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118. Masao Tomita,*1 Hiroshi Furukawa,*1 Sheng-Teh Lu,*1 and S. Morris Kupchan*2 : The Constitution of Thalicarpine.*3,4

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Reinvestigation on the constitution of thalicarpine, previously, isolated from *Thalictrum* and *Hernandia* species, was descrived. Ullmann condensation product of L-6′-bromolaudanosine and N-methyllaurotetanine was identified with natural thalicarpine.

Accordingly, the revised constitution of thalicarpine was established to have the formula I.

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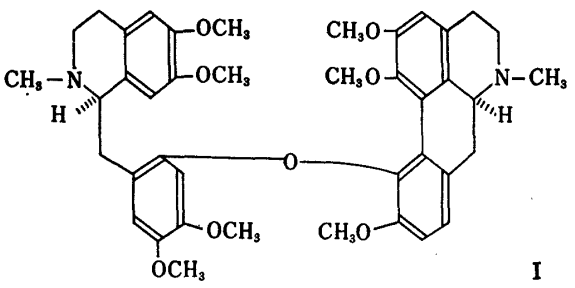
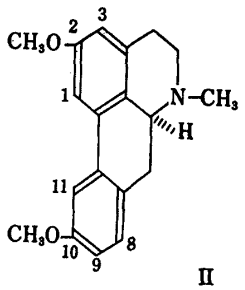
Thalicarpine is a novel dimeric aporphine-benzylisoquinoline alkaloid isolated from *Thalictrum dasycarpum* FISCH. and LALL.[1] and from *T. minus* var. *elatum* JACQ.[2]. Recently, the isolation of thalicarpine from *Hernandia ovigera* L. (Japanese name "*Hasunohagiri*," Hernandiaceae) collected in Formosa was also reported,[3] and its identity was confirmed by direct comparison with the sample from *T. dasycarpum*.

An earlier structural study of thalicarpine led to proposal of constitution I for the base.[4] However, recent spectral studies of thalicarpine indicated that the alkaloid shows several properties not readily explicable on the basis of structure I. Thus : (a) In the aporphine series, the nuclear magnetic resonance (NMR) signal of the C-11 hydrogen has been reported to occur at a lower field than that of other aromatic hydrogens (3.00~3.62τ).[5] As shown in Fig. 1, the occurrence of a one-proton singlet at 1.82τ in the NMR spectrum of thalicarpine is in accord with the view that thalicarpine carries no substituent at C-11. (b) The UV spectrum of thalicarpine (Fig. 4) 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.[6] (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.



I



II

Chart 1.

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*3 Alkaloids of Hernandia ovigera L. (3). Part 2. : H. Furukawa, S.-T. Lu : Yakugaku Zasshi, **86**, 1143 (1966)
*4 Preliminary communication of this work appeared in Tetrahedron Letters, **1965**, 4309.

1) S.M. Kupchan, K.K. Chakravarti, N. Yokoyama : J. Pharm. Sci., **52**, 985 (1963).
2) N.M. Mollov, H.B. Dutschewska : Tetrahedron Letters, **1964**, 2219.
3) M. Tomita, S.-T. Lu, Y.-Y. Chou : Yakugaku Zasshi, **86**, 763 (1966)
4) S.M. Kupchan, N. Yokoyama : J. Am. Chem. Soc., **86**, 2177 (1964).
5) S. Goodwin, J.N. Shoolery, L.F. Johnson : Proc. Chem. Soc., **1958**, 306; M. Shamma, W.A. Slusarchyk: Chem. Revs., **64**, 73 (1964).
6) A.W. Sangster, K.L. Stuart : *Ibid.*, **65**, 86 (1965).

