Notes

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Capaurimine and Related Compounds. II.[1] Syntheses of Position Isomers of Capaurimine and Capauridine (Studies on the Syntheses of Heterocyclic Compounds. CCCXIII[2])

Tetsuji Kametani,[3a] Hideo Iida, Toyohiko Kikuchi,[3b] Kazumi Ohkubo, and Keiichiro Fukumoto[3a]

Pharmaceutical Institute, Tohoku University[3a] *and Tokyo College of Pharmacy*[3b]

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Capaurimine, capaurine and capauridine, which were isolated from several *Corydalis* species,[4] were assigned to structure I,[5] II and III,[6] respectively, through the chemical degradations by Manske. Kametani, *et al.*[7] have recently proved the stereostructure of capaurine to be *cis*-quinolizidine type compound by X-ray analysis. Recently, the alkaloids having methoxyl and/or hydroxyl groups at 5-, 6- and 7-positions on isoquinoline rings such as takatonine (IV),[8] thalifendlerine (V)[9] and preocoteine (VI)[10] were isolated and had an interesting point on their biogeneses. On the other hand, several protoberberines showed very interesting physiological activities,[11] but those of pentasubstituted protoberberines had not been investigated. On the basis of the above points we synthesized two new protoberberines (VII) and (VIII) which were two kinds of position isomers of capaurimine and capauridine, respectively.

The former protoberberine, 5,6,13,13a-tetrahydro-4,9-dihydroxy-2,3,10-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (VII), was synthesized with the method which was exploited by Kametani[12] in the synthesis of scoulerine (IX).

Bischler–Napieralski cyclization of the amide (X), which was prepared by the fusion of 2-benzyloxy-3,4-dimethoxyphenethylamine (XI)[13] with 5-benzyloxy-2-bromo-4-methoxyphenethylamine (XII), gave the 3,4-dihydroisoquinoline (XIII). After reduction of this compound (XIII) with sodium borohydride, followed by debenzylation of tetrahydroisoquinoline (XIV) with hydrochloric acid, the resulting phenolic base (XV) was subjected to Mannich reaction to give the corresponding bromoprotoberberine (XVI). Debromination of base (XVI) with zinc and alkali gave our expected 4,9-dihydroxy-2,3,10-trimethoxyprotoberberine (VII), whose structure was assigned by Bohlmann band in the IR spectrum and AB quartet (J=8.0 cps, C_{11}–H and C_{12}–H) at 6.58 and 6.81 ppm in the NMR spectrum.[1] This fact revealed that the aromatic protons on ring D were vicinal each other.

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3) Location: *a*) *Aobayama, Sendai*; *b*) *Kashiwagi, Shinjuku, Tokyo.*
4) R.H.F. Manske, *Can. J. Res.*, **18B**, 80 (1940); **20B**, 49 (1942).
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10) M. Shamma, R.J. Shine, and B.S. Dudock, *Tetrahedron*, **23**, 2887 (1967).
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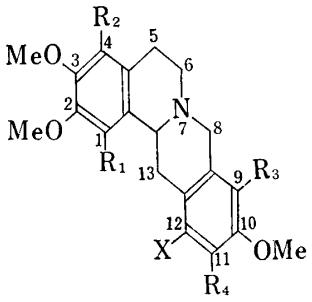
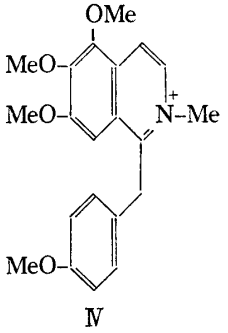
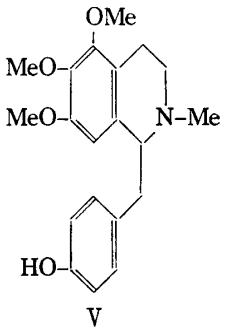
13) T. Kametani, S. Kano, Y. Watanabe, and T. Kikuchi, *Yakugaku Zasshi*, **87**, 406 (1967).





