THREE NEW BRIDGED ISOQUINOLINE ALKALOIDS[1]

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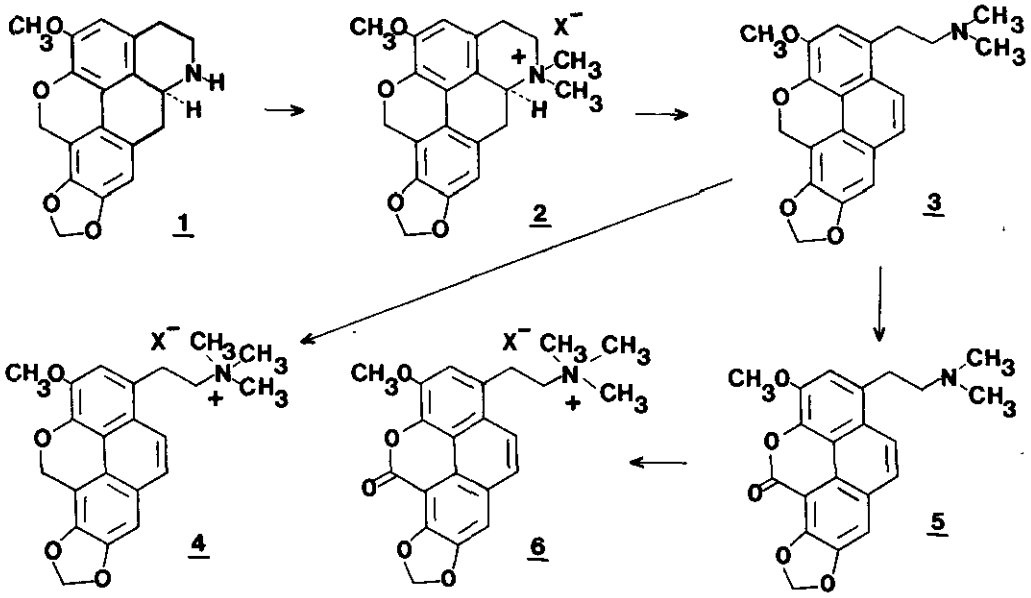
Bisnorthalphenine (1), thaliglucine methochloride (4), and thaliglucinone methochloride (6), have been obtained from Thalictrum polygamum Muhl. (Ranunculaceae).

One of the more interesting aporphines found in Thalictrum polygamum Muhl. (Ranunculaceae) is thalphenine (2) which, of the more than 100 aporphines known so far,[2] has been the only one to possess the unusual methylenoxy bridge bonding C-1 to C-11.[3] We now wish to describe three relatives of thalphenine, also found in T. polygamum, namely bisnorthalphenine (1), thaliglucine methochloride (4), and thaliglucinone methochloride (6).

Bisnorthalphenine (1), $C_{19}H_{17}NO_4$, mp 124-125° (ether), $[\alpha]_D^{25}$ +81° (c = 1.12, MeOH), HCl salt mp 238° (MeOH-ether), exhibits λ_{max}^{EtOH} 220, 232sh, 279, 289, 316 and 325sh nm (log ε 4.30, 4.27, 3.88, 3.90, 3.80 and 3.74). The nmr spectrum (Table) is very similar to that reported for thalphenine.[3] The mass spectrum shows intense ions m/e 323 (M^+), 322 (M^+ - H) (base), and 294 (M^+ - CH_2=NH). N-Methylation with MeI furnished (+)-thalphenine iodide, identical with the natural product in terms of uv, ir, nmr and mass spectra, tlc, and mixture mp. Bisnorthalphenine is, therefore, the second aporphine recognized to incorporate a methylenoxy bridge.

Thaliglucine methochloride (4), $C_{22}H_{24}NO_4Cl$, mp 249-250° (MeOH-ether), shows λ_{max}^{EtOH} 233sh, 260, 272, 282, 295sh, 326, 340, 359 and 370 nm (log ε 4.22, 4.42, 4.46, 4.45, 4.23, 3.82, 3.71, 3.32 and 3.32). The mass spectrum shows

a base peak at m/e 73 ($C_4H_{11}N$) instead of the m/e 58 (C_3H_8N) peak shown by the free base thaliglucine (3). The nmr spectrum of 4 (Table) is very similar to that of 3, except for the presence of a signal for the additional N-methyl group.[3,4] Quaternization of an authentic sample of thaliglucine (3)[3,4] with MeI, followed by resin anion exchange to chloride gave rise to 4, identical in all respects with the natural product.



The third new alkaloid, thaliglucinone methochloride (6), $C_{22}H_{22}NO_5Cl$, yellow crystals mp 274-275° (MeOH), exhibited ν_{max} 1735 cm^{-1}, λ_{max}^{EtOH} 225sh, 237, 257sh, 267, 288, 313, 333sh and 400 nm (log ε 4.15, 4.26, 4.36, 4.50, 3.85, 3.99, 3.71 and 3.61). Treatment of an authentic sample of thaliglucinone (5)[3,4] with MeI followed by anion exchange to chloride yielded material indistinguishable from 6.