The foregoing considerations led to re-examination of the condensation of D-6′-bromolaudanosine (VI) and isocorydine (V) and the earlier result was not reproducible. The IR spectrum of the colorless oily product was found to show distinct differences

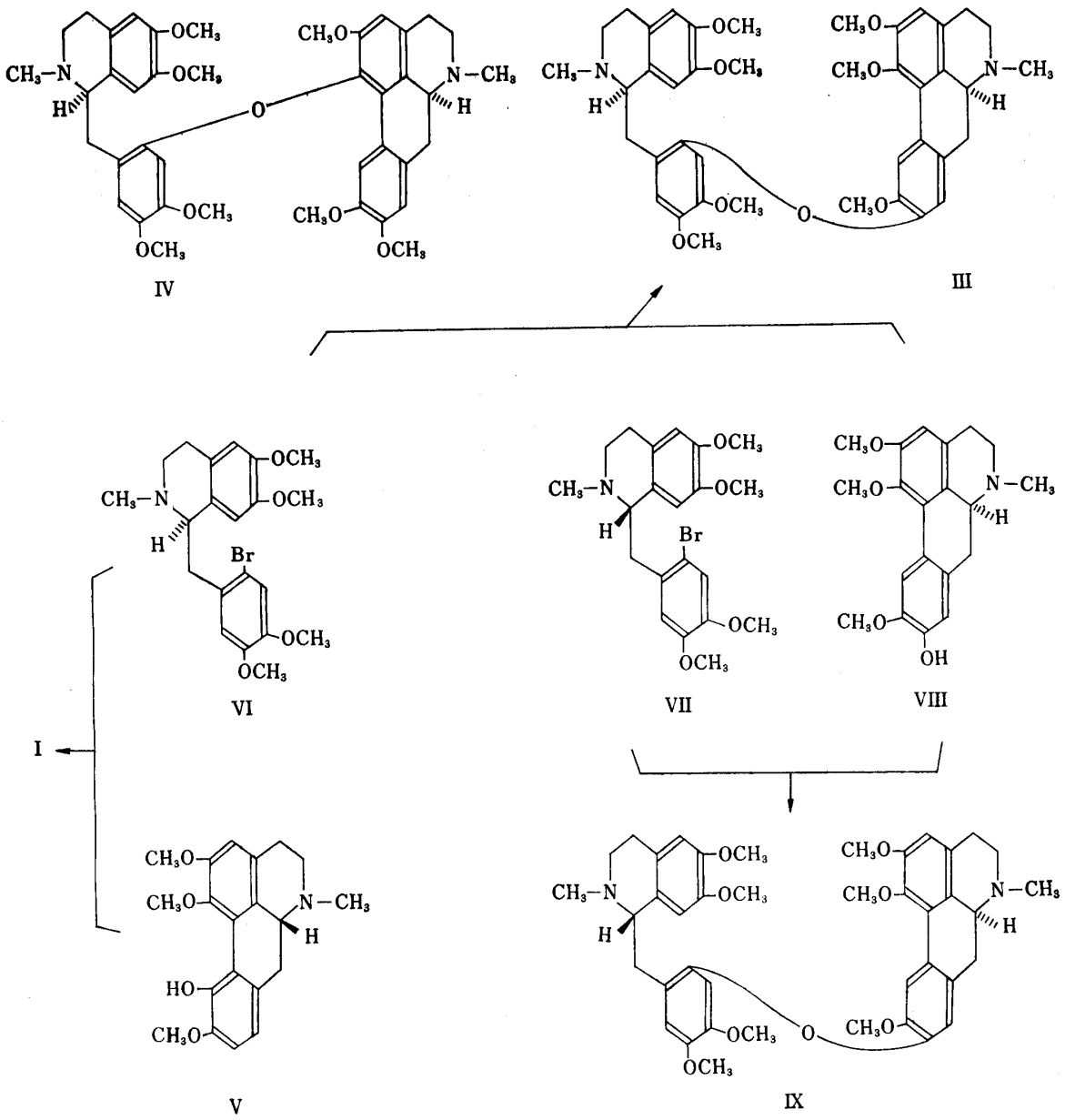


Chart 2.

from that of thalicarpine. In its NMR spectrum (Fig. 2), the C-8 and C-9 protons of the aporphine moiety gave rise to a pair of doublets centered at 3.05τ and 2.84τ (J=8.5 c.p.s.). The UV spectrum of the condensation product (I) showed a maximum at 280~282 mμ, and was different from that of thalicarpine (see Fig. 4).

In the earlier structural study,[4] it was found that sodium-liquid ammonia treatment of thalicarpine afforded (−)-6′-hydroxylaudanosine*[5] and (+)-2,10-dimethoxyaporphine (II). On the basis of this degradative evidence and the spectral data mentioned above, a plausible structure for thalicarpine might be either III or IV, because

*[5] The absolute configuration of (−)-6′-hydroxylaudanosine is discussed below.

