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ALKALOIDS OF THALICTRUM. XIX.¹⁾

REVOLUTOPINE AND THALIPINE, NEW APORPHINE-BENZYLISOQUINOLINE DIMERS FROM THALICTRUM REVOLUTUM

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Revolutopine and thalipine, new alkaloids from the tops of Thalictrum revolutum have been assigned the aporphine-benzylisoquinoline structures 1 and 2, on the basis of physical and chemical evidence.

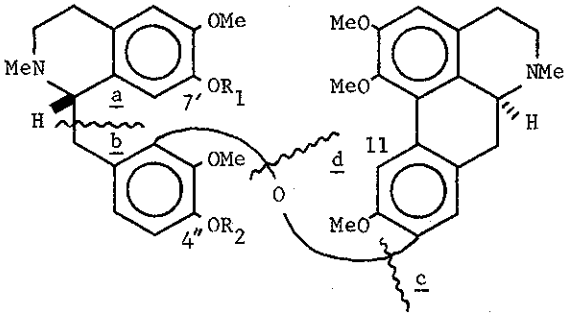
In an earlier study,[2] the roots of Thalictrum revolutum DC. had yielded thalicarpine (3). Recently, an analysis of the above-ground portion of this plant gave from the tertiary nonphenolic fraction seven alkaloids, and from the tertiary phenolic fraction eleven alkaloids of which two, revolutopine (1) and thalipine (2)[3] are new aporphine-benzylisoquinoline dimers present in very minor amounts.[4]

Revolutopine (1) was isolated as an amorphous solid, $[\alpha]_D^{25}$ +126° (c, 0.1 MeOH), uv λ_{max}^{MeOH} nm (log ϵ): 281 (4.40), 302 (4.24) and 314 shld

(4.15) with a bathochromic shift and hyperchromic effect under strong alkaline conditions to 284 (4.39) and 300 (4.39); and ir (KBr) band at ν_{max} 3410 cm^{-1} (-OH) but no absorption in the carbonyl region. The nmr spectrum (60 MHz, $CDCl_3$, TMS, δ in ppm) showed two N-methyl peaks at δ 2.29 and 2.43, five aromatic O-methyls at δ 3.65, 3.75, 3.83, 3.86 and 3.96, seven aromatic protons as five singlets at δ 6.33, 6.46 (2H), 6.56, 6.67 (2H), and 8.16 (characteristic of H-11 in aporphine),$^{5)}$ and a broad two-proton singlet at δ 5.23 (D_2O exchanged) for the phenolic hydroxyls.

The spectral data pointed to revolutopine (**1**) as a diphenolic aporphine-benzylisoquinoline alkaloid with one phenolic group at C-7' since the characteristic C-7' O-methyl at δ~3.58 was lacking and the H-8' proton was present at δ 6.33, a position downfield from that (δ~6.23) expected for a proton *ortho*- to a methoxy.$^{6)}$ In addition, the ms of revolutopine (**1**) showed a peak for fragment *a* (R_1 = H) at *m/e* 192 (100%), and for *b* (R_2 = H) at *m/e* 476. The molecular ion was observed at *m/e* 668 (1.5%) in agreement with the adopted formula, $C_{39}H_{44}N_2O_8$.

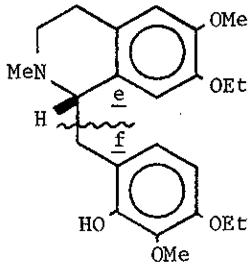
Treatment of revolutopine (**1**) with excess diazomethane produced the amorphous base **4** containing seven O-methyl groups, as the nmr spectrum ($CDCl_3$) exhibited peaks at δ 3.59, 3.67, 3.79, 3.81, 3.88 (double intensity) and 3.96. Comparison of the ir and nmr spectra, and the tlc mobility of **4** with O-methyl fetidine$^{7)}$ showed them to be identical, thereby establishing the carbon skeleton and the oxygenation pattern for revolutopine (**1**). This alkaloid is only the second example of a fetidine-type aporphine-benzylisoquinoline dimer containing the 2,3,4-trioxygenated benzyl unit.$^{8)}$ The configuration was determined as *S,S* on the basis that its cd spectrum (MeOH) showed maxima at $[\theta]_{305}$ -4,700, $[\theta]_{275}$ -5,300 and $[\theta]_{240}$ +43,000 in