I : $R_1=R_3=OH$, $R_2=R_4=X=H$
II : $R_1=OH$, $R_2=R_4=X=H$, $R_3=OMe$
III : racemate of II
VII : $R_1=R_4=X=H$, $R_2=R_3=OH$
VIII : $R_1=R_3=X=H$, $R_2=R_4=OMe$
XVI : $R_1=R_4=H$, $R_2=R_3=OH$, X=Br



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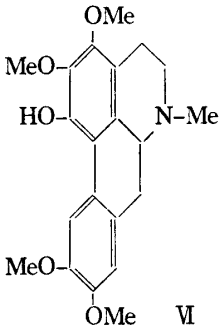

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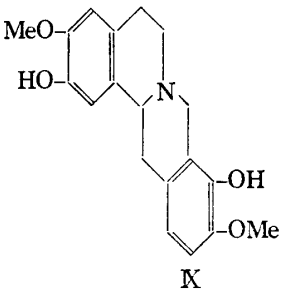
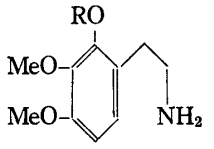
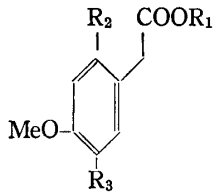


IX

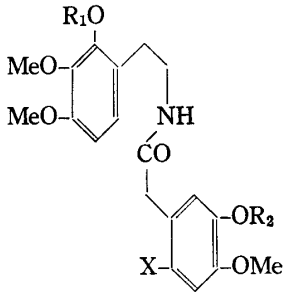
Chart 1



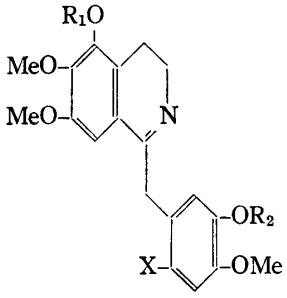
XI : $R=CH_2Ph$
XVII : R=Me



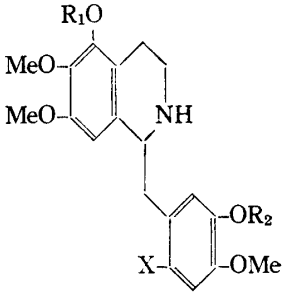
XII : $R_1=Me$, $R_2=Br$, $R_3=OCH_2Ph$
XVIII : $R_1=R_2=H$, $R_3=OMe$



X : $R_1=R_2=CH_2Ph$, X=Br
XIX : $R_1=R_2=Me$, X=H



XIII : $R_1=R_2=CH_2Ph$, X=Br
XX : $R_1=R_2=Me$, X=H



XIV : $R_1=R_2=CH_2Ph$, X=Br
XV : $R_1=R_2=H$, X=Br
XXI : $R_1=R_2=Me$, X=H

Chart 2

The second protoberberine, 5,6,13,13a-tetrahydro-2,3,4,10,11-pentamethoxy-8H-dibenzo-[*a*,*g*]quinolizine (VIII), was synthesized by usual method as follows. The fusion of 2,3,4-trimethoxyphenethylamine (XVII) and homoveratric acid (XVIII), followed by Bischler–Napieralski reaction, gave 3,4-dihydroisoquinoline (XX), whose reduction with sodium borohydride afforded 1,2,3,4-tetrahydroisoquinoline (XXI). Mannich reaction of the above isoquinoline (XXI) gave the protoberberine (VIII), whose structure was characterized by its IR and NMR spectra described in experimental section. The physiological activities of these synthetic protoberberines are under examination.

Experimental[14]

N-(2-Benzyloxy-3,4-dimethoxyphenethyl)-2-(5-benzyloxy-2-bromo-4-methoxyphenyl)acetamide (X)——A mixture of 2.8 g of 2-benzyloxy-3,4-dimethoxyphenethylamine[13] (XI) and 3.6 g of methyl 5-benzyloxy-2-bromo-4-methoxyphenylacetate (XII) was heated at 170—180° in an oil-bath for 5 hr to give a viscous syrup, whose recrystallization from EtOH afforded 5.4 g of the amide (X) as colorless needles, mp 128—130°. *Anal.* Calcd. for $C_{33}H_{34}O_6NBr$: C, 63.87; H, 5.52; N, 2.26. Found: C 63.45; H 5.55; N, 2.58. IR cm^{-1} ($CHCl_3$): ν_{NH} 3390, $\nu_{C=O}$1670.

5-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (XIII)——A mixture of 5 g of the preceding amide (X), 15 ml of $POCl_3$ and 50 ml of dry benzene was heated on a water-bath for 3 hr. After an excess of hexane had been added to the above reaction mixture, it was allowed to stand overnight. Collection of the precipitate and recrystallization from MeOH–ether afforded 4 g of 3,4-dihydroisoquinoline (XIII) hydrochloride as colorless needles, mp 208—210°. *Anal.* Calcd. for $C_{33}H_{32}O_5NBr \cdot HCl$: C, 62.00; H, 5.20; N, 2.29. Found: C, 62.42; H, 5.34; N, 2.52.