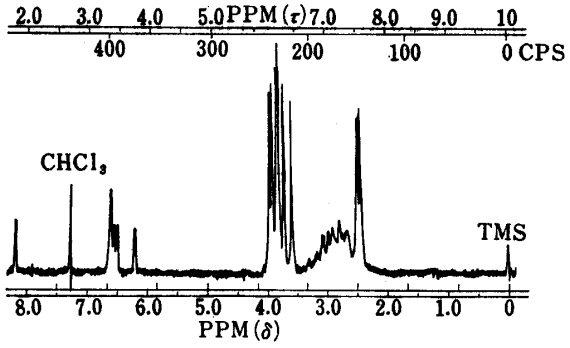


Fig. 1. NMR Spectrum of Thalicarpine (Ⅸ)

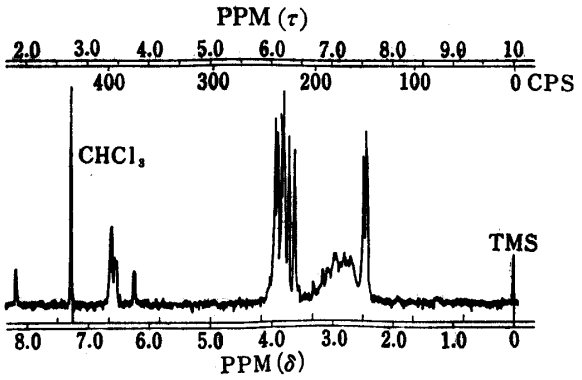


Fig. 3. NMR Spectrum of Compound Ⅲ

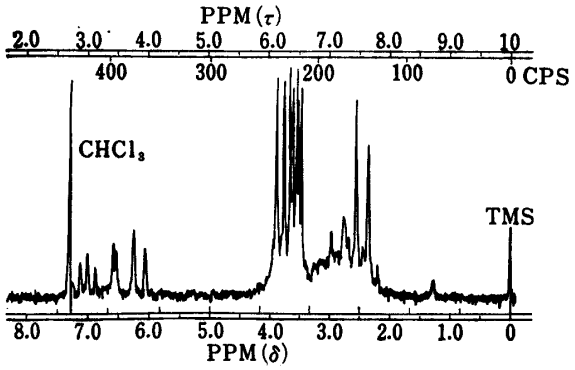


Fig. 2. NMR Spectrum of Compound I

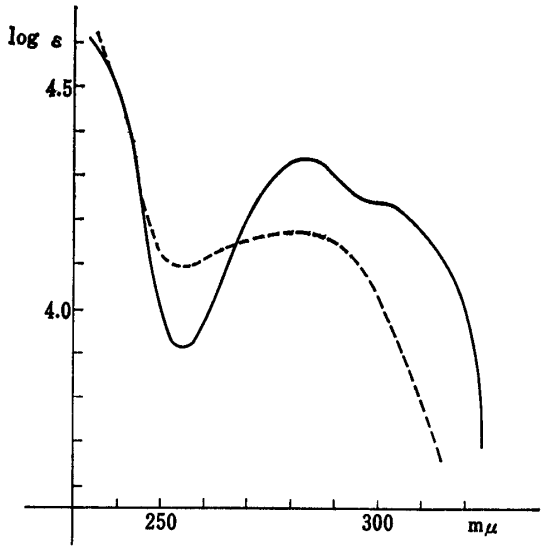


Fig. 4. UV Spectra of Thalicarpine (Ⅸ) and Compound I

——— : Thalicarpine (Ⅸ)
: Compound I

1,2,9,10-tetrasubstituted aporphines, like 1,2,10,11-tetrasubstituted aporphines, have been shown to yield 2,10-disubstituted aporphines upon sodium-liquid ammonia reduction.[7]

In order to clarify the problem, compound Ⅲ was synthesized. Ullmann condensation between D-6′-bromolaudanosine (Ⅵ) prepared from D-tetrahydropapaverine,[8] and

Table I.

