Two Isoquinoline Alkaloids with a Methylenoxy-bridge

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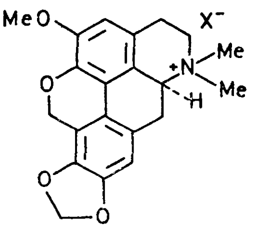
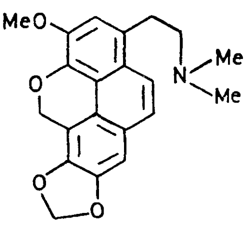
Summary Thalphenine (**1**) and thalphenine methine (**2**) have been isolated from *Thalictrum polygamum* Muhl., interrelated chemically, and their structures confirmed by *X*-ray crystallographic analysis of thalphenine iodide.

From the quaternary alkaloid fraction of *Thalictrum polygamum* Muhl. (Ranunculaceae) we have isolated the non-phenolic salt thalphenine (**1**) chloride, $C_{21}H_{22}ClNO_4$, m.p. 185—186° (MeOH–acetone), $[\alpha]_D$ +69° (EtOH, *c* 1·3), the first aporphine alkaloid with a methylenoxy-bridge.



(1)



(2)

The u.v. spectrum of thalphenine chloride, λ_{max} (EtOH) 221, 230sh, 280sh, 288, 317, and 328sh nm (log ε 4·32, 4·21, 3·69, 3·83, 3·97, and 3·87) resembles somewhat that of aporphines.[1] The main features in the 60 MHz n.m.r. spectrum [in $(CD_3)_2SO$] were peaks at δ 3·05 (s) and 3·45 (s) (6H, N^+Me_2), 3·76 (s, 3H, OMe), 5·00 (ABq, 2H, CH_2O, J_{gem} 14 i.c.s. 28 Hz), 6·02 (d, 2H, $O{\cdot}CH_2{\cdot}O$, J_{gem} 2·5 Hz), and 6·82 (s) and 6·79 p.p.m. (s, 2H, 3- and 10-H). The absence of any 11-H peak around δ 8·00 p.p.m. indicated that this position is substituted. The mass spectrum showed intense peaks at *m/e* 351 $(M-1)^+$, 293 $(M-1-CH_2NMe_2)^+$, and 250 (293 − Me − CO).†

Treatment of the alkaloid chloride with hot methanolic KOH afforded optically inactive thalphenine methine (**2**), $C_{21}H_{21}O_4N$, m.p. 122° (from EtOH), λ_{max} (EtOH) 221, 250, 260, 272sh, 287sh, 317, 350, and 370 nm (log ε 4·26, 4·41, 4·36, 4·13, 3·81, 3·36, and 3·36); δ (100 MHz; $CDCl_3$) 2·37 (s, 6H, NMe_2), 4·00 (s, 3H, OMe), 6·06 (s, 2H, $O{\cdot}CH_2{\cdot}O$) 7·07 (s) and 7·11 (s) (2H, ArH), and 7·59 (ABq, 2H, $J_{9,10}$ 9, i.c.s. 19·5 Hz). The most significant n.m.r. absorption was a singlet at δ 5·56 p.p.m. (methylenoxy-bridge). Double irradiation at δ 4·00 p.p.m. resulted in an 18% NOE of the δ 7·11 aromatic proton, thus allowing unambiguous assignment of this aromatic singlet to 2-H. The mass spectrum of (**2**) was identical with that of (**1**).

From the tertiary alkaloid fraction of *T. polygamum* we have obtained as the major base a colourless, crystalline compound, identical in all respects with the methine (**2**), so that (**2**) is also a natural product.[2]

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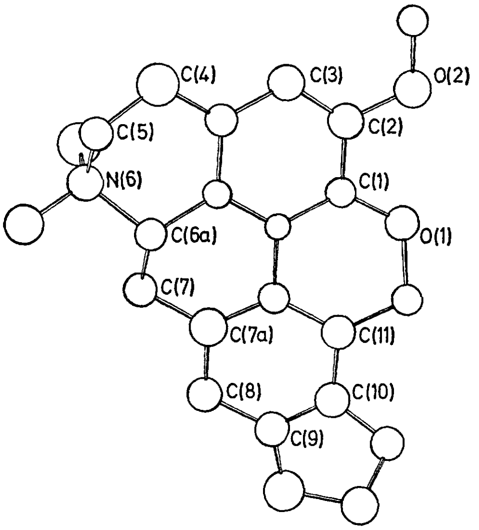
† This spectrum is actually that of the Hofmann elimination product generated thermally from (**1**) in the heated inlet.

The structural assignments for thalphenine (**1**) and thalphenine methine (**2**) were confirmed by a single-crystal X-ray analysis of the pale-yellow plates of thalphenine iodide, m.p. 198—199° (from water–acetone).



FIGURE

Crystal Data: $C_{21}H_{22}IO_4N,2H_2O$; monoclinic, $P2_1$; $a = 8{\cdot}036(20)$, $b = 11{\cdot}473(28)$, $c = 23{\cdot}422(17)$ Å, $\beta = 92{\cdot}62(2)°$; $D_m = 1{\cdot}585$ g cm^{-3}; $D_c = 1{\cdot}586$ for $Z = 4$. Intensity data for 2900 reflections, $(\sin\theta/\lambda)_{\max} = 0{\cdot}54$, were collected on a Syntex computer-controlled diffractometer using Cu-K_α radiation. Of these, 2336 with $I \geqslant 3\sigma(I)$ were corrected for absorption and used in the solution and refinement of the structure. At the present stage of least-squares refinement, with anisotropic temperature factors for the two iodide ions and isotropic parameters for all other atoms, $R = 0{\cdot}07$. A perspective view of one of the molecules of (**1**) in the asymmetric unit is shown in the Figure.[3] The absolute configuration of thalphenine is derived from its positive rotation,[1] and has been confirmed by the anomalous dispersion method.[4] The doubly bridged biphenyl system has a skew angle of 18·1°, significantly less than that of singly bridged biphenyl systems.[5]

The methine base (**2**) must be biogenetically derived from thalphenine (**1**). The origin of the methylenoxy-carbon atom is, however, unclear. It could be derived from a methoxy or a methylenedioxy group or even from formaldehyde, but a more intriguing possibility involves cleavage of the N(7)–C(8) bond of a tetrahydroprotoberberine precursor to form a retrograde tetrahydrobenzylisoquinoline which could eventually lead to thalphenine. Retrograde tetrahydrobenzylisoquinolines have, in fact, been postulated as intermediates in the biogenesis of the isoquinoline alkaloids (—)-orientalidine and (—)-mecambridine.[6]

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[1] (a) M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, 1964, **64**, 57; (b) M. Shamma in "The Alkaloids," ed. R. H. F. Manske, vol. 9, Academic Press, New York, p. 1, and references cited therein.

[2] The independent isolation and characterization of base (**2**), as thaliglucine, from *T. rugosum* has recently been reported: N. M. Mollov, Le Nyat Thuan, and P. P. Panov, *Compt. rend. Acad. Bulg. Sci.*, 1971, **24**, 1047.

[3] Equivalent bond distances and angles for both molecules of (**1**) in the asymmetric unit agreed closely and had values within the accepted limits; see 'Tables of Interatomic Distances and Configuration in Molecules and Ions,' *Chem. Soc. Spec. Publ.*, 1965, No. 18, ed., L. E. Sutton.

[4] J. Ibers and W. C. Hamilton, *Acta Cryst.*, 1964, **17**, 781; W. C. Hamilton, *ibid.*, 1965, **18**, 502.

[5] T. Ashida, R. Pepinsky, and Y. Okaya, *Acta Cryst.*, 1963, **16**, A48. See also ref. 1(a).

[6] V. Preininger, L. Hruban, V. Šimȧnek and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1970, **35**, 124; V. Šimȧnek, V. Preininger, P. Sedmera, and F. Santavý, *ibid.*, p. 1440.