5-Benzyloxy-1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (XIV)——To a stirred solution of 3.0 g of the above hydrochloride of XIII in 100 ml of $CHCl_3$ was added portionwise 3.0 g of $NaBH_4$ at room temperature, and the resultant mixture was refluxed on a water-bath for 1 hr. After the solvent had been distilled *in vacuo*, the residue was decomposed with 5% NaOH aq. solution and the resulting alkaline solution was extracted with ether in order to remove the precipitate. The ethereal extract was washed with water, dried over K_2CO_3, and evaporated to give the crystals, whose recrystallization from MeOH gave 1.8 g of 1,2,3,4-tetrahydroisoquinoline derivative (XIV) as colorless needles, mp 91—92°. *Anal.* Calcd. for $C_{33}H_{34}O_5NBr \cdot H_2O$[15]: C, 62.60; H, 5.79; N, 2.25, Found: C, 62.75; H, 5.65; N 2.61.

1-(2-Bromo-5-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-5-hydroxy-6,7-dimethoxyisoquinoline (XV)——A mixture of 2.0 g of the above compound (XIV) and 50 ml of EtOH–conc.HCl (1:1) was heated on a water-bath for 2 hr. After the solvent had been distilled *in vacuo*, recrystallization of the residue from MeOH–ether afforded 1.2 g of the HCl salt of XV as colorless prisms, mp 175—177° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_5NBr \cdot HCl \cdot 1.5H_2O$[15]: C, 46.78; H, 5.37; N, 2.87. Found: C, 46.75; H, 5.07; N, 2.54.

12-Bromo-5,6,13,13a-tetrahydro-4,9-dihydroxy-2,3,10-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (XVI)——A mixture of 500 mg of the above hydrochloride of XV, 15 ml of water and 15 ml of 37% CH_2O was heated on a water-bath for 3 hr. After cooling, the reaction mixture was basified with NH_4OH and extracted with EtOAc. The extract was washed with water, dried over K_2CO_3, and evaporated to give 400 mg of a syrup, whose recrystallization from MeOH afforded the bromo-compound (XVI) as colorless needles, mp 103—105°. *Anal.* Calcd. for $C_{20}H_{22}O_5NBr \cdot 0.5H_2O$[15]: C, 53.94; H, 5.20; N, 3.15. Found: C, 53.83; H, 5.22; N, 3.06.

5,6,13,13a-Tetrahydro-4,9-dihydroxy-2,3,10-trimethoxy-8H-dibenzo[*a*,*g*]quinolizine (VII)——A mixture of 200 mg of the above bromide (XVI), 5 ml of 10% NaOH aq. solution and 300 mg of Zn powder was refluxed at 130—140° in an oil-bath for 3 hr. After the precipitate had been removed by filtration, the filtrate was made basic with crystalline NH_4Cl and extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and evaporated to give a syrup, whose recrystallization from MeOH afforded 100 mg of the 4,9-dihydroxy-derivative (VII) as colorless needles, mp 245—247°. *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.00; H, 6.40; N, 3.81. IR cm^{-1} ($CHCl_3$): ν_{OH} 3410. NMR (ppm) [$(CD_3)_2SO$]: 3.69 (3H, singlet, OCH_3), 3.79 (6H, singlet, two OCH_3), 6.47 (1H, singlet, C_1–H), and 6.58, 6.81 (2H, two doublets, J=8.0 cps, C_{11}–H and C_{12}–H).

N-(2,3,4-Trimethoxyphenethyl)-3,4-dimethoxyphenylacetamide (XIX)——A mixture of 4.2 g of 2,3,4-trimethoxyphenethylamine (XVII) and 4.0 g of 3,4-dimethoxyphenylacetic acid (XVIII) was heated at 180° in a current of N_2 for 2 hr. After cooling, the mixture was taken in $CHCl_3$ and the extract was washed with 5% HCl aq. solution, 5% NaOH aq. solution and water. The extract was then dried over K_2CO_3 and the solvent was distilled to leave 7.5 g of the amide (XIX) as a yellowish-orange viscous syrup, which was recrystallized from EtOH to give colorless needles, mp 104—105°. *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99; N, 3.60. Found: C, 65.02; H, 7.18; N, 3.62. IR cm^{-1} ($CHCl_3$): ν_{NH} 3390, $\nu_{C=O}$ 1655.

3,4-Dihydro-5,6,7-trimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (XX)——A mixture of 5.7 g of the amide (XIX), 110 ml of dry benzene, and 6.0 g of $POCl_3$ was refluxed on a water-bath for 2 hr. The excess of $POCl_3$ and benzene were distilled off *in vacuo* and the residue was washed with ether to afford 7.0 g of 3,4-dihydroisoquinoline (XX) hydrochloride as a yellowish-orange viscous syrup, whose perchlorate was

14) All melting points were not corrected.