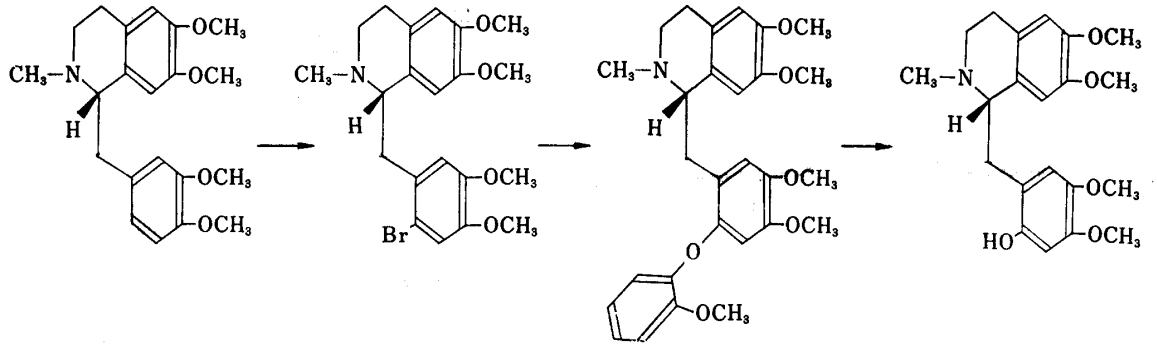
	Synthetic compound Ⅲ	Natural thalicarpine	Synthetic compound Ⅸ	Synthetic compound I
m.p.	——	153～155°	152～154°	——
$[\alpha]_D$ (MeOH)	−58°	+131°	+136°	−65°
IR ($CHCl_3$)	\—identical—/		\—identical—/	
IR (KBr)	——	\—identical—/		——
NMR	(Fig. 3)	\—identical—/		(Fig. 2)
UV λ_{max}	282(4.26)	282(4.33)	282(4.32)	280～282(4.17)
mμ (log ε)	301(4.20)	301(4.22)	301(4.21)	

7) M. Tomita, K. Fukagawa : Yakugaku Zasshi, **83**, 293 (1965).
8) M. Tomita, Y. Okamoto : unpublished results.

N-methyllaurotetanine (Ⅷ) was carried out in pyridine solution in the presence of anhydrous potassium carbonate and cupric oxide, to afford a colorless oily base Ⅲ. The IR spectrum in chloroform and UV spectrum of this synthetic base were found to be superimposable upon those of thalicarpine. However, as shown in Table I, the specific rotation of the base in methanol solution was distinctly different from that of thalicarpine. Furthermore, the NMR spectrum showed a somewhat different pattern near 3.47τ although the overall spectral pattern was quite similar and showed a singlet at 1.83τ, assigned to the C-11 proton in the aporphine moiety (Fig. 1, Fig. 3).

The striking similarity of the NMR, IR, and UV spectra of thalicarpine and base Ⅲ supported the view that thalicarpine might have a structure diastereomeric with Ⅲ. The L-configuration of the aporphine moiety of thalicarpine was well-established, because the absolute configuration of (+)-2,10-dimethoxyaporphine (Ⅱ), one of the cleavage reaction products of thalicarpine, had previously been established by Tomita, *et al.*[7] However, no chemical proof of the absolute configuration of (−)-6′-hydroxylaudanosine, the benzylisoquinoline base of thalicarpine, had yet been presented.

In order to confirm its absolute cofiguration, compound Ⅻ was synthesized from L-laudanosine (X), by the route X→Ⅶ→Ⅺ→Ⅻ. Ullmann condensation of L-6′-bromolaudanosine (Ⅶ) (prepared from L-laudanosine (X)) and guaiacol afforded the compound Ⅺ, and cleavage of the diphenyl ether linkage of compound Ⅺ with sodium-liquid ammonia treatment in the usual manner furnished L-6′-hydroxylaudanosine (Ⅻ).



X VII XI XII

Chart 3.

Table Ⅱ.

	$[\alpha]_D$ ($CHCl_3$)		$[\alpha]_D$ ($CHCl_3$)
X	+48°	Ⅺ	+65°
Ⅶ	+44°	Ⅻ	−91°

As shown in Table Ⅱ, the synthetic base Ⅻ showed a negative value of $[\alpha]_D$ in chloroform solution. From the foregoing, the L-configuration of the benzylisoquinoline moiety of thalicarpine was established.

