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THALIHAZINE, A NEW PHENANTHRENE ALKALOID

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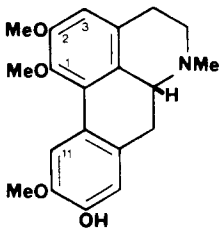
Thalictrum species (Ranunculaceae) are well known to be an abundant source of isoquinoline alkaloids. We became interested, therefore, in studying the alkaloidal content of the small herb *Thalictrum hazarica* R.R.S., which had not previously been investigated. The plant was collected in the Northwest Frontier Province of Pakistan and may be readily recognized because of its relatively large leaves.

Three alkaloids were present in sufficient amounts for characterization purposes. These proved to be the known aporphine (+)-*N*-methyllaurotetanine [**1**] (1), the previously reported phenanthrene thalicthuberine [**2**] (1), and the new phenanthrene thalihazine [**3**].



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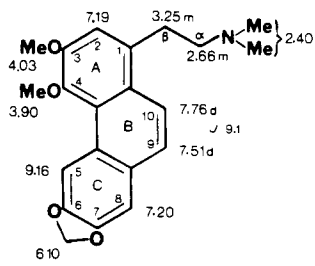

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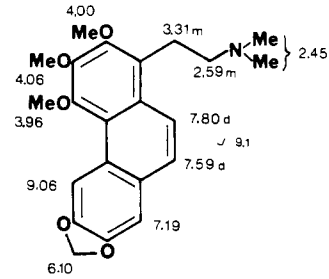

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The alkaloid thalicthuberine had been originally characterized in the 1950s, and no mass or nmr spectral data had been reported (1). In order to ascertain the disposition of the substituents for the material we had isolated and believed to be thalicthuberine, a complete nmr nOe study was carried out. The results clearly indicated that ring A bears the two methoxyl substituents, while the methylenedioxy was attached to the bottom ring. Significant reciprocating nOes could be observed between the C-β methylene protons of the side chain (δ 3.25) and H-2 (δ 7.19) on the one hand, and H-10 (δ 7.76) on the other. Additionally, strong reciprocating nOes were detected between H-8 (δ 7.20) and H-9 (δ 7.51) (see Experimental section). It follows that our alkaloid corresponds, indeed, to thalicthuberine.

The new phenanthrene alkaloid thalihazine [**3**] presented in its mass spectrum the characteristic base peak *m/z* 58 $[CH_2N(CH_3)_2]^+$. Loss of this dimethylaminomethylene fragment from the molecular ion, *m/z* 383 (7%), led to the formation of ion *m/z* 325 (6%).

The nmr spectrum of thalihazine [**3**] is close to that of thalicthuberine but with the difference of one additional methoxyl and one less aromatic proton. Nmr nOe studies allowed us to make complete assignments for the three methoxyl substituents. It should be noted that the most downfield methoxyl signal belongs to that methoxyl lying between the other two. Interestingly, aporphines bearing three methoxyls on ring A exhibit exactly the same nmr spectral pattern (1).

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Another point of coincidence between the nmr spectra of thalihazine [**3**] and aporphines concerns the chemical shift of H-5. Whenever a methoxyl substituent is present at C-3 of an aporphine, the H-11 signal undergoes an upfield shift of $\simeq 0.1$ ppm (2). Correspondingly, in the thalihazine case, H-5 appears slightly upfield at δ 9.06, while this proton is found at δ 9.16 in the case of thalicthuberine, which does not bear a methoxyl at C-2.

The present finding of the new phenanthrene alkaloid thalihazine, which is unsubstituted at C-5, is in accord with the observation that aporphines unsubstituted at C-11 are generally more likely to undergo Hofmann β-elimination of their *N*-metho salts than the corresponding aporphine salts substituted at C-11 (3). Additionally, it has already been noted that the genus *Thalictrum* has a particular tendency for producing aporphinoids trioxygenated on ring A, and thalihazine [**3**] follows this trend (4).

EXPERIMENTAL

GENERAL.—Column chromatography was on Si gel 60 (70-230 mesh). Tlc was on Merck F-254 Si gel glass plates.

PLANT COLLECTION AND EXTRACTION.—*T. hazarica* (2.3 kg, dry weight, whole plant) was collected in the Kaghan Valley of the Northwest Frontier Province of Pakistan during the month of August 1984. The plant was identified by Dr. E. Nasir of the National Herbarium in Islamabad, where a specimen was deposited. The powdered plant was extracted with cold EtOH. The solvent was evaporated without excessive heat. The residue was extracted with 5% HCl. The acidic layer was separated and basified with NH_4OH and then extracted with $CHCl_3$. Evaporation of the organic solvent left a dark residue which was placed on a Si gel column (320 g). Elution was with $CHCl_3$ gradually enriched with MeOH. Final purification was by tlc using the system C_6H_6-$CHCl_3$-MeOH-iPrOH-NH_4OH (50:50:10:1:1). Alkaloids obtained were thalihazine (21 mg), thalicthuberine (14 mg), and (+)-*N*-methyllaurotetanine (6 mg). All were amorphous. (+)-*N*-Methyllaurotetanine was identified by comparison with literature data (1).

THALICTHUBERINE [**2**]—Ms *m/z* 353 (M^+, 2), 326 (0.3), 295 (1), 280 (0.2), 58 (100); principal nmr nOe's are MeO-3 to H-2 (17%), H-2 to MeO-3 (13%), H-2 to H-β (1%), H-β to H-2 (17%), H-β to H-10 (21%), H-10 to H-β (9%), H-9 to H-8 (29%), H-8 to H-9 (14%), MeO-5 to H-4 (8%), MeO-4 to H-5 (22%).

THALIHAZINE [**3**].—$C_{22}H_{25}NO_5$; uv λ max (MeOH) 261, 283, 315, 344 nm (log ϵ 4.30, 3.77, 3.37, 2.90); ms *m/z* 383 (M^+, 7), 325 (5), 310 (1), 295 (2), 280 (1), 267 (3), 58 (100); principal nmr nOe's are MeO-2 to H-β (5%), H-β to MeO-2 (2%), H-β to H-10 (21%), H-10 to H-β (10%), H-α to H-10 (7%), H-10 to H-α (5%), H-9 to H-8 (30%), H-8 to H-9 (16%), H-5 to MeO-4 (10%), MeO-4 to H-5 (19%).

ACKNOWLEDGMENTS

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