrogen center of thalistyline.

The second major sodium-ammonia cleavage product was the phenolic base **3**, mp 221-222° with molecular ion at *m/e* 299 (0.3%) for formula $C_{18}H_{21}NO_3$ and fragment *e* at *m/e* 192 (100%) and *f* at *m/e* 107 (11%), respectively. The proton NMR (Pyr-d_5) spectrum had peaks at δ 2.52 (N-methyl), 3.63 (O-methyl), 6.33 and 6.73 (*J* 2.5 Hz) for meta positioned aromatic protons as well as a four proton AA'BB' pattern at δ 7.10 and 7.30 with apparent coupling of *J*~8 Hz. The CD spectrum showed three Cotton effect maxima, $[\theta]_{287}-3,300$, $[\theta]_{272}+2,200$ and $[\theta]_{230}+38,800$ supporting *S* absolute configuration. Methylation of **3** by diazomethane formed base **4** with NMR ($CDCl_3$) exhibiting three O-methyl groups at δ 3.56 and 3.76 (double intensity). Comparison of **4** with the nonphenolic product formed from hernandezine with established stereochemistry by sodium and ammonia showed them to be identical.[3]

Since the reduction products **2** and **3** account for the original five methoxyl groups of thalistyline (**1**) and it is well established that ether cleavage can occur in highly oxygenated benzene rings, the methylenedioxy group had been lost in part, generating the phenolic group of the tetrahydroisoquinoline portion of compound **3**. The other phenolic group resulted from the cleavage of the diphenyl ether. Products of potassium permanganate oxidation of thalistyline established the location of the methylenedioxy group and the diphenyl ether as in **1**; one was the isoquinolone (**5**), mp 136-137°, identical in physical properties to that reported for an oxidation product of thalmelatidine[4], confirmed by synthesis and also isolated as the natural product thalfavine.[5] Another was the dicarboxylic acid **6** which was characterized as the dimethyl ester **7** and found to be identical to an authentic sample prepared by synthesis.

The CD curve of thalistyline chloride (**1**, X = Cl) showed two positive maxima, $[\theta]_{284}+12,500$ and $[\theta]_{225}+105,000$ as did thalistyline methodiiodide, $[\theta]_{280}+13,500$ and $[\theta]_{226}+134,000$. These curves are similar to that for a related alkaloid, thalibrine[6] with established *S,S*-configuration and opposite to that for dauricine and dauricine dimethiodide with *R,R*-configuration and with maxima at $[\theta]_{285}-14,800$ and $[\theta]_{225}-70,200$, and $[\theta]_{280}-15,400$ and $[\theta]_{226}-131,000$, respectively.

Careful examination of the quaternary and chloroform-soluble tertiary alkaloid fraction of both *Thalictrum* species yielded minor quantities of thalistyline metho salt isolated as the diiodide identical with that produced from thalistyline and methyl iodide. In addition, the tertiary alkaloid fraction revealed also in minor amounts the nonquaternary analogue of thalistyline, N-desmethylthalistyline, isolated as an amorphous solid and characterized by conversion to thalistlyine methodiiodide. The three alkaloids of this report represent the first examples of bisbenzylisoquinoline alkaloids in which both isoquinoline portions contain a trioxygenated benzene ring.



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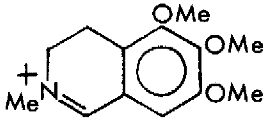
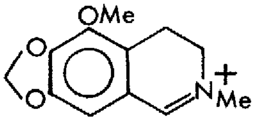


a



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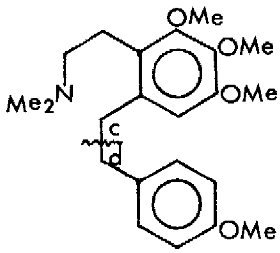

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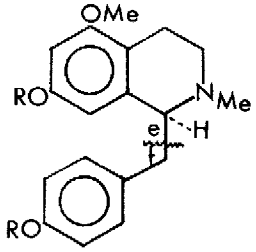

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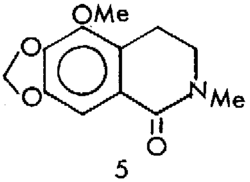
4 R=Me



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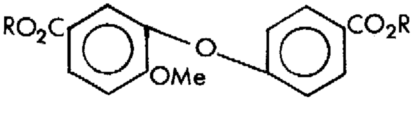

6 R=H
7 R=Me

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2. Pharmacological results will be reported elsewhere at a later date.

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