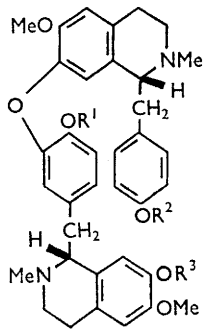
A Total Synthesis of Isoliensinine*

By **T. Kametani** and **S. Takano,** Pharmaceutical Institute, School of Medicine, Tohoku University, Kitayobancho, Sendai
H. Iida and **M. Shinbo,** Tokyo College of Pharmacy, Kashiwagi, Shinjuku, Tokyo, Japan

Cyclisation of the amide (VI) prepared by condensation of 4-methoxyphenylacetic acid and 4-benzyloxy-3-methoxyphenethylamine, gave the 3,4-dihydroisoquinoline (VII), the methiodide of which, on reduction, afforded the tetrahydroisoquinoline (IX). Ullmann reaction between (±)-(X) and (±)-(XI) afforded a mixture of the diastereoisomeric racemates of *OO*-dibenzylisoliensinine (V), the debenzylation of which gave a mixture of diastereoisomeric racemates of isoliensinine (II). Finally, total synthesis of optical active isoliensinine has been achieved.

THE isolation of liensinine (I) from the Chinese drug ' Lien Tze Hsin,' embryo lotti, was reported in 1962 and its structure was confirmed by chemical degradation [1,2] and by its total synthesis.[3,4] Isoliensinine was recently isolated from Formosan ' Lien Tze Hsin ' and structure (II) was assigned to it on the basis of the cleavage of its *OO*-diethyl ether (III) by sodium in liquid ammonia and the synthesis of its *OO*-dimethyl ether (IV).[5] However, a total synthesis of isoliensinine has not yet been reported.

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.



(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) $R^1 = R^3 = CH_2Ph$, $R^2 = Me$

Condensation of 4-benzyloxy-3-methoxyphenethylamine with 4-methoxyphenylacetic acid at 180—190° gave the amide (VI) which in a Bischler–Napieralski reaction[6] afforded a pale yellow syrup (VII);[7] with methyl iodide this was converted into the methiodide (VIII). Sodium borohydride reduction of (VIII) in ethanol gave 7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (IX), the debenzylation of which with a mixture of benzene and 20% hydrochloric acid gave 4′-*O*-methyl-*N*-methylcoclaurine (X).

Next an investigation of the Ullmann reaction between the two racemic isoquinolines (X) and (XI) was carried out. Ullmann reaction between the isoquinoline (X) and 4′,7-*OO*-dibenzyl-3′-bromo-*N*-methylcoclaurine (XI)[6] afforded the diastereoisomeric racemates of *OO*-dibenzylisoliensinine (V) as a brown syrup; this was chromatographed. After the first chloroform eluate (1·5 l.) [fractions 1—15 (100 ml. each)] showed a positive Beilstein test and the second chloroform eluate (2 l.; fractions 16—35), had been discarded, the third fraction of chloroform–methanol (1 : 1) (4 l.; fractions 36—75) was distilled to give *OO*-dibenzylisoliensinine as a pale yellow syrup, the n.m.r. spectrum of which showed *N*-methyl protons at τ 7·61, the signals of methyl protons in three methoxy-groups at τ 6·37, 6·28, and 6·23, and the protons of the methylene of two benzyloxy-groups at τ 5·17 and 5·02. These facts exclude a symmetrical structure such as a biphenyl derivative which would be formed by bimolecular condensation of (XI).

Hydrolysis of *OO*-dibenzylisoliensinine (V) with ethanol–concentrated hydrochloric acid (1 : 1) gave the diastereoisomeric racemates of isoliensinine (II) as a pale yellow syrup; the racemates were purified *via* their perchlorates to give compound (II). Specimens of both synthetic and natural isoliensinine behaved similarly on t.l.c. The i.r. spectrum (in chloroform) of (II) was superimposable on that of natural isoliensinine donated by Prof. M. Tomita and Dr. H. Furukawa.

