Pharmaceutical Institute, School of Medicine,
Tohoku University

A Total Synthesis of (±)-Isoliensinine

Tetsuji Kametani, Seiichi Takano, and Kazuko Satoh

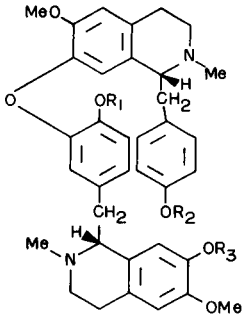
Sir:

The isolation of liensinine (I) from the Chinese drug "Lien Tze Hsin", *Embryo lotti* was reported in 1962 (1) and its structure was confirmed by chemical degradation (1) and its total synthesis (2, 3). Isoliensinine was recently isolated from Formosan "Lien Tze Hsin" and its structure was assigned formula II on the basis of the cleavage reaction with sodium in liquid ammonia of its *OO*-diethyl ether (III) and of the synthesis of its *OO*-dimethyl ether (IV) (4). However, a total synthesis of isolinesinine has not yet been achieved.

The purpose of the present investigation was to study the Ullmann reaction between both tetrahydroisoquinoline derivatives, (X) and (XI), in order to obtain *OO*-dibenzylisoliensinine (V) as a possible intermediate for the synthesis of (±)-isoliensinine.

Condensation of 4-benzyloxy-3-methoxyphenylethylamine with 4-methoxyphenylacetic acid in a current of nitrogen at 180-190° gave the amide (VI), which was recrystallised from benzene-*n*-hexane to afford colourless needles, m.p. 107-108°. Bischler-Napieralski reaction (5) of VI gave a pale yellow syrup (VII), which was converted into the methiodide (VIII) by heating with methyl iodide at 60° in a current of carbon dioxide. Recrystallisation of VIII from ethanol afforded yellow plates, m.p. 167-168°, which were changed to a reddish oil in case of repeated recrystallisation because of its instability and therefore used in the following reaction without further purification. Sodium borohydride reduction of VIII in ethanol gave 7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (IX) as a pale yellow syrup, whose picrate was recrystallised from ethanol to yield yellow prisms, m.p. 190.5°. Debenzylation of IX with a mixture of benzene and 20% hydrochloric acid (*ca.* 1:1) under reflux in a current of nitrogen gave 4'-*O*-methyl-*N*-methylcoclaurine (X) as a brown syrup, whose picrate was recrystallised from ethanol to give yellow plates, m.p. 169-170°.

Ullmann reaction between the preceding isoquinoline (X) and 7,4'-*OO*-dibenzyl-3'-bromo-*N*-methylcoclaurine (XI) (6) afforded *OO*-dibenzylisoliensinine (V) as a brown oil, which was chromatographed on alumina. In this case, the first benzene eluate (3.5 l.) (F_1-F_{35}: each fraction, 100 ml.) showed a positive Beilstein test, and, after removal of the second chloroform-benzene (1:1) eluate (F_{36}-F_{60}: 2.5 l.), F_{61} fraction (100 ml.) was distilled to give *OO*-dibenzylisoliensinine as a pale yellow syrup, whose NMR spectrum showed the signal of three



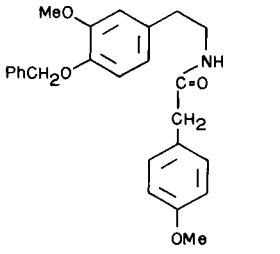
I $R_1 = R_2 = H$, $R_3 = Me$

II $R_1 = R_3 = H$, $R_2 = Me$

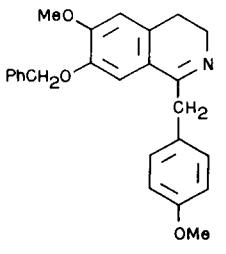
III $R_1 = R_3 = Et$, $R_2 = Me$

IV $R_1 = R_2 = R_3 = Me$

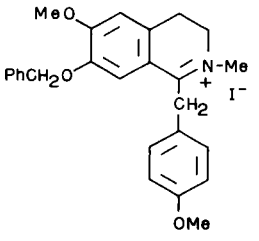
V $R_1 = R_3 = CH_2Ph$, $R_2 = Me$



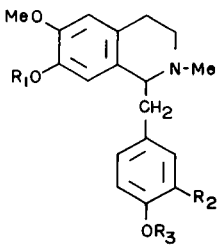
VI



VII



VIII



IX $R_1 = CH_2Ph$, $R_2 = H$, $R_3 = Me$

X $R_1 = R_2 = H$, $R_3 = Me$

XI $R_1 = R_3 = CH_2Ph$, $R_2 = Br$

methoxyl groups at τ 6.08, 6.10, and 6.14 and the protons of the methylene of two benzyloxy-groups at τ 6.23 and 6.29 (7). Purification of the diperchlorate from acetone gave a glassy substance, m.p. 122-124° (8).

Reductive hydrolysis of the above *OO*-dibenzylisoliensinine (V) with zinc powder and concentrated hydrochloric acid gave (±)-isoliensinine (II) as a pale yellow syrup, which was washed with hot ether to give the pure compound (II). The synthetic isoliensinine and the natural one behaved similarly on a thin layer chromatogram. The IR spectrum (in chloroform) was superimposable with that of natural isoliensinine donated by Prof. M. Tomita and Dr. H. Furukawa, but attempted purification in a crystalline state at this stage failed.

These facts reveal that the total synthesis of the racemic isoliensinine has been accomplished.

We thank Prof. M. Tomita and Dr. H. Furukawa, Department of Pharmaceutical Science, Kyoto University for a gift of natural isoliensinine.

REFERENCES

(1) Chao Tse-yuan, Chou Yen-lee, Young Tao-tsin, and Chou Tsanquo, *Scientica Sinica*, **11**, 215 (1962); Pan Pei-chuan, Chou Yun-lee, Sun Tsun-tsi, and Yee-sheng, *ibid.*, **11**, 321 (1962).

(2) Y. Y. Hsin, P. C. Pan, W. C. Chen, and Y. S. Kao, *ibid.*, **13**, 2020 (1964).

(3) T. Kametani, S. Takano, K. Masuko, and F. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **14**, 67 (1966).

(4) M. Tomita, H. Furukawa, Tsang-Hsiung Yang, and Tsung-Jen Lin, *ibid.*, **13**, 39 (1965).

(5) This cyclization reaction was carried out in the presence of phosphoryl chloride in dry toluene in a current of nitrogen at 80-85° for 2.5 hours.

(6) T. Kametani, S. Takano, and K. Masuko, *Yakugaku Zasshi*, **86**, 976 (1966).

(7) Nuclear magnetic resonance spectrum was measured on a Varian A-60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference.

(8) Satisfactory analyses were obtained for all compounds reported.

Received December 3, 1966 Sendai, Japan