CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 16 No. 5 May 1968

[Chem. Pharm. Bull. 16(5) 773—777 (1968)]

UDC 547.94.07:547.833.9.07

Bisbenzylisoquinoline Alkaloids and Related Compounds. Part XII.[1] Synthesis of Stereoisomeric Mixture of Cuspidaline (Studies on the Syntheses of Heterocyclic Compounds. CCXXIX[2])

Tetsuji Kametani and Fumio Satoh

Pharmaceutical Institute, Tohoku University School of Medicine[3]

(Received February 20, 1967)

Bischler–Napieralski reaction of the diamide (IX), which was obtained by Schotten–Baumann reaction of 4–hydroxy–3–methoxyphenethylamine (V) with the acid chloride (VII), gave the dihydroisoquinoline derivative (X), which was converted into the dimethiodide (XI). Reduction with sodium borohydride of the above dimethiodide, followed by hydrolysis with an ethanolic sodium hydroxide solution, afforded the stereoisomeric mixture of cuspidaline (I), mp 110° (sinters at 85°), which was also characterized as its O,O–dimethylcuspidaline (XIII), namely, O–methyldauricine. Furthermore, the attempt to obtain the quarternary salt of II and/or III by phenolic oxidative coupling of the dimethiodide (XIV) of I was examined, but resulted in failure.

Among three new phenolic bisbenzylisoquinoline alkaloids, namely, cuspidaline (I), limacine (II), and limacusine (III), which were isolated from *Limacia cuspidata* (Miers) Hook. f. et Thom. (Menispermaceae) collected in Borneo, the former cuspidaline (I) was obtained as a colorless oil or as an amorphous styphnate by Tomita and Furukawa.[4]

The purpose of the present investigation was to study the cyclization of the diamide (IX) in order to obtain the corresponding dihydroisoquinoline derivative (X) and its methiodide (XI) as possible intermediates for the synthesis of stereoisomeric mixture of cuspidaline (I). Furthermore, an attempt to obtain the quarternary salt of II and/or III by phenolic oxidative coupling of the methiodide (XIV) of I was examined.

Schotten–Baumann reaction of 4–hydroxy–3–methoxyphenethylamine (V), which was obtained by basification of the compound[5] (IV) with 1 N sodium hydroxide solution, with a solution of the acid chloride (VII) obtained from the acid (VI)[6] afforded the diamide (VIII), which was converted into the diamide (IX) by ethoxycarbonylation. This diamide (IX) showed a maximum at 3400 cm^{-1} (NH) and both carbonyl bands at 1755 (ester)

1) Part XI: T. Kametani, R. Yanase, S. Kano, and K. Sakurai, *Chem. Pharm. Bull.* (Tokyo), **15**, 56 (1967).
2) Part CCXXVIII: Yakugaku Zasshi, **88**, 583 (1968).
3) Location: *No. 85, Kita–4–bancho, Sendai.*
4) M. Tomita and H. Furukawa, *Tetrahedron Letters*, **No. 36**, 4293 (1966).
5) T. Kametani, S. Takano, and E. Karibe, *Yakugaku Zasshi*, **83**, 1035 (1963).
6) T. Kametani and K. Fukumoto, *Tetrahedron Letters*, **1964**, 2771; *J. Chem. Soc.*, **1964**, 6141.

