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THE CONSTITUTION OF THALICARPINE

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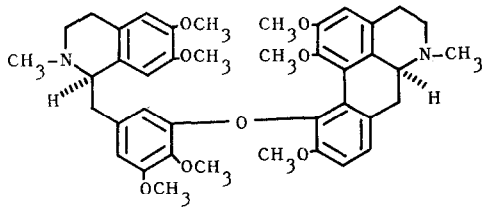
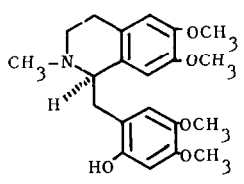
Thalicarpine is a novel dimeric aporphine-benzylisoquinoline alkaloid isolated from Thalictrum dasycarpum Fisch. and Lall.[1] and Thalictrum minus var. elatum Jacq.[2]. Recently, the authors also isolated thalicarpine from Hernandia ovigera L. collected in Formosa. Its identity was established by direct comparison (IR[3], NMR[4], and mixed m.p.) with the sample from T. dasycarpum.

An earlier study of the structure of thalicarpine led to proposal of structure I for the base[5]. However, recent spectral studies of thalicarpine and structurally-related compounds indicated that the alkaloid shows several spectral properties not readily explicable on the basis of structure I . Thus: (a) In the aporphine series, the NMR signal of the 11-hydrogen has been reported to occur in a lower field (1.95-2.43τ) than that of other aromatic hydrogens (3.00-3.62τ)[6].

The occurrence of a one-proton singlet at 1.82τ in the NMR spectrum (FIG. 1) of thalicarpine is in accord with the view that the aporphine moiety of thalicarpine carries no substituent at C-11. (b) The UV spectrum of thalicarpine shows maxima at 282 mμ (log.ε 4.33) and 301 mμ (log.ε 4.22), supporting the presence of a C-11 unsubstituted aporphine moiety[7]. (c) No AB-type quartet, expected for the C-8 and C-9 hydrogen atoms of the aporphine moiety of I , is observed in the aromatic proton region in the NMR spectrum of thalicarpine. The foregoing considerations led to re-examination of the condensation of D-(-)-6'-bromolaudanosine (IV, see below) and L-isocorydine (V. m.p. 183-185°, $[\alpha]_D$+206° (MeOH))[5], and the earlier result was not reproducible. The IR (FIG. 5), NMR (FIG. 2), and UV spectra of the colorless oily product were found to show distinct differences from those of thalicarpine.



I



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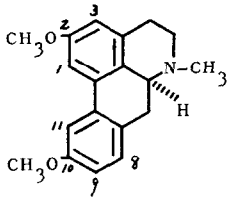