The final proof of the structure of thalicarpine came from the synthesis of the diastereomer Ⅸ. Condensation between L-6′-bromolaudanosine (Ⅶ) and N-methyllaurotetanine (Ⅷ) was carried out in the manner described above. The synthetic product Ⅸ was obtained in crystalline form, m.p. 152~154°, $[\alpha]_D$ +136° (in methanol), and was shown to be identical to thalicarpine in every respect, as shown in Table I.

On the basis of the experimental evidence described above, thalicarpine is assigned the revised constitution Ⅸ.

Experimental*6

Ullmann Condensation between Isocorydine (V) and D-6′-Bromolaudanosine (VI)——The condensation of isocorydine (V) (m.p. 183~185°, $[\alpha]_D$ +206°(MeOH)) (190 mg.) and D-6′-bromolaudanosine[9] (VI) (m.p. 141~142°, $[\alpha]_D$ −39°($CHCl_3$)) (200 mg.) was carried out in pyridine solution (3 ml.) in the presence of CuO (40 mg.) and anhyd. K_2CO_3 (200 mg.). The reaction mixture was heated at 140~145° for 6 hr. under N_2 stream with stirring, and brought to dryness under reduced pressure. The residue was dissolved in 10% HCl, and made alkaline with NH_4OH and extracted with ether. The ethereal extract was washed with 5% NaOH and with water, dried over anhyd. K_2CO_3 and evaporated to yield an oily product, which was chromatographed on alumina. The first benzene eluate gave a small amount of laudanosine. Continued elution with $CHCl_3$ afforded a colorless oily base (60 mg.). TLC[b] 1 spot. NMR signals: 7.67 (3H), 7.45 (3H): 2 N-CH_3; 6.55 (3H), 6.48 (6H), 6.40 (3H), 6.35 (3H), 6.27 (3H), 6.15 (3H): 7 O-CH_3; 3.92 (1H), 3.47 (1H), 3.42 (1H), 3.74 (2H): aromatic-H; 3.05, 2.84 (2H, quartet, J=8.5 c.p.s., C-8, C-9 -H) (Fig. 2). $[\alpha]_D^{25}$ −64.5°(c=1.24, MeOH). UV λ_{max}^{EtOH} 280~282° mμ (log ε 4.17) (Fig. 4).

Ullmann Condensation of N-Methyllaurotetanine (VIII) and D-6′-Bromolaudanosine (VI)——A mixture of N-methyllaurotetanine (VIII) (m.p. 155~156°, $[\alpha]_D$ +121°($CHCl_3$)) (250 mg.), D-6′-bromolaudanosine (VI) (200 mg.), CuO (30 mg.), anhyd. K_2CO_3 (100 gm.), and dry pyridine (4 ml.) was heated at 140~145° with stirring under N_2 stream. After 4 hr., the reaction mixture was dissolved in $CHCl_3$, filtered and evaporated to dryness. The residue was treated in the usual manner to afford an oily non-phenolic base fraction (200 mg.). This was purified by alumina column chromatography. The benzene eluate yielded a small amount of VI, and continued elution with benzene–ether (1:1) gave a colorless oily product (80 mg.). Attempts at crystallization of this product were unsuccessful. TLC[a]: 1 spot. $[\alpha]_D^{25}$ −57.6°(c=0.52, MeOH). NMR signals: 7.58 (3H), 7.52 (3H): 2 N-CH_3; 6.39 (3H), 6.28 (3H), 6.23 (3H), 6.20 (3H), 6.17 (3H), 6.10 (3H), 6.07 (3H): 7 O-CH_3; 3.77 (1H), 3.47 (1H), 3.44 (1H), 3.38 (3H), 1.83 (1H): aromatic-H (Fig. 3). UV: λ_{max}^{EtOH} mμ (log ε): 282 (4.26), 301 (4.20).

L-6′-(2-Methoxyphenoxy)laudanosine (XI)——A mixture of L-6′-bromolaudanosine (VII) (450 mg.), guaiacol (1 ml.), CuO (50 mg.), anhyd. K_2CO_3 (200 mg.), and dry pyridine (3 ml.) was heated at 145~150° under N_2 stream with stirring for 2.5 hr. The basic product was isolated in the usual way, and crystallized from MeOH to give XI as colorless needles (260 mg.), m.p. 128~130°, $[\alpha]_D^{26}$ +68.6°(c=1.12, $CHCl_3$). NMR signals: 7.67 (3H): N-CH_3; 6.45 (3H), 6.27 (6H), 6.18 (3H), 6.12 (3H): 5 O-CH_3; 3.85 (1H), 3.50~2.98 (7H): aromatic-H. *Anal.* Calcd. for $C_{28}H_{33}O_6N$: C, 70.01; H, 6.88. Found: C, 69.76; H, 6.63.

L-6′-Hydroxylaudanosine (XII)——A small amount of sodium metal was dissolved in a mixture of liq. NH_3 (70 ml.) and anhyd. ether (50 ml.) at −55~−50°. To this blue colored solution was added a solution of compound XI (130 mg.) in anhyd. toluene (5 ml.) with stirring. After 30 min., the excess of Na was destroyed with NH_4Cl which was added until the blue color had disappeared. The reaction mixture was allowed to stand overnight to evaporate the ammonia. The residue was dissolved in ether and extracted with dil. HCl. The acidic solution was made alkaline with NH_4OH and extracted with ether. The ether solution was washed with water, dried over anhyd. K_2CO_3, and evaporated to yield an oily product (85 mg.). The product showed a single spot on a slica gel thin-layer chromatogram. $[\alpha]_D^{26}$ −90.5°(c=1.16, $CHCl_3$). NMR signals: 7.40 (3H): N-CH_3; 6.28 (3H), 6.20 (3H), 6.18 (6H): 4 O-CH_3; 3.60 (1H), 3.55 (1H), 3.49 (1H), 3.36 (1H): aromatic-H. Hydroiodide: colorless prisms from acetone, m.p. 191~193°. *Anal.* Calcd. for $C_{21}H_{27}O_5N \cdot HI \cdot \frac{1}{2}H_2O$: C, 49.42; H, 5.49. Found: C, 49.33; H, 6.06.

Synthesis of Thalicarpine (IX)——N-Methyllaurotetanine (VIII) (250 mg.) and L-6′-bromolaudanosine (VII) (m.p. 139~141°, $[\alpha]_D$ +44°($CHCl_3$)) (200 mg.) were dissolved in dry pyridine (3 ml.), and CuO (35 mg.) and finely powdered anhyd. K_2CO_3 (200 mg.) were added. The mixture was heated with stirring in an oil bath at 140~145° under nitrogen. After 3 hr., the reaction mixture was dissolved in $CHCl_3$, filtered and evaporated to dryness under reduced pressure. The residue was dissolved in 10% HCl and washed with ether. The acidic solution was made alkaline with NH_4OH and extracted with ether. The ethereal extract was washed with 5% NaOH solution, then water, dried (K_2CO_3), and evaporated to give an oily product, which was chromatographed on alumina. The benzene–$CHCl_3$ eluate gave colorless needles, m.p. 152~154°, $[\alpha]_D^{25}$ +136°(c=1.0, MeOH). NMR signals: 7.60 (3H), 7.52 (3H): 2 N-CH_3; 6.41 (3H), 6.29 (3H), 6.22 (3H), 6.20 (3H), 6.17 (3H), 6.10 (3H), 6.06 (3H): 7 O-CH_3; 3.78 (1H), 3.48 (1H), 3.37 (3H), 1.81 (1H): aromatic-H (Fig. 1). This base was shown to be identical with natural thalicarpine by direct comparisons of IR ($CHCl_3$ and KBr disk), NMR, UV spectra and TLC[a] (Table I).

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*6 NMR spectra were measured in $CDCl_3$, on Varian A-60 spectrometer. Chemical shifts are reported in τ values, using TMS as the internal standard. TLC (thin-layer chromatography): *a*) aluminum oxide $CHCl_3$. *b*) silica gel–MeOH.

9) M. Tomita, K. Ito: Yakugaku Zasshi, **78**, 103 (1958).