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STUDIES ON THE ALKALOIDS OF LOTI EMBRYO. (1). STRUCTURE OF ISOLIENSININE.

M. Tomita and H. Furukawa

Faculty of Pharmaceutical Sciences, Kyoto University

Kyoto, Japan

T. H. Yang and T. J. Lin

School of Pharmacy, Taipei Medical College

Taipei, Formosa

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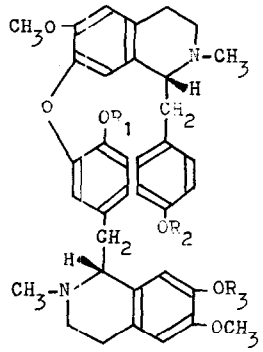
In 1962, Pan Pei-chuan et al.[1] reported the isolation of liensinine from Chinese drug "Lien Tze Hsin", embryo loti, (embryo of the seed of Nelumbo nucifera GAERTN., Fam. Nymphaeaceae) and its structure was shown to be I [2], based on the result of its Hofmann degradation and permanganate oxidation reactions.

Recently we isolated a new phenolic bisbenzylisoquinoline alkaloid from Formosan "Lien Tze Hsin", for which we proposed the name isoliensinine.

Isoliensinine (II) is a colorless oily base, which showed $[\alpha]_D^{22}$ +49.3° (acetone), $[\alpha]_D^{29}$ -43.3° ($CHCl_3$), I.R. $\nu_{max.}^{CHCl_3}$ 3500 cm^{-1} (OH), U.V. $\lambda_{max.}^{95\%EtOH}$ 286 mμ (log ε 4.04), n.m.r. signals[3]

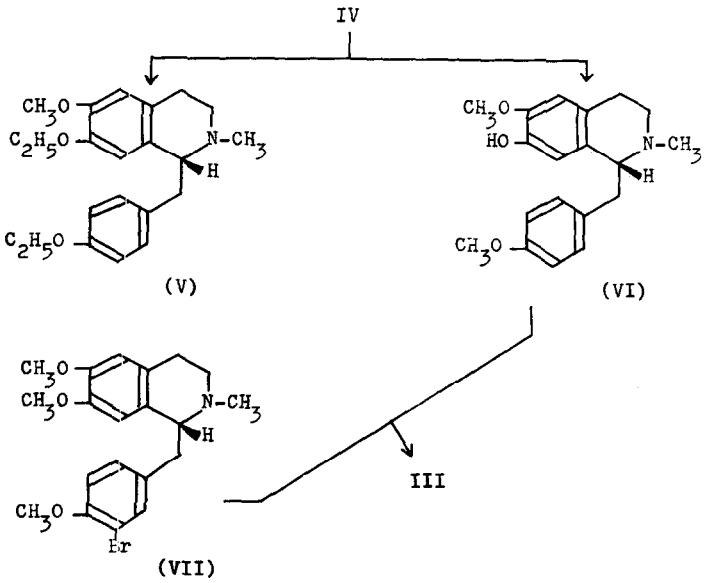


(I) $R_1, R_2 = H$, $R_3 = CH_3$ (liensinine)

(II) $R_1, R_3 = H$, $R_2 = CH_3$ (isoliensinine)

(III) $R_1, R_2, R_3 = CH_3$

(IV) $R_1, R_3 = C_2H_5$, $R_2 = CH_3$



at 7.51, 7.62 τ(6H, two N-CH_3), 6.24 τ(6H, two O-CH_3), 6.30 τ (3H, O-CH_3), and 4.12 τ(2H, broad, two -OH). It gave several crystalline salts : e.g., perchlorate, $C_{37}H_{42}O_6N_2 \cdot 2HClO_4 \cdot H_2O$, m.p. 200-203°, $[\alpha]_D^{22}$ -70.0° (acetone) ; hydrochloride, $C_{37}H_{42}O_6N_2 \cdot 2HCl \cdot 4H_2O$, m.p. 185-186°.

Methylation of isoliensinine (II) with diazomethane yielded O,O-dimethylisoliensinine (III), which was characterized as the crystalline styphnate, m.p. 133-135°, $C_{39}H_{46}O_6N_2 \cdot 2C_6H_3O_8N_3 \cdot C_2H_5OH$ (ethanol adduct), $[\alpha]_D^{27}$ -81.5° (acetone). It showed n.m.r. signals at 6.19, 6.22, 6.23, 6.29, 6.40 τ(15H, five O-CH_3) and 7.56, 7.58 τ(6H, two N-CH_3).

