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THALIBRUNIMINE, A NEW IMINOBISBENZYLISOQUINOLINE ALKALOID; CONFORMERS OF THALSIMINE[1]

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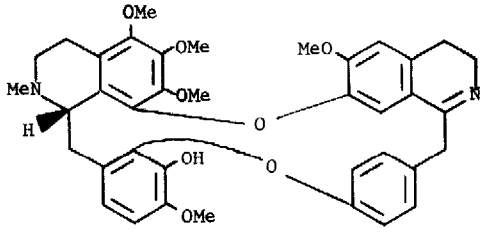
Countercurrent separation of the tertiary bases of Thalictrum rochebrunianum[2,3] has yielded a number of fractions showing cytotoxic activity in the KB cell system. We now report the isolation from one of these fractions of thalibrunimine (1), a new member of the small imine sub-group of the bisbenzylisoquinoline alkaloids.

Thalibrunimine, $C_{38}H_{40}N_2O_8$, crystallized from methanol as needles, mp 198-200°, $[\alpha]_D$ +28° (c = 0.19 $CHCl_3$); uv λ_{max}^{EtOH} (ε) 241 sh, nm (30,000), 283 (10,400) and 300 sh (8,200). Its nmr spectrum (C_5D_5N) indicated the presence of five methoxyls (δ 3.88, 3.83, 3.79, 3.55 and 3.21) and only one N-methyl (δ 2.38). In addition, one unusually low-field benzylic methylene (s, δ 4.40) and eight aromatic protons (m, 6.42-7.58) were observed. The most significant ions in the mass spectrum of thalibrunimine are the molecular ion (m/e 652, 100%) and the M-1 ion (m/e 651, 85%), in accord with an iminobisbenzylisoquinoline structure.[4]

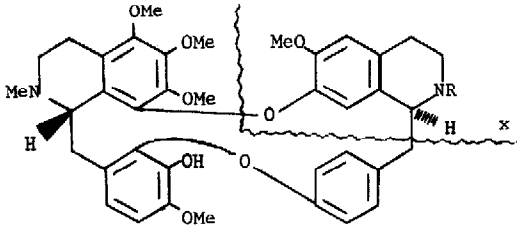
Sodium borohydride reduction of thalibrunimine gave a very difficultly separable 4:1 mixture of two dihydro derivatives, from which only the major constituent was obtained in a pure state. This compound, $[\alpha]_D$ +100° ($CHCl_3$), M^+ = 654, was assigned the structure of 2'-N-northalibrunine (2); N-methylation (formalin-borohydride) yielded crystalline thalibrunine (3) identical (mmp, ir, ms, nmr) with the authentic alkaloid.[2] As expected, the nmr ($CDCl_3$) of northalibrunine showed the presence of five methoxyls (δ 3.88, 3.81, 3.76, 3.35 and 3.23) but only one N-methyl (δ 2.48).

A comparison of the mass spectra of thalibrunine and northalibrunine clearly indicated that the ring-D nitrogen of the latter is the unmethylated nitrogen. Of particular significance

are the peaks shown by the nor-base 2 at m/e 477 (22%) and m/e 178 (12%), due to the fragments M-x and x + H, respectively.