Finally, an Ullmann reaction between the optically active compounds † (—)-(Xa) and (—)-(XIa), obtained by methylation of compound (XIIa) with diazomethane, was carried out in order to obtain *OO*-dibenzylisoliensinine (Va), the hydrolysis of which would afford the optically active synthetic isoliensinine (IIa). The u.v. (in EtOH) and n.m.r. (in $CDCl_3$) spectral data of the above samples were identical with those of natural isoliensinine; the optical rotations of both specimens were also very close. Furthermore, the m.p., optical rotation, and spectroscopic data of *OO*-dimethylisoliensinine (IVa), which was obtained by methylation of (IIa), were also identical with those of the natural *O*-methyl derivative.[5]

* Preliminary communication, T. Kametani, S. Takano, and K. Satoh, *J. Heterocyclic Chem.*, 1966, **3**, 546.

† In this case suffix ' a ' means the corresponding optically active compounds, and this sign is used in the following compounds.

[1] Chao Tse-yuan, Chou Yun-lee, Young Tao-tsin, and Chou Tsenquo, *Scientica Sinica*, 1962, **11**, 215.

[2] Pan Pei-chuan, Chou Yun-lee, Sun Tsun-tsi, and Yee-sheng, *Scientica Sinica*, 1962, **11**, 321.

[3] Y. Y. Hsin, P. C. Pan, W. C. Chen, and Y. S. Kao, *Scientica Sinica*, 1964, **13**, 2020.

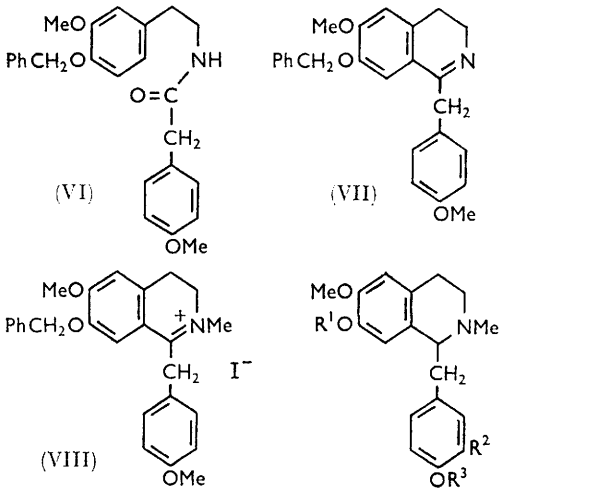
[4] T. Kametani, S. Takano, K. Masuko, and F. Sasaki, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 67.

[5] M. Tomita, H. Furukawa, Tsang-Hsiung Yang, and Tsung-Jen Lin, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 39.

[6] T. Kametani, S. Takano, and K. Masuko, *J. Pharm. Soc. Japan*, 1966, **86**, 976.

[7] M. Tomita, K. Nakaguchi, and S. Takagi, *J. Pharm. Soc. Japan*, 1950, **70**, 152.

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



(IX) $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = Me$
(X) $R^1 = R^2 = H$, $R^3 = Me$
(XI) $R^1 = R^3 = CH_2Ph$, $R^2 = Br$
(XII) $R^1 = CH_2Ph$, $R^2 = R^3 = H$

EXPERIMENTAL

I.r. and n.m.r. spectra were measured in deteuriochloroform (tetramethylsilane as internal reference) on a Type EPI-2 Hitachi recording spectrophotometer and a Varian A-60 spectrophotometer.

N-(4-Benzyloxy-3-methoxyphenethyl)-2-(4-methoxyphenyl)-acetamide (VI).—A mixture of 4-benzyloxy-3-methoxyphenethylamine (7·7 g.) and 4-methoxyphenylacetic acid (5 g.) was heated under reflux at 180—190° for 3 hr. under nitrogen. The resultant mixture was cooled and extracted with chloroform (100 ml.). The extract was washed with 3% hydrochloric acid, water, 10% sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, it was then dried (Na_2SO_4). Removal of the solvent gave the amide (VI) (11·5 g.) as a solid, which was crystallised from benzene–hexane and then methanol as needles, m.p. 117° (lit.,[5] m.p. 116—117°) (Found: C, 73·6; H, 6·8; N, 3·6. $C_{25}H_{27}NO_4$ requires C, 74·05; H, 6·7; N, 3·45%).

