Pharmaceutical Institute, School of Medicine
Tohoku University and Tokyo College of Pharmacy

Studies on the Syntheses of Heterocyclic Compounds. CLXXIV (1). An Approach to the Synthesis of Oxyacanthine and Berbamine.

Tetsuji Kametani, Hideo Iida, Shinzo Kano, Sadao Tanaka,
Keiichiro Fukumoto, Shiroshi Shibuya, and Haruhiko Yagi .

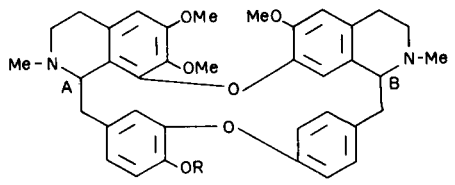
Schotten-Baumann reaction of the amine (X) with 4-benzyloxy-3,4'-oxydiphenylacetyl chloride (XI) gave two amides, (XIIa) and (XIIb), which were cyclized to give the corresponding 3,4-dihydroisoquinolines, respectively. Methylation of the above 3,4-dihydroisoquinolines, followed by hydrolysis, afforded the compounds having the same composition as berbamine (Ia) and oxyacanthine (Ib), whose structures are under examination.

The alkaloids oxyacanthine and berbamine found in the roots of *Berberis vulgaris* L., *B. aquifolium* Pursh (2,3), and in *B. thunbergii* DC. have been known for a long time, and their structures were investigated by Bruchhausen (4,5), Inubushi (6), Fujita (7), and Tomita (8,9). The formula (Ia) was given for berbamine, m.p. 170-172°, and formula (Ib) was given for oxyacanthine, m.p. 216-217°. Pycnamine (IIa) and repandine (IIb) are diastereoisomers of berbamine (Ia) and oxyacanthine (Ib). Furthermore, pycnamine (10) (IIa), m.p. 186-187°, and repandine (11,12) (IIb), m.p. 255°, have been examined. Synthetic attempts to obtain the tetrandrine (Ie) which has the same planar structure as berbamine have hitherto been made by Kondo and coworkers (13,14), but total synthesis of berbamine and oxyacanthine have not yet been achieved.

The purpose of the present investigation was to study the cyclization of the diamides (XIIa) and (XIIb) in order to obtain the corresponding 3,4-dihydroisoquinolines (XIIIa, XIIIb, XIIIc, or XIIId), which were converted into the 1,2,3,4-tetrahydroisoquinolines (XIVa, XIVb, XIVc, or XIVd) as possible intermediates for the syntheses of the compound having the same composition as berbamine and oxyacanthine; further methylation, followed by hydrolysis, was studied, leading eventually to the syntheses of two diastereoisomeric mixtures having the same composition as the natural products, (Ia) and (Ib).

The attempted preparation of the amine (X) by various methods (13,15,16) gave a poor yield. Among them, Tomita, *et al.*, (16) reported that the Ullmann reaction between 5-bromo-3,4-dimethoxybenzaldehyde acetal (VI) and vanillin acetal gave the expected compound (VII) in about 10% yield. In this case, since vanillin acetal was found to be labile especially to distillation (17), the Ullmann reaction between compound VI and acetylvanillin acetal (V), obtained by the reaction of acetylvanillin (IV) with ethyl orthoformate, gave the expected diacetal (VII) in 53% yield. Hydrolysis of VII with 20% hydrochloric acid in acetic acid gave the dialdehyde (VIII) in 95%

Chart I

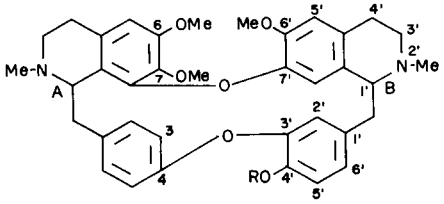


Ia: R = H; A = R, B = S

IIa: R = H; A = R, B = R

IIIa: R = CH_2Ph

Ie: R = Me; A = S, B = S



Ib: R = H; A = S, B = R

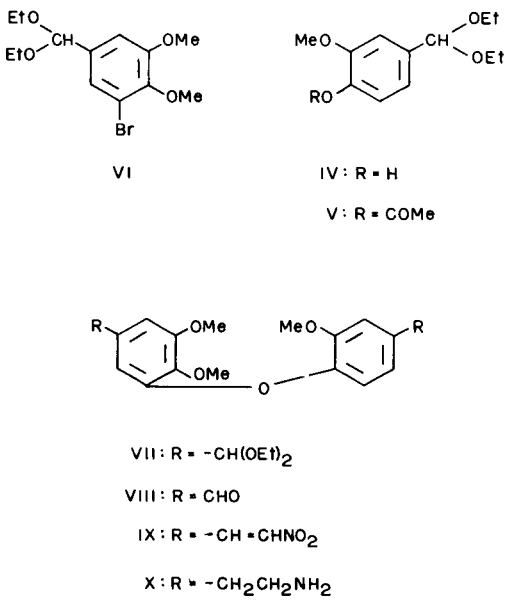
IIb: R = H; A = S, B = S

IIIb: R = CH_2Ph

yield, which was converted into the ω-nitrostyrene derivative (IX) by condensing it with nitromethane. Reduction of IX with lithium aluminum hydride gave the amine (X), whose oxalate was identical with an authentic sample (13a).

The Schotten-Baumann reaction of the amine (X) with 4-benzyloxy-3,4'-oxydiphenyldiacetyl chloride (18) (XI) gave a mixture of amides (XIIa) and (XIIb), whose alumina-chromatography afforded two compounds, (A_1), m.p. 92° dec. and (B_1), m.p. 177-183°. During the chromatographic separation each fraction from the various mixed solvents was inspected by thin-layer chromatography. Although the infrared spectra of both amides (A_1 and B_1) were very similar and could not be differentiated, the R_F values were different, however at this stage it was not possible to ascertain which of the amides corresponded to the structures XIIa and XIIb.

Chart 2



The Bischler-Napieralski cyclization of compound A_1 with phosphoryl chloride in a large amount of chloroform as the solvent gave the 3,4-dihydroisoquinoline derivative (A_2), which was converted into the methiodide (A_3). Reduction of the compound (A_3), followed by hydrolysis of the resultant compound (A_4), gave the compound (A_5) as a grayish-white powder, m.p. 190-195°.

On the other hand, cyclization of compound (B_1) under the same condition gave the 3,4-dihydroisoquinoline derivative (B_2), which was converted into 1,2,3,4-tetrahydroisoquinoline derivative (B_3) by sodium borohydride reduction. Methylation of the compound (B_3) by the Eschweiler-Clarke reaction, followed by hydrolysis of the resultant *O*-benzyl derivative (B_4), afforded the compound (B_5) as a pale yellow powder, m.p. 195-200°.

After repeated recrystallization and preparative thin-layer chromatography of both compounds (A_5) and (B_5), the infrared spectra of both synthetic specimens were found to be similar to those of natural berbamine and oxyacanthine as shown in Figures 1-4, however, there are slight differences

Chart 3