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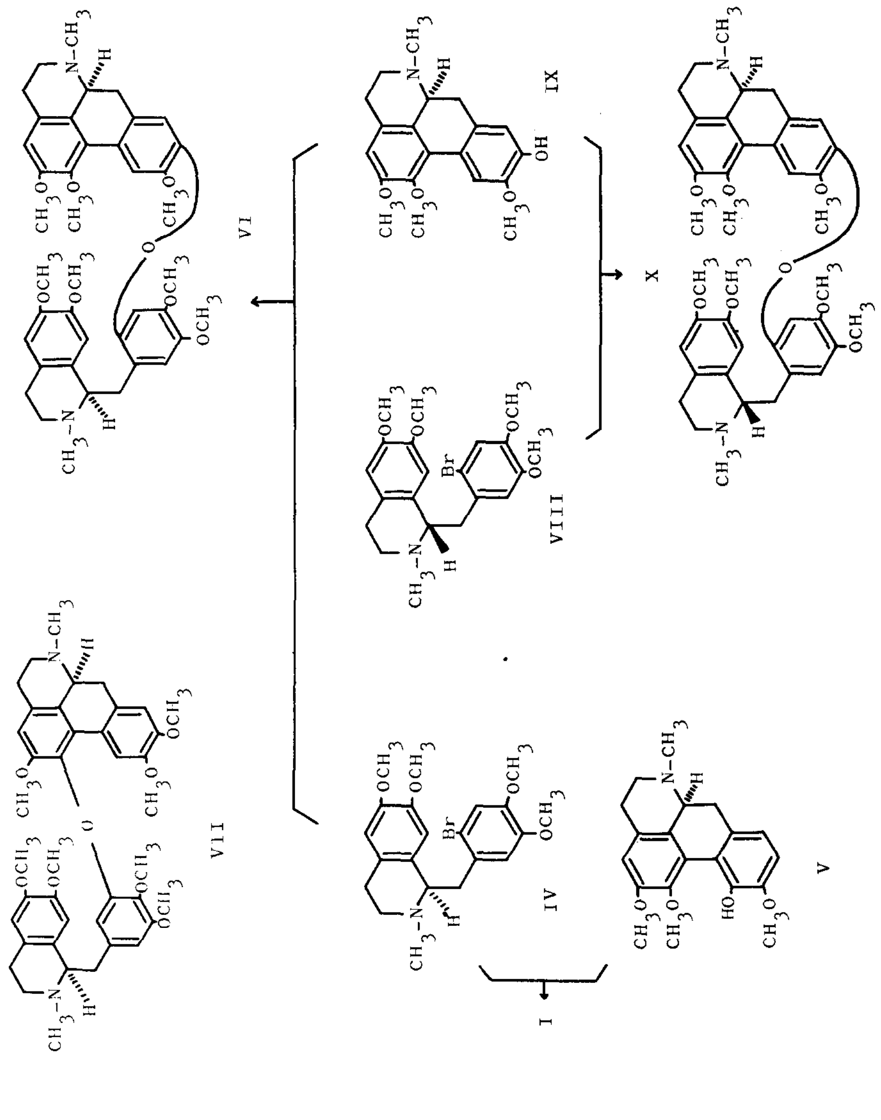

VI
VII
IX
VIII
X
IV
V
I

In the earlier structural study, it was found that sodium-liquid ammonia treatment of thalicarpine afforded (-)-6'-hydroxy-laudanosine and (+)-2,10-dimethoxyaporphine (III)[5]. On the basis of this degradative evidence and the spectral data discussed above, a plausible structure for thalicarpine might be VI. (At this point in the structural argument, the alternative structure VII could not be precluded, since 1,2,10,11-tetra-substituted and 1,2,9,10-tetrasubstituted aporphines have been shown to yield the same 2,10-disubstituted aporphine upon sodium-liquid ammonia reduction[8].)

In order to clarify the problem, compound VI was synthesized. Ullmann condensation between D-6'-bromolaudanosine (IV [9], m.p. 141-142°, $[\alpha]_D$-39°($CHCl_3$)), prepared from D-tetrahydro-papaverine[10], and L-N-methyllaurotetanine (IX[11], m.p. 155-156°, $[\alpha]_D$+121°($CHCl_3$)) was carried out in pyridine solution in the presence of anhydrous potassium carbonate and cupric oxide[12], to afford a colorless oily base VI. The IR spectrum of this synthetic base (VI) was found to be superimposable upon that of thalicarpine. However, the specific rotation of base VI was distinctly different from that of thalicarpine (TABLE 1), and the NMR spectrum showed a somewhat different pattern near 3.47τ, although the over all spectral pattern was quite similar (FIG. 3).

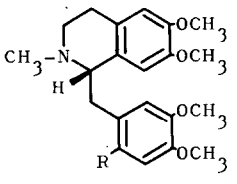
The hypothesis was next considered that thalicarpine might have a structure diastereomeric with VI. The L-configuration of the aporphine moiety of thalicarpine was well-established, but the absolute configuration of the benzylisoquinoline moiety could be L (S), since no chemical proof of the absolute configu-

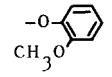
TABLE 1.

	Synthetic compound VI	Natural thalicarpine	Synthetic compound X	Synthetic compound I
m.p.	-----	153-155°	152-154°	-----
$[\alpha]_D$(MeOH)	-58°	+131°	+136°	-65°
IR($CHCl_3$)	identical	identical		(FIG. 5)
IR(KBr)	-----	identical		-----
NMR	(FIG. 3)	identical		(FIG. 2)
UV $\lambda_{max.}$ (log.ϵ)	282(4.26) 301(4.20)	282(4.33) 301(4.22)	282(4.32) 301(4.21)	280-282(4.17)

ration of (-)-6'-hydroxylaudanosine (XIII) had yet been presented. To test this possibility, compound XIII was synthesized from L-laudanosine by the route XI ⟶ VIII ⟶ XII ⟶ XIII. From the data in TABLE 2, it is clear that (-)-6'-hydroxylaudanosine possesses the L(S)-configuration.

TABLE 2.



	R	$[\alpha]_D$ ($CHCl_3$)
XI	-H	+48°
VIII	-Br	+44°
XII		+65°
XIII	-OH	-91°

The diastereomer X was then synthesized from L-6'-bromolaudanosine (VIII, m.p. 139-141°, $[\alpha]_D$+44°($CHCl_3$)) and L-N-methyllaurotetanine (IX) in the manner described above.

The synthetic condensation product X was shown to be identical to thalicarpine in every respect (TABLE 1).

On the basis of the experimental evidences summarized above, thalicarpine is assigned the revised constitution X . The structure of thalmelatine[2] should be revised accordingly.

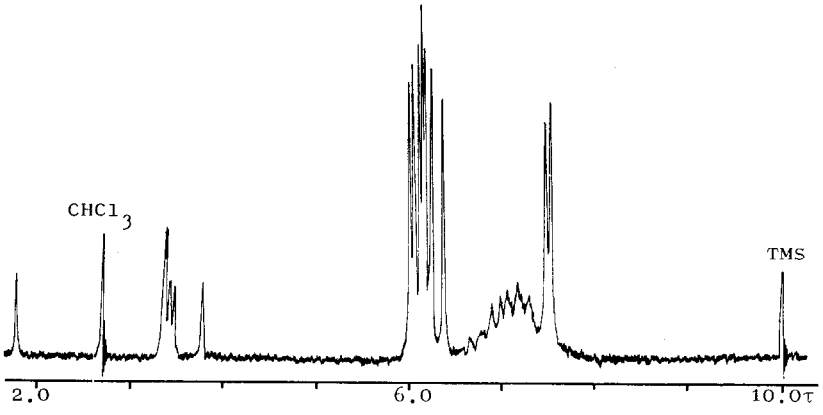


FIG. 1 NMR spectrum of thalicarpine (X).

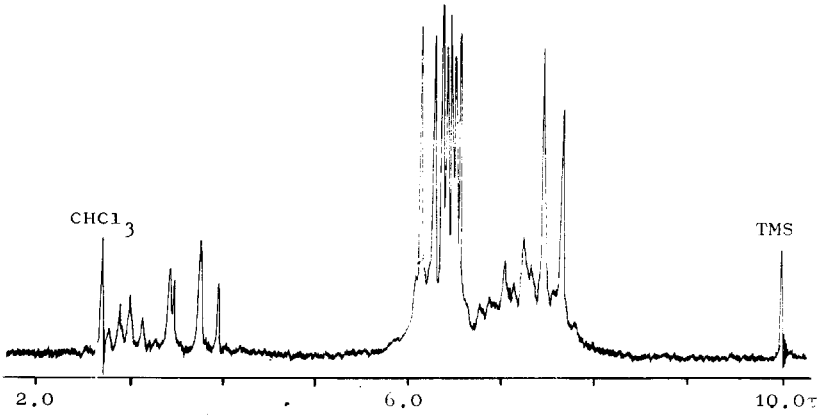


FIG. 2 NMR spectrum of I .

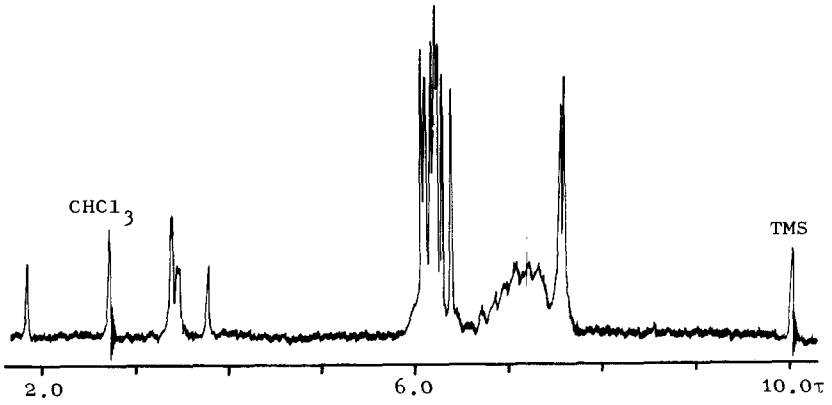


FIG. 3 NMR spectrum of VI.

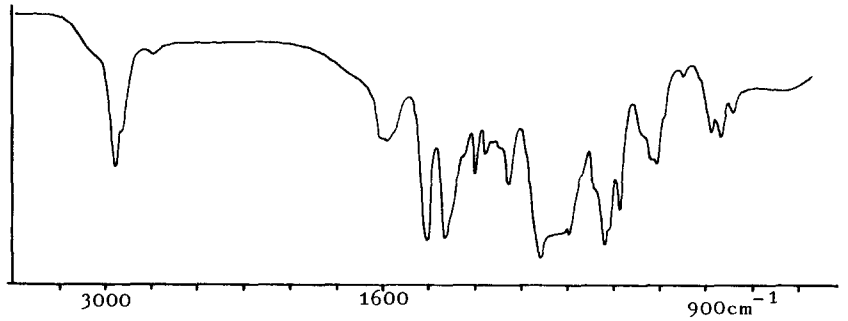


FIG. 4 IR spectrum of thalicarpine (X).

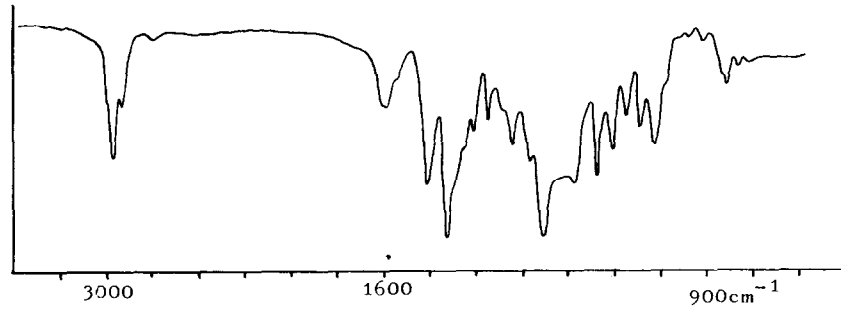


FIG. 5 IR spectrum of I .

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REFERENCES

The homogeneity of all compounds was evaluated by thin layer chromatography and NMR spectroscopy.

(1) S. M. Kupchan, K. K. Chakravarti, N. Yokoyama, J. Pharm. Sci., 52, 985.(1963).

(2) N. M. Mollov, H. B. Dutschewska, Tetrahedron Letters, 2219.(1964).

(3) All IR spectra reported in this communication were taken in $CHCl_3$, unless otherwise specified.

(4) NMR spectra were measured in $CDCl_3$ on a Varian A-60 spectrometer with TMS as the internal standard.

(5) S. M. Kupchan, N. Yokoyama, J. Am. Chem. Soc., 86, 2177 (1964).

(6) S. Goodwin, J. N. Shoolery, L. F. Johnson, Proc. Chem. Soc. (London), 306 (1958).
M. Shamma, W. A. Slusarchyk, Chem. Rev., 64, 73 (1964).

(7) A. W. Sangster, K. L. Stuart, Chem. Rev., 65, 86 (1965).

(8) M. Tomita, K. Fukagawa, Yakugaku Zasshi, 83, 293 (1963).

(9) C. Schöpf, K. Thierfelder, Ann., 537 143 (1939).
M. Tomita, K. Itoh, Yakugaku Zasshi, 78, 103 (1958).

(10) M. Tomita, Y. Okamoto, unpublished results.

(11) M. Tomita, S.-T. Lu, P.-K. Lan, F.-M. Lin, Yakugaku Zasshi, 85, 593 (1965).

(12) M. Tomita, K. Fujitani, Y. Aoyagi, Chem. Pharm. Bull. (Tokyo), in press.