7-Benzyloxy-3,4-dihydro-6-methoxy-1-(4-methoxybenzyl)-isoquinoline Methiodide (VIII).—A mixture of the amide (VI) (4 g.), phosphoryl chloride (4 ml.), and dry toluene (40 ml.) was heated at 80—85° for 2·5 hr. under nitrogen. An excess of ligroin (400 ml.) was added to the reaction mixture and the yellow precipitate was collected by decantation and washed with hexane (2 × 100 ml.); it was then dissolved in chloroform (200 ml.) and the solution was poured into cooled ammonium hydroxide solution with stirring. The solvent layer was separated, washed with water, and dried (K_2CO_3). The solvent was removed to give a pale yellow syrup (3·7 g.) which was dissolved in methyl iodide (8 ml.) and heated at 60° in a current of carbon dioxide; the methiodide (VIII) was obtained in quantitative yield and crystallised from ethanol as yellow plates, m.p. 167—168°. Since the compound gave a reddish oil on repeated recrystallisation or upon exposure to air it was used in the following reaction without purification.

(±)-*7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline* (IX).—Sodium borohydride (4 g.) was added portionwise to a stirred and cooled suspension of the methiodide (VIII) (5·5 g.) in ethanol (100 ml.); the reaction mixture became colourless. The ethanol was removed and the residue was basified with 10% sodium hydroxide solution, and then extracted with benzene. The extract was washed with water, dried (K_2CO_3), and evaporated to give the 1,2,3,4-tetrahydroisoquinoline derivative (IX) (3·2 g.) as a pale yellow syrup, the picrate of which crystallised from ethanol as *cubes*, m.p. 190·5° (Found: C, 61·0; H, 5·4; N, 8·8. $C_{26}H_{29}NO_3,C_6H_3N_3O_7$ requires C, 60·75; H, 5·1; N, 8·85%).

(±)-*4′-O-Methyl-N-methylcoclaurine* (X).—A mixture of (IX) (3·0 g.), benzene (50 ml.), and 20% hydrochloric acid (40 ml.) was heated under reflux at 130° for 3 hr. in a current of nitrogen. The benzene layer was separated and washed with water (50 ml.); the aqueous washing was combined with the aqueous layer. Basification of the acidic solution with 10% ammonium hydroxide gave a viscous syrup which was again dissolved in 10% sodium hydroxide solution and filtered. An excess of ammonium chloride was added to the filtrate to give a colourless precipitate (pH kept at 8·2). The precipitate was extracted with benzene and the extract was dried (K_2CO_3); removal of solvent gave the base (X) (1·2 g.) as a pale brown syrup, the picrate of which was crystallised from methanol as *plates*, m.p. 169—170° (Found: C, 55·5; H, 5·3; N, 10·1. $C_{19}H_{23}NO_3,C_6H_3N_3O_7$ requires C, 55·35; H, 4·8; N, 10·3%).

A Mixture of Diastereoisomeric Racemates of OO-Dibenzylisoliensinine (V).—A stirred mixture of (±)-(X) (3·0 g.), (±)-(XI) (5·0 g.),[6] copper powder (480 mg.), potassium carbonate (1·75 g.), potassium iodide (163 mg.), and dry pyridine (16 ml.) was heated at 155—160° for 53 hr. in a current of nitrogen. The resultant mixture was cooled and extracted with benzene; the extract was filtered, washed with water, and dried (K_2CO_3). Removal of the solvent gave a brown viscous syrup (6·5 g.), which was chromatographed on silicic acid column (40 × 3·5 cm.).

Elution with chloroform (1·5 l.) and evaporation of each fraction (100 ml.) gave a viscous, oily base with a positive Beilstein test. The R_F value of this compound was identical with that of (XI). The column was eluted with chloroform (25 × 100 ml.) and then with chloroform–methanol (10 : 1) (4 l.); evaporation of the latter eluant mixture gave a mixture of diastereoisomeric racemates of *OO*-dibenzylisoliensinine (V) (1·1 g., 15·9%) as a pale yellow syrup with a negative Beilstein test. N.m.r. ($CDCl_3$): τ 7·61 (6H, s, 2 NCH_3), 6·37 (3H, s, OCH_3), 6·28 (3H, s, OCH_3), 6·23 (3H, s, OCH_3), 5·17 (2H, s, OCH_2Ph), 5·02 (2H, s, OCH_2Ph).

Recrystallisation of the dipicrate from benzene–hexane afforded *prisms*, m.p. 132—135° (Found: C, 60·35; H, 4·9; N, 8·6. $C_{51}H_{54}N_2O_6,2C_6H_3N_3O_7$ requires C, 60·55; H, 4·85; N, 8·95%). Purification of the perchlorate from acetone gave a glassy *product*, m.p. 122—124° (Found: C, 60·8; H, 6·1. $C_{51}H_{54}N_2O_6,2HClO_4,H_2O$ requires C, 60·7; H, 5·8%), $\nu_{max.}$ ($CHCl_3$) 3500 $cm.^{-1}$ (OH, water of crystallisation).

A Mixture of Diastereoisomeric Racemates of Isoliensinine (II).—A mixture of the base (V) (270 mg.), ethanol (70 ml.), and concentrated hydrochloric acid (70 ml.) was heated under reflux for 2 hr. in a current of nitrogen. The solvent was distilled off and the residue was basified with concentrated ammonium hydroxide solution and extracted with chloroform; the extract was dried (K_2CO_3) and the solvent

was removed to leave a brown syrup (180 mg.), the *perchlorate* of which was crystallised with ethanol–ether as prisms, m.p. 200—205° (decomp.) (Found: C, 53·55; H, 5·6; N, 3·4. $C_{37}H_{42}NO_6,2HClO_4,H_2O$ requires C, 53·1; H, 5·55; N, 3·7%). The i.r. spectrum ($CHCl_3$) of this free base (II) was identical with that of natural isoliensinine (donated by Prof. Tomita and Dr. Furukawa). Both specimens behaved similarly on t.l.c.

D-(−)-7-*Benzyloxy*-1,2,3,4-*tetrahydro*-6-*methoxy*-1-(4-*methoxybenzyl*)-2-*methylisoquinoline* (IXa).—To a solution of D-(−)-7-benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline [8] (XII) (2 g.) in methanol (100 ml.) and tetrahydrofuran (100 ml.) was added a solution of diazomethane in ether (50 ml.) [prepared from nitrosomethylurea (25 g.)]; the mixture was set aside at room temperature for 24 hr. Upon work up the non-phenolic base (IXa) (2 g.) was obtained as a yellow syrup, $[\alpha]_D^{10}$ −55·1° (*c* 3·27 in $CHCl_3$); the picrate crystallised (EtOH) as *cubes*, m.p. 78—80° (Found: C, 60·35; H, 5·25; N, 8·95. $C_{26}H_{29}NO_3,C_6H_3N_3O_7$ requires C, 60·75; H, 5·1; N, 8·85%).

D-(−)-1,2,3,4-*Tetrahydro*-7-*hydroxy*-1-(4-*methoxybenzyl*)-6-*methoxy*-2-*methylisoquinoline* (Xa).—A mixture of compound (IXa) (1·4 g.), ethanol (10 ml.), and concentrated hydrochloric acid (20 ml.) was heated under reflux on a water-bath for 2 hr. in a current of nitrogen. After the solvent had been distilled off, the residue was basified with concentrated ammonium hydroxide solution and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a pale yellow syrup (0·7 g.), $[\alpha]_D^{15}$ −114° (*c* 1·36 in MeOH) (lit.,[5,9] $[\alpha]_D^{20}$ −137°, in MeOH). Crystallisation of the picrate from chloroform–hexane afforded yellow *cubes*, m.p. 109—112° (lit.,[5,9] m.p. 136°) (Found: C, 55·05; H, 4·85; N, 10·25. $C_{19}H_{23}NO_3,C_6H_3N_3O_7$ requires C, 55·35; H, 4·85; N, 10·35%).

OO-*Dibenzylisoliensinine* (Va).—A stirred mixture of D-(−)-(XIa) [6] (1·7 g.), D-(−)-(Xa) (1·1 g.), copper powder (0·1 g.), potassium carbonate (0·58 g.), potassium iodide (0·55 g.), and pyridine (20 ml.) was heated and stirred at 160—170° in a current of nitrogen. After 53 hr., t.l.c. [silica gel, and chloroform–methanol (10 : 1) or chloroform–acetone (5 : 3)] showed that the spot corresponding to that of (XIa) had almost disappeared and the reaction mixture was then extracted with chloroform (200 ml.). The extract was filtered and the solvent was evaporated off under reduced pressure to give a brown syrup (1 g.), which was chromatographed on alumina (10 cm., inside diam., 1·5 cm.) with benzene as eluant. The eluate, which showed a different R_F value from the above two starting materials, no hydroxy-absorption in its i.r. spectrum, and a negative Beilstein test, was collected and evaporated to give a pale yellow syrup (300 mg.), the picrate of which crystallised from benzene–hexane as yellow *prisms*, m.p. 136—138° (Found: C, 60·55; H, 5·25; N, 8·8. $C_{51}H_{54}N_2O_6,2C_6H_3N_3O_7$ requires C, 60·55; H, 4·85; N, 8·95%), $[\alpha]_D^{15}$ −30° (*c* 1·41 in $CHCl_3$); n.m.r. ($CDCl_3$) [free base (Va)]: τ 7·65 (6H, s, $2NCH_3$), 6·31 (3H, s, OCH_3), 6·23 (3H, s, OCH_3), 6·18 (3H, s, OCH_3), 6·11 (2H, s, OCH_2Ph), 4·94 (2H, s, OCH_2Ph).

Isoliensinine (IIa).—A mixture of compound (Va) (210 mg.), ethanol (8 ml.), and concentrated hydrochloric acid (10 ml.) was heated on a water-bath for 2·5 hr. in a current of nitrogen. After removal of the solvent, the residue was made basic with concentrated ammonia and the resultant ammoniacal solution was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried (K_2CO_3), and evaporated to give a powder (150 mg.), which crystallised from chloroform–hexane to give isoliensinine (IIa), m.p. 96—98° * (Found: C, 70·95; H, 7·4; N, 4·0. $C_{37}H_{42}N_2O_6,H_2O$ requires C, 70·7; H, 7·05; N, 4·45%), $[\alpha]_D^{10}$ −39·2° (*c* 1·24 in EtOH) [lit.,[5,9] $[\alpha]_D^{29}$ −43·3° (*c* 0·95 in $CHCl_3$)], $\lambda_{max.}$ (95% EtOH) 286 mμ (log ε 4·01) [lit.,[5,9] $\lambda_{max.}$ (95% EtOH) 286 mμ (log ε 4·05)], ($CDCl_3$) τ 7·59 (3H, s, NCH_3), 7·48 (3H, s, NCH_3), 6·24 (3H, s, OCH_3), 6·17 (6H, s, $2OCH_3$) [lit.,[5] 7·62 (3H, NCH_3), 7·51 (3H, NCH_3), 6·30 (3H, OCH_3), 6·24 (6H, $2OCH_3$)].

OO-*Dimethylisoliensinine* (IVa).—To a solution of isoliensinine (IIa) (45 mg.) in methanol (20 ml.) was added an etheral solution (20 ml.) of diazomethane [prepared from nitrosomethylurea (2 g.)], and the mixture was set aside at room temperature for 2 days. The solvent was removed and the resultant pale yellow syrup (40 mg.) was chromatographed on alumina with chloroform as an eluant to give a syrup (20 mg.), the t.l.c. of which showed one spot, τ ($CDCl_3$) 7·56 (3H, s, NCH_3), 7·58 (3H, s, NCH_3), 6·40 (3H, s, OCH_3), 6·29 (3H, s, OCH_3), 6·23 (3H, s, OCH_3), 6·22 (3H, s, OCH_3), 6·19 (3H, s, OCH_3). The distyphnate crystallised as needles (ethanol), m.p. 133—135° (lit.,[5] m.p. 133—135°), $[\alpha]_D^{20}$ −81·6° (*c* 0·77 in acetone) [lit.,[5] $[\alpha]_D^{27}$ −81·5° (*c* 0·65 in acetone)], the n.m.r. spectrum and optical rotation of which were identical with those of an authentic sample, derived from natural isoliensinine.[5]

We thank Professor M. Tomita and Dr. Furukawa, Department of Pharmaceutical Sciences, Kyoto University for a gift of natural isoliensinine perchlorate. We are also grateful to Miss R. Kobayashi, Miss N. Nanjo, Miss A. Satoh, Miss R. Hasebe, and Miss T. Yamaki for microanalyses and to Miss Y. Tadano for n.m.r. spectra, in Tohoku University.

[8/283 *Received, February 27th*, 1968]

* Though our synthetic isoliensinine was obtained as a powder, the natural product was not available in this form. Therefore, synthetic and natural isoliensinines were compared as the corresponding *OO*-dimethylisoliensinine; their physical data were completely identical.

[8] T. Kametani and H. Yagi, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 1283.

[9] M. Tomita and H. Furukawa, *Tetrahedron Letters*, 1964, 2637.