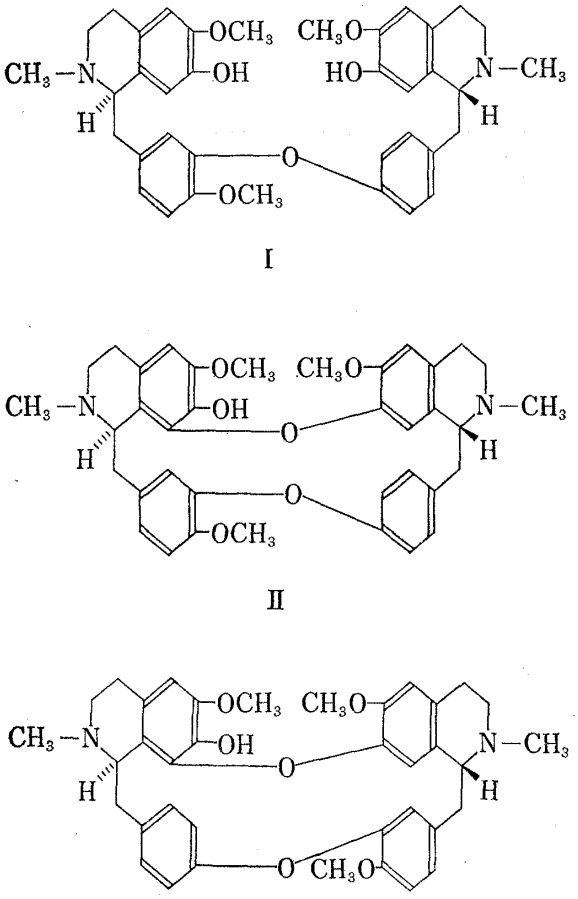

Chart 1

and 1653 (amide) cm^{-1}. Bischler–Napieralski reaction of the diamide (IX) with phosphoryl chloride in benzene gave the dihydroisoquinoline derivative (X), which was converted into the dimethiodide (XI) on being allowed to stand at room temperature in an excess of methyl iodide. Reduction of the compound (XI) with sodium borohydride in methanol–chloroform (1:1) gave the tetrahydroisoquinoline derivative (XII). Removal of the ethoxycarbonyl group by hydrolysis with an ethanolic sodium hydroxide solution afforded the compound (I) as a yellow powder, whose infrared spectrum showed a maximum at 3497 (OH) and N–methyl group at 2800 cm^{-1} (in $CHCl_3$). Recrystallization from chloroform–hexane gave a yellow powder, mp 110° (sinters at 85°), with the correct analysis, whose thin–layer chromatography showed one spot. The NMR spectrum of this compound revealed the presence of two N–methyl groups (7.54, 7.58 τ) and three methoxyl groups (6.20 τ), which were almost identical with those of natural cuspidaline (I) reported in the literature.[4]

In this case all the attempts to separate one of the two diastereoisomers in a crystalline state under a variety of chromatography were examined, among which chromatography on silicic acid, followed by recrystallization from chloroform–hexane, gave a small amount of colorless needles, mp 140.5—147.5°. Perhaps one of two diastereoisomers is thought to be obtained, but precise elucidation is under examination.

The natural cuspidaline was not available for comparison. Accordingly, methylation of the stereoisomeric mixture of synthetic cuspidaline with diazomethane gave O,O–dimethylcuspidaline, namely, O–methyldauricine (XIII), whose infrared spectrum was superimposable on that of natural O–methyldauricine in chloroform. The latter natural product was obtained by methylation of natural dauricine donated by Dr. R.H.F. Manske. The infrared spectra of the picrate of both specimens were also identical completely. These facts show that a synthesis of the stereoisomeric mixture of cuspidaline has been accomplished.

Furthermore, the patterns of NMR spectrum of synthetic O,O–dimethylcuspidaline (XIII) were similar to those of O–methyldauricine, but the IR spectra of both specimens were completely identical in chloroform. Moreover, it is well known that the IR spectrum of synthetic compound is identical with that of natural product having the same plane formula and a different configuration in case of bisbenzylisoquinoline derivatives containing one diphenyl ether linkage.[1,3–11]

7) T. Kametani, S. Takano, K. Masuko, and F. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **14**, 67 (1966).
8) T. Kametani and H. Yagi, *Tetrahedron Letters*, **No. 15**, 953 (1965); *idem*, *Chem. Pharm. Bull.* (Tokyo), **14**, 78 (1966).
9) T. Kametani, S. Takano, R. Yanase, C. Kibayashi, H. Iida, S. Kano, and K. Sakurai, *Chem. Pharm. Bull.* (Tokyo), **14**, 73 (1966).
10) T. Kametani, R. Yanase, S. Kano, and K. Sakurai, *J. Heterocyclic Chem.*, 3, 239 (1966).
11) T. Kametani, S. Takano, and K. Satoh, *J. Heterocyclic Chem.*, 3, 546 (1966).