The O,O-diethyl ether (IV) of isoliensinine was then prepared by the treatment with diazoethane. Its n.m.r. spectrum revealed the presence of two ethoxyl groups (8.68 τ , triplet, J 7.0 c.p.s., 3H, O-$CH_2\underline{CH_3}$; 8.72 τ, triplet, J 7.0 c.p.s., 3H, O-$CH_2\underline{CH_3}$). Thus the rational formula of isoliensinine should be $C_{32}H_{25}O(OCH_3)_3(OH)_2(NCH_3)_2$.

When treated with metallic sodium in liquid ammonia in the usual manner, O,O-diethylisoliensinine (IV) was cleaved to give two coclaurine type bases. The one was found to be nonphenolic base, which gave the crystalline oxalate, m.p. 177-179°, $C_{23}H_{29}O_3N \cdot C_2H_2O_4$, $[\alpha]_D^{26}$ -113.3° (50% MeOH, H_2O) and its free base showed n.m.r. signals at 6.20 τ (3H, O-CH_3), 8.61, 8.67 τ(triplet, J 7.0 c.p.s., 6H, two O-$CH_2\underline{CH_3}$) and 7.48 τ(3H, N-CH_3). Infrared spectra of this

base and the oxalate were found to be superimposable with those of D(−)-O,O-diethyl-N-methylcoclaurine (V) (in $CHCl_3$) and its oxalate[4] (in KBr). The other, a phenolic base, was obtained as a colorless oil, $[\alpha]_D^{22}$ -87.7° (MeOH). This substance was identified with D(-)-1-(4′-methoxybenzyl)-2-methl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (VI)[5] by infrared comparison (in $CHCl_3$).

These observations led us to suppose that isoliensinine might have the analogous structure with liensinine (I). In order to confirm this assumption, we attempted to synthesize O,O-dimethylliensinine (III).

Ullmann condensation between D(-)-3′-bromo-O-methyl-armepavine (VII)[6] and D(-)-1-(4′-methoxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (VI) was carried out in pyridine solution in the presence of potassium carbonate and copper powder. Alumina chromatography of the product afforded a colorless oily base which was characterized as the crystalline styphnate, m.p. 133-135°, $C_{39}H_{46}O_6N_2 \cdot 2C_6H_3O_8N_3 \cdot C_2H_5OH$ (ethanol adduct), $[\alpha]_D^{24}$ -76.9° (acetone).

As shown in Table I, properties of the synthesized compound were shown to be quite identical with those of O,O-dimethylisoliensinine .

TABLE I .

		O,O-Dimethyl-isoliensinine	Synthetic sample (III)
Free base	I.R.($CHCl_3$)	identical	
	N.M.R.	identical	
	T.L.C.[7]	identical	
Styphnate	formula	$C_{39}H_{46}O_6N_2 \cdot 2C_6H_3O_8N_3 \cdot C_2H_5OH$	$C_{39}H_{46}O_6N_2 \cdot 2C_6H_3O_8N_3 \cdot C_2H_5OH$
	appearence	yellow needles	yellow needles
	m.p. (°C)	133-135	133-135
	$[\alpha]_D$(acetone)	-81.5°	-76.9°
	I.R.(KBr)	identical	

On the bases of these experimental evidences, the structure of isoliensinine is unambiguously assigned to the formula II .

REFERENCES

Satisfactory analyses have been obtained for products with cited empirical formulas.

1. Chao Tse-yuan, Chou Yun-lee, Young Pao-tsin, Chou Tsan-quo, Scientia Sinica, 11, 216 (1962); Pan Pei-chuan, Chou Yun-lee, Sun Tsun-tsi, Kao Yee-sheng, ibid., 11, 321 (1962).
2. The absolute configuration of two asymmetric centers of liensinine (I) has not been determined.

3. The n.m.r. spectra were taken on a Varian Associates recording spectrometer (A-60) at 60 Mc. in deuterated chloroform. Chemical shifts are reported in τ values, using tetramethylsilane as the internal reference.
4. M.Tomita, T.Kikuchi, Yakugaku Zasshi, 77, 238 (1957).
5. M.Tomita, Y.Sasaki, Pharm. Bull.(Tokyo), 2, 375 (1954).
6. M.Tomita, K.Ito, H.Yamaguchi, Pharm. Bull.(Tokyo), 3, 449 (1955).
7. Thin Layer Chromatography : a) Kieselgel G nach Stahl; solvent, methanol-acetone (1:1). b) Aluminiumoxyd G nach Stahl; solvent, chloroform.