15) These compounds (XIV), (XV) and (XVI) were dried on P_2O_5 at 50° for 2 days under reduced pressure. In this case the presence of water of crystallization could not be detected because of the existence of hydroxy and amino groups in the IR spectra, but, since the final compound (VII) showed the correct analysis, the composition of the above three compounds was found to be correct.

recrystallized from EtOH to give pale yellow needles, mp 227—229°. *Anal.* Calcd. for $C_{21}H_{25}O_5N \cdot HClO_4$: C, 53.45; H, 5.55; N, 2.97. Found: C, 53.36; H, 5.50; N, 2.72. IR cm^{-1} (KBr): $\nu_{C=\overset{+}{N}H}$ 1655.

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (XXI)——To a suspension of 0.20 g of 3,4-dihydroisoquinoline (XX) perchlorate in 50 ml of MeOH was added portionwise 0.2 g of $NaBH_4$ with stirring at room temperature, and the stirring was continued for further 1 hr at room temperature. After refluxing for 1 hr, the reaction mixture was worked up as usual, and the benzene extract was dried over K_2CO_3 and the solvent was removed by distillation to leave 141 mg of 1,2,3,4-tetrahydroisoquinoline (XXI) as a pale yellow viscous syrup, whose oxalate was recrystallized from EtOH to give colorless needles, mp 205—207°. *Anal.* Calcd. for $C_{21}H_{27}O_5N \cdot C_2H_2O_4$: C, 59.60; H, 6.31; N, 3.02. Found: C, 59.21; H, 6.49; N, 2.87.

5,6,13,13a-Tetrahydro-2,3,4,10,11-pentamethoxy-8H-dibenzo[*a*,*g*]quinolizine (VIII)——1,2,3,4-Tetrahydroisoquinoline (XXI) hydrochloride (387 mg), prepared from the oxalate of XXI as usual, was mixed with 10 ml of 37% CH_2O and 10 ml of water, and the resultant mixture was heated on a water-bath for 2 hr. After cooling, the reaction mixture was basified with conc. NH_4OH aq. solution and extracted with benzene. The extract was washed with water and dried over K_2CO_3. Removal of the solvent afforded 238 mg of quinolizine derivative (VIII) as a pale yellowish-orange viscous syrup, which was recrystallized from EtOH to give colorless needles, mp 135—136°. *Anal.* Calcd. for $C_{22}H_{27}O_5N$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.86; H, 7.19; N, 3.44. IR cm^{-1} (KBr): ν_{max} 2720—2800 (Bohlmann bands). NMR (ppm) (CCl_4): 3.72 (9H, singlet, three OCH_3), 3.76 (3H, singlet, OCH_3), 3.78 (3H, singlet, OCH_3), 6.41 (2H, singlet, aromatic protons), and 6.49 (1H, singlet, aromatic proton).

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Studies on Application of Amino Acid as Medicinal Agent. II.[1] Reaction of Amino Acid Ester with Difunctional Grignard Reagent

SEIGORO HAYASHI, MITSURU FURUKAWA, YOKO FUJINO,[2a] and TADASHI OHKAWARA[2b]

Faculty of Pharmaceutical Sciences, Kumamoto University[2a] and Tanabe Seiyaku Co., Ltd.[2b]

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In the previous paper, in order to find non-narcotic analgesis, a number of substituted amino-*tert*-alcohol derivatives were synthesized by the reaction of various substituted amino acid esters with a variety of Grignard reagents. Later, we attempted to prepare cyclic amino-*tert*-alcohols. This paper deals with the reaction of N,N-disubstituted α- and β-amino acid ester with difunctional Grignard reagent containing polymethylene group.

The reaction was carried out using ethyl piperidino and pyrrolidinoacetate as α-amino acid ester, and ethyl N,N-dimethyl-β-amino, N,N-diethyl-β-amino, β-piperidino and β-pyrrolidinopropionate as β-amino acid ester. These amino acid esters were prepared by the reaction of ethyl chloroacetate and ethyl acrylate with the corresponding amines, respectively. While, difunctional Grignard reagent was prepared by treating polymethylenedihalide, containing more than two carbon atoms in polymethylene group, with magnesium in absolute ether

1) Part I: S. Hayashi, M. Furukawa, Y. Fujino, and T. Ohkawara, *Chem. Pharm. Bull.* (Tokyo), 17, 145 (1969).

2) Location: *a*) *Oe-hon-machi, Kumamoto*; *b*) *Kashima-cho, Higashiyodogawa, Osaka.*