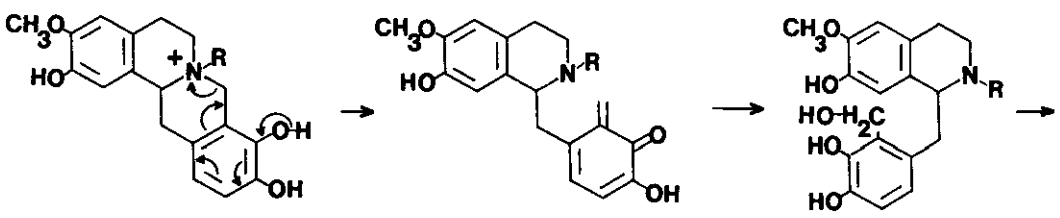
TABLE

Main NMR Resonances (δ) for Bridged Isoquinoline Alkaloids

Compound	N-CH_3	O-CH_3	Ar-CH_2-O	O-CH_2-O	C-3 H	C-8 H	C-9,10 H
Bisnorthalphenine (1)		3.88 s (3H)	5.14 ABq J = 14 Hz (2H)	6.00 s (2H)	6.55 s (1H)	6.63 s (1H)	
Thaliglucine methochloride (4)	3.27 s (9H)	3.99 s (3H)	5.53 s (2H)	6.08 s (2H)	7.08 s (1H)	7.15 s (1H)	7.47 ABq J = 9 Hz (2H)
Thaliglucinone methochloride (6)	3.32 s (9H)	4.10 s (3H)	- -	6.34 s (2H)	7.25 s (1H)	7.36 s (1H)	7.65 ABq J = 9 Hz (2H)

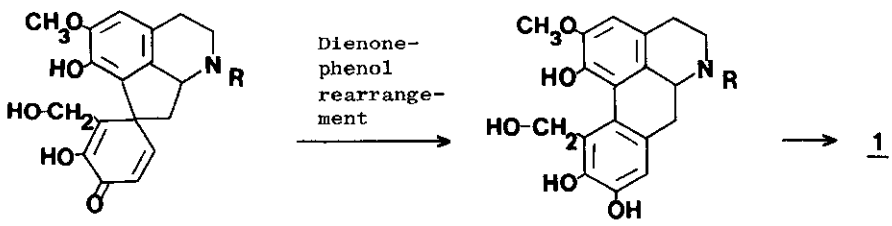
The occurrence of alkaloids 1-6 in T. polygamum leads us to speculate that bisnorthalphenine (1) is probably the precursor of this bridged series, since O-demethylation does not appear to be a favored process among the isoquinoline alkaloids.[6,7] The biogenetic sequence envisioned would then be 1→2→3→4 and 3→5→6. Two possible mechanistic sequences for the formation of the methylenoxy bridge are presented below, assuming an ionic mechanism. Scheme A incorporates a retrobenzylisoquinoline species while Scheme B involves enzymic oxidation of a methoxyl group to an oxonium intermediate. However, no firm conclusion concerning the mechanism of formation of the methylenoxy bridge can be reached prior to in vivo studies using labeled precursors.

Scheme A

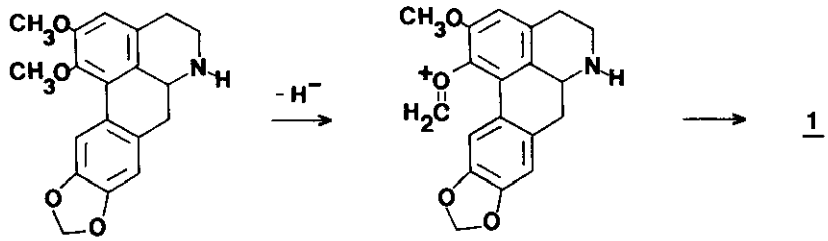


A protoberberine salt

A retrobenzylisoquinoline



Scheme B



References

1. This research was supported by grant CA-11450 from the National Institutes of Health. All compounds gave satisfactory analyses by high resolution mass spectroscopy and/or elemental analysis. NMR spectra at 60 MHz were obtained in $CDCl_3$ with TMS as internal standard.

2. For a recent review on the aporphines, see M. Shamma and S.S. Salgar, Specialist Periodical Reports, The Alkaloids, Vol. 4, The Chemical Society (London), 1974, in press.

3. M. Shamma, J.L. Moniot, S.Y. Yao and J.A. Stanko, Chem. Commun., 408 (1972).

4. N.M. Mollov, Le Nyat Thuan and P.P. Panov, Compt. rend. Acad. Bulg. Sci., 24, 1047 (1971).

5. (a) Thaliglucinone was obtained from T. polygamum in this Laboratory, S.Y. Yao, Ph.D. Thesis, The Pennsylvania State University (1972); Diss. Abstr. Int. B, 33, 3012 (1972); as well as at The Ohio State University, S.A. Gharbo, J.L. Beal, R.W. Doskotch and L.A. Mitscher, Lloydia, 36, 349 (1973).

(b) Thaliglucinone is also found in T. rugosum Ait., see Ref. 4 above.

6. For a discussion of the biogenesis of the isoquinoline alkaloids, see M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York, N.Y. (1972).

7. N-Demethylation is known, however, in the nicotine series, see E. Leete, Accounts Chem. Res., 4, 100 (1971).

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