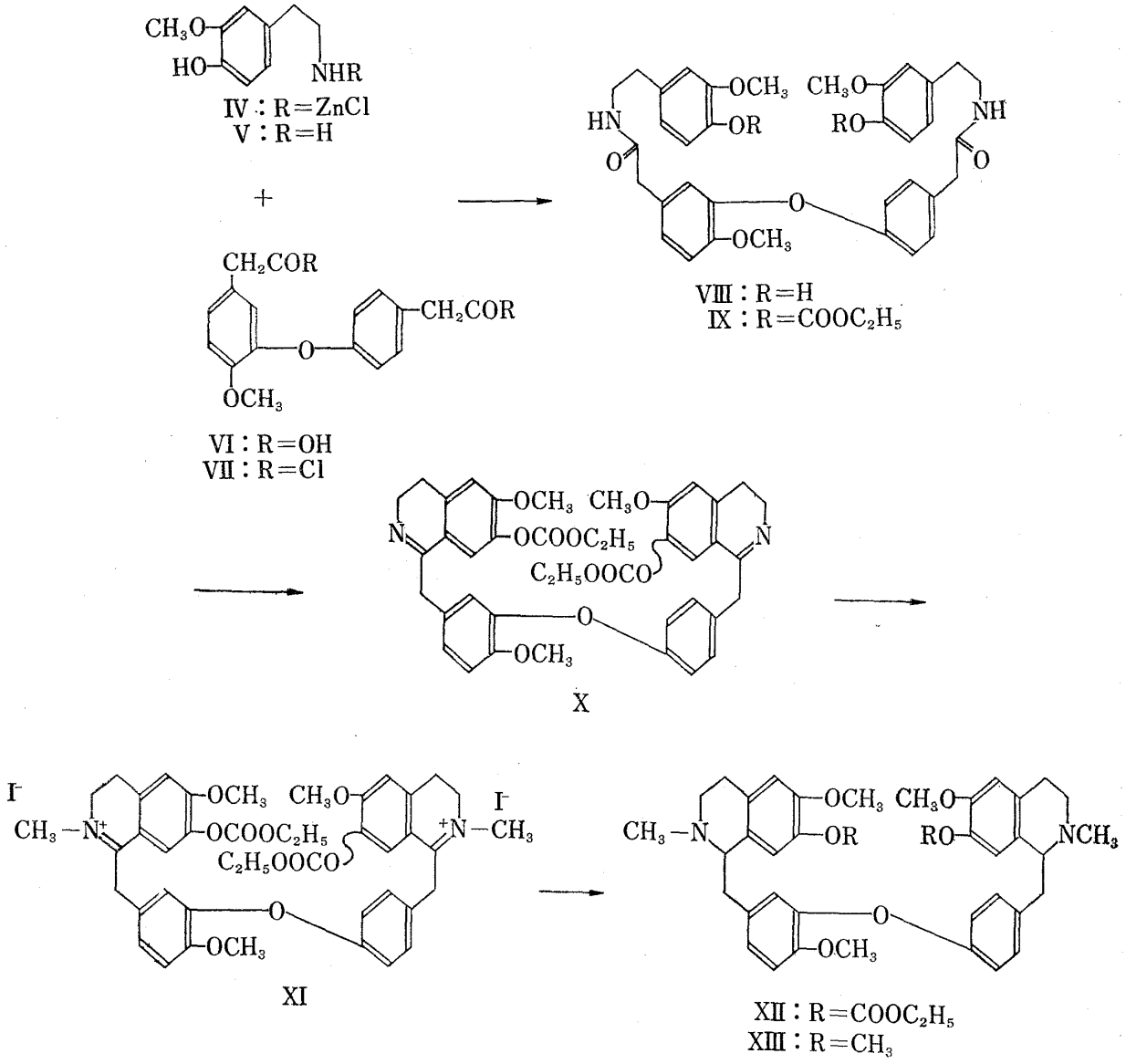

Chart 2

Finally, if the limacine (II) and limacusine (III) alkaloids would be derived from I by phenolic oxidation, it seems to be very interesting from the biogenetical point of view. Therefore, the attempts to obtain the methiodide of II and/or III by phenolic oxidative coupling of the methiodide (XIV) of I with potassium ferricyanide under various conditions were examined, but resulted in failure.