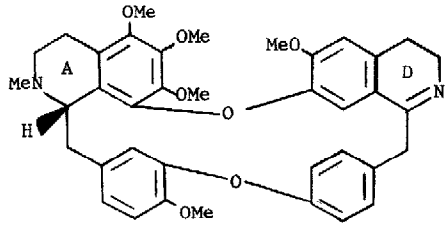


1



2, R = H

3, R = Me



4,

A different alkaloid fraction from T. rochebrunianum afforded a second imine base, $C_{38}H_{40}N_2O_7$, mp 149-150°, $[\alpha]_D$ +22.6° (c = 0.7 $CHCl_3$), identified by its properties as thalsimine (4, lit.[5] mp 140-142°, $[\alpha]_D$ +27.5°). In accord with the literature, 4 could be reduced to a mixture of two dihydro derivatives, one of which gave crystalline hernandezine[2] on N-methylation. The mass spectra of our thalsimine and of its dihydro derivatives indicated no contamination of our material by an isomer of 4 having the imino function in ring A and the N-methyl in ring D. Also, the properties of our thalsimine were unchanged by ptlc, crystallization, or extensive countercurrent purification. Despite these facts, the nmr spectrum of pure thalsimine (C_5D_5N) at room temperature indicates a 1:1 mixture of isomers, showing ten methoxyls (δ 3.93, 3.91, 3.88, 3.83 double intensity, 3.78, 3.63, 3.52, 3.46 and 3.39) and two N-methyls (δ 2.33 and 2.28).[6] These isomers proved to be simply surprisingly stable conformers, since on heating to 95° the above spectrum showed only the normal number of methyl peaks (δ 3.82 double intensity, 3.89, 3.54, 3.47 and 2.29). A similar phenomenon has been observed in the case

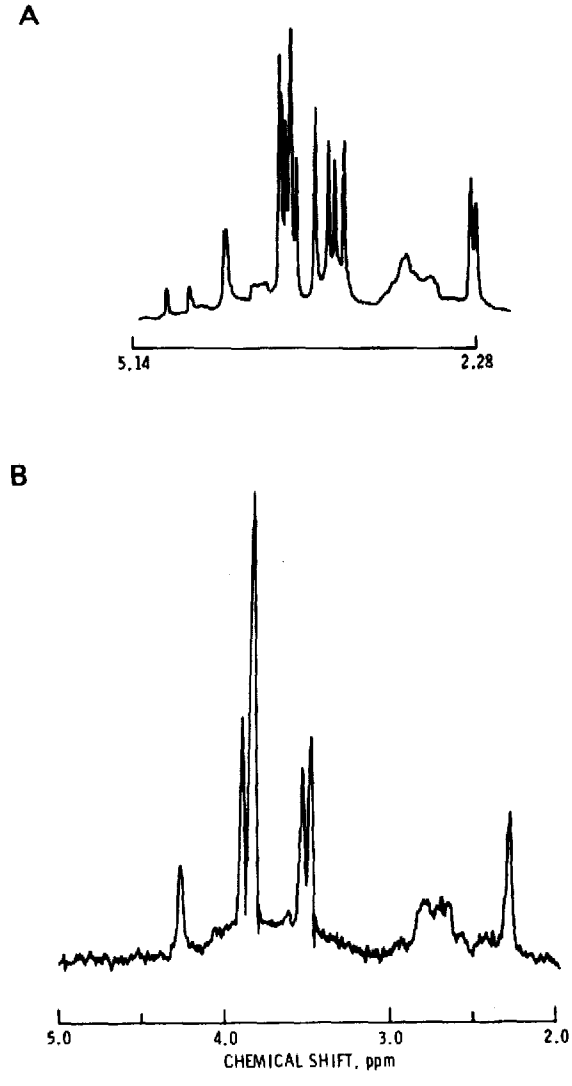


Fig. 1. — NMR spectra of thalsimine in C_5D_5N:

A) At 23° C.

B) At 95° C.

of a related synthetic imino base[7] but, to our knowledge, thalsimine represents the first example of a natural bisbenzylisoquinoline alkaloid which exhibits such a clearly misleading room temperature nmr spectrum due to conformers. We feel that other workers in the field should be alerted to this situation, which can otherwise lead to much lost effort in attempts to separate non-existent structural isomers.

References

1. This work was supported by National Institutes of Health Grants (CA 11445 and HL 07502); molecular compositions were determined by high resolution mass spectrometry by Dr. C. Costello (Massachusetts Institute of Technology). Nmr spectra were determined using a Jeol 100 MHz spectrometer. One of us (J. M. S.) thanks the Fundación Juan March for a supporting fellowship.
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6. The anomaly in the N-methyl signal of thalsimine in $CDCl_3$ solution has been observed though not explained by earlier workers, who described it as appearing "in the form of a 3 proton doublet at 7.80 ppm (J = 10.0 Hz)"; methoxyls were reported only "in a narrow region at 6.16-6.26 ppm". See Z. F. Ismailov, M. R. Yagudaev, S. Yu. Yunusov, Khim. Prirod. Soedinenii, 4, 262 (1968); [C. A., 70, 58083 r (1969)].
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