1, $R_1 = R_2 = H$

4, $R_1 = R_2 = Me$

5, $R_1 = R_2 = Et$



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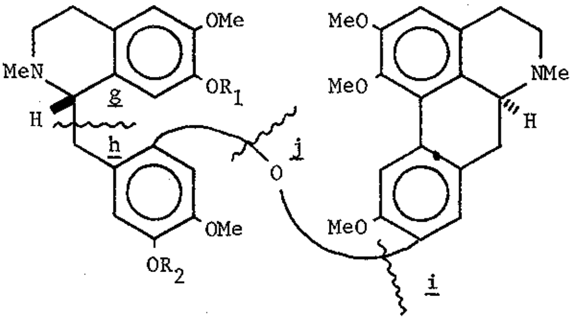

2, $R_1 = R_2 = H$

3, $R_1 = R_2 = Me$

7, $R_1 = H$, $R_2 = Me$

8, $R_1 = Me$, $R_2 = H$

agreement with those for (+)-fetidine (structure 4, with C-1 phenolic) at $[\theta]_{305}$ -24,500, $[\theta]_{272}$ -14,200 and $[\theta]_{234}$ +148,000.

The second phenolic group of revolutopine (1) was placed in the benzyl unit at C-4" since in the mass spectrum peaks at m/e 324 (9%, fragment c) and 340 (9%, fragment d) require that the aporphine unit contain three O-methyls, and a negative Gibbs' indophenol test[9)] demands a para-substituted phenol. Confirmation of this assignment was obtained from the di-O-ethyl derivative 5, prepared from revolutopine (1) and diazoethane, which exhibited ms peaks at m/e 220 (100%) for fragment a (R_1 = Et), 504 (4) for b (R_2 = Et), 324 (1) for c, 340 (1) for d and M^+ at 724 (0.7). Sodium-ammonia cleavage of the diethyl derivative 5 produced the phenolic base 6, $[\alpha]_D^{25}$ -116° (c, 0.2 MeOH), with nmr (90 MHz, $CDCl_3$) peaks for two ethyl groups; the methyl triplets were centered at δ 1.36 and 1.47 (J = 7Hz) and the ethylene quartet of double intensity was located at δ 4.08 (J = 7Hz). In addition, there appeared an N-methyl at δ 2.59, two O-methyls at δ 3.78 and 3.80, an AB quartet (J = 8Hz) centered at δ 6.20 and 6.54 for the two aromatic ortho-protons, and two other aromatic protons as singlets at δ 6.48 and 6.59. The ms of base 6 showed a peak at m/e 401 (0.8%) corresponding to the accepted formula $C_{23}H_{31}NO_5$, base peak at m/e 220 for fragment e, and fragment f at m/e 181 (1.3%). Base 6 gave a positive Gibbs' indophenol test.[9)]

Thalipine (2) was isolated as an amorphous solid, $[\alpha]_D^{25}$ +141° (c, 0.19 MeOH), uv λ_{max}^{MeOH} nm (log ε): 282 (4.49), 303 shld (4.34) and 316 shld (4.19) with a hyperchromic change in strong base to 282 (4.51) and 303 (4.49); ir ($CHCl_3$) ν_{max} 3550 cm^{-1} for unassociated hydroxyl; nmr (90 MHz, $CDCl_3$) peaks for two N-methyls at δ 2.34 and 2.47, five O-methyls at δ 3.68, 3.79 (double intensity), 3.88 and 3.96, and seven aromatic protons as five singlets at δ 6.44, 6.49 (2H), 6.59 (2H), 6.81 and 8.17; and ms peaks at *m/e* 668 (0.9%, M$^+$), 192 (100, *g* for R_1 = H), 476 (3, *h* for R_2 = H), 324 (10, *i*) and 340 (38, *j*). The physical data suggested a phenolic aporphine-benzylisoquinoline dimer and methylation of thalipine (**2**) with diazomethane afforded a heptamethoxy product identical with thalicarpine (**3**) when compared directly with an authentic sample. The cd spectrum of thalipine showed the same pattern as thalicarpine$^{10)}$ with maxima at $[\theta]_{302}$ -14,800, $[\theta]_{271}$ -19,000 and $[\theta]_{235}$ +214,000. Thus, thalipine is a diphenolic analogue of thalicarpine with both phenolic groups in the benzylisoquinoline part.

Partial methylation of thalipine (**2**) with diazomethane formed two monomethylated products that were separated by careful adsorption chromatography and were shown to be thalmelatine (**7**)$^{11)}$ and pennsylvanine (**8**)$^{12)}$ by direct comparison of spectra (ir and nmr) and tlc mobility with those of authentic samples. Thalipine (**2**) is the third known diphenolic thalicarpine-type alkaloid; the other two are thalictrogamine$^{6a)}$ and pennsylvanamine.$^{12)}$

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