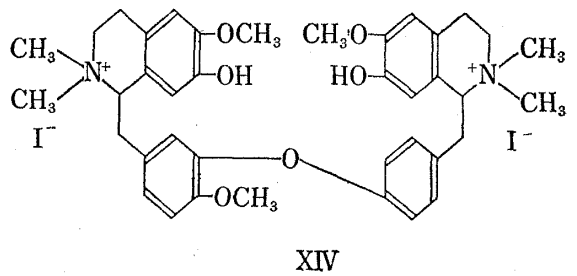

Chart 3

Experimental[12]

2-Methoxy-4′,5-di-(4-hydroxy-3-methoxyphenethylaminocarbonylmethyl)diphenyl Ether (VIII)——The acid (VI) (1 g) was refluxed on a water-bath for 1 hr with an excess of $SOCl_2$, and then the excess of $SOCl_2$

12) All melting point were not corrected.

was removed by distillation to give VII as a pale yellow syrup. The crude acid chloride (VII) was dissolved in 50 ml of abs. $CHCl_3$, to which solution was added dropwise with stirring a mixture of 2 g of amine zinc chloride complex (IV) and a calculated amount of 10% NaOH aq. solution within 30 min. The mixture was stirred at room temperature for 1 hr, and then extracted with $CHCl_3$. The solvent was washed with 10% HCl, saturated $NaHCO_3$ and NaCl aq. solution, dried on Na_2SO_4, and distilled to give 2.31 g of a brown syrup, which could not be crystallized and therefore was used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): ν_{OH} 3500, ν_{NH} 3400, ν_{-CH_2-} 2920, 2830, $\nu_{C=O}$ 1653 (amide).

2-Methoxy-4′,5-di(4-ethoxycarbonyloxy-3-methoxyphenethylaminocarbonylmethyl)diphenyl Ether (IX)——The preceding amide (VIII) (2.25 g) was dissolved in 100 ml of abs. $CHCl_3$ with 2.7 g of diethylamine. To the above solution was added gradually on cooling a solution of 2.7 g of ethyl chlorocarbonate in 50 ml of abs. $CHCl_3$. The mixture was allowed to stand at room temperature for 2 hr and then washed with saturated NaCl aq. solution. The solvent was dried on Na_2SO_4, and distilled off, to give 2.12 g of IX as a pale brown syrup, whose recrystallization was so difficult that it was used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1755 (ester), $\nu_{C=O}$ 1653 (amide).

2-Methoxy-4′,5-bis-(7-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-isoquinolylmethyl)diphenyl Ether (I) (Stereoisomeric Mixture of Cuspidaline)——A mixture of 2.17 g of the diamide (IX), 50 ml of dry benzene, and 7 ml of $POCl_3$ was refluxed on a water-bath for 4.5 hr. An excess of *n*-hexane (300 ml) was added to the reaction mixture, and it was allowed to stand overnight. The upper layer was then removed by decantation. The residue was repeatedly washed with *n*-hexane and then dissolved in 200 ml of $CHCl_3$, whose organic solvent layer was washed with saturated $NaHCO_3$ aq. solution and water, and dried on K_2CO_3. Removal of the solvent in the presence of N_2 gave 2.1 g of the 3,4-dihydroisoquinoline derivative (X) as a brown syrup, which could not be purified and used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1755 (ester), $\nu_{C=N}$ 1623.

A mixture of 2.1 g of the above compound (X) and 20 ml of MeI was allowed to stand at room temperature for 2 hr, and removal of the excess of MeI gave 2.3 g of XI. $NaBH_4$ (2 g) was added in small portions with shaking to a solution of the above dried dimethiodide (XI) in 100 ml of MeOH–$CHCl_3$ (1:1). The mixture was stirred for 1 hr and then the solvent was removed by distillation, a brown residue being treated with a small amount of water, made basic with saturated $NaHCO_3$ aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried on Na_2SO_4, and distilled off, to give 2 g of the tetrahydroisoquinoline derivative (XII) as a yellowish-brown syrup, which was used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): ν_{N-Me} 2790, $\nu_{C=O}$ 1755 (ester).

A mixture of 1.58 g of the above compound (XII), 3 g of NaOH and 100 ml of EtOH was heated under reflux for 2 hr. After the reaction, the solvent was removed by distillation *in vacuo* and the residue was mixed with a small amount of water. An ammoniacal solution, which was obtained by the addition of crystalline NH_4Cl to the above aqueous solution, was extracted with $CHCl_3$. The solvent layer was separated, washed with saturated NaCl aq. solution, dried on Na_2SO_4, and distilled off, to give 1.4 g of I as a brown syrup, whose recrystallization from $CHCl_3$–*n*-hexane afforded 400 mg of a yellow powder, mp 110° (sinters at 85°). Thin-layer chromatography on Wakogel B-5 using a solution of $CHCl_3$–MeOH (6:1) showed one spot. *Anal.* Calcd. for $C_{37}H_{42}O_6N_2$: C, 69.14; H, 6.59; N, 4.36. Found: C, 69.04; H, 6.69; N, 3.94. IR cm^{-1} ($CHCl_3$): ν_{OH} 3497, ν_{N-Me} 2800, $\nu_{>C=C<}$ 1605. NMR (τ) ($CDCl_3$): 7.54 (3H, singlet, N-Me), 7.58 (3H, singlet, N-Me), 6.20 (3H, singlet, OCH_3), 5.50 (1H, broad singlet, OH), 6.90—7.72 (11H, multiplet, aromatic protons).

The above yellow powder was chromatographed on silicic acid using $CHCl_3$–MeOH as solvent to give a pale yellow powder, whose recrystallization from $CHCl_3$–hexane afforded colorless needles, mp 140.5—147.5°, whose IR spectrum was identical with that of the above sample in $CHCl_3$.

Stereoisomeric Mixture of O,O-Dimethylcuspidaline (O-Methyldauricine) (XIII)——To a solution of 40 mg of the above compound (I) in a mixture of 30 ml of MeOH–$CHCl_3$–dioxane (1:1:1) was added a solution of an excess of CH_2N_2 in ether, and the mixture was allowed to stand in a refrigerator for 2 days. After the reaction, removal of the solvent gave a yellow syrup which was chromatographed on alumina to give 25 mg of a yellow syrup. The IR spectrum of this synthetic sample was superimposable on that of natural O-methyldauricine.[1] Recrystallization of the dipicrate from EtOH gave a yellow powder, mp 120—125°.[13]

Stereoisomeric Mixture of O,O-Dimethylcuspidaline Dimethiodide (XIV)——To a solution of 100 mg of (XIII) in 100 ml of abs. MeOH was added 10 ml of MeI, and the mixture was allowed to stand at room temperature for 2 hr. After the reaction, removal of the excess of MeI gave 140 mg of XIV as a brown syrup, which could not be obtained in a crystalline state. Recrystallization of O-picrate, which was derived

13) Regarding the mp of synthetic O-methyldauricine, we have reported the melting point 145° (sinters at 130°).[1] Furthermore, Popp, *et al.*[14] recently reported mp 137—140° for it. Since the synthetic methods and the formation-ratio of both diasteroisomers are different respectively, the difference between the melting points of the samples seems to be a matter of course.

14) F.D. Popp, H.W. Gibson, and A.C. Noble, *J. Org. Chem.*, 31, 2296 (1966).

by treatment of XIV with sodium picrate in MeOH, from Me_2CO–ether afforded a yellow powder, mp 145—155°. *Anal.* Calcd. for $C_{38}H_{48}O_6N_2 \cdot 2C_6H_2O_7N_3 \cdot 5H_2O$:[15] C, 51.69; H, 5.24. Found: C, 51.85; H, 5.61.

Acknowledgement We thank Miss R. Kobayashi and Miss R. Hasebe in the Pharmaceutical Institute, Tohoku University School of Medicine for microanalyses.

15) This was dried on P_2O_5 at room temperature for 2 days, but, since it was very hygroscopic, it absorbed moisture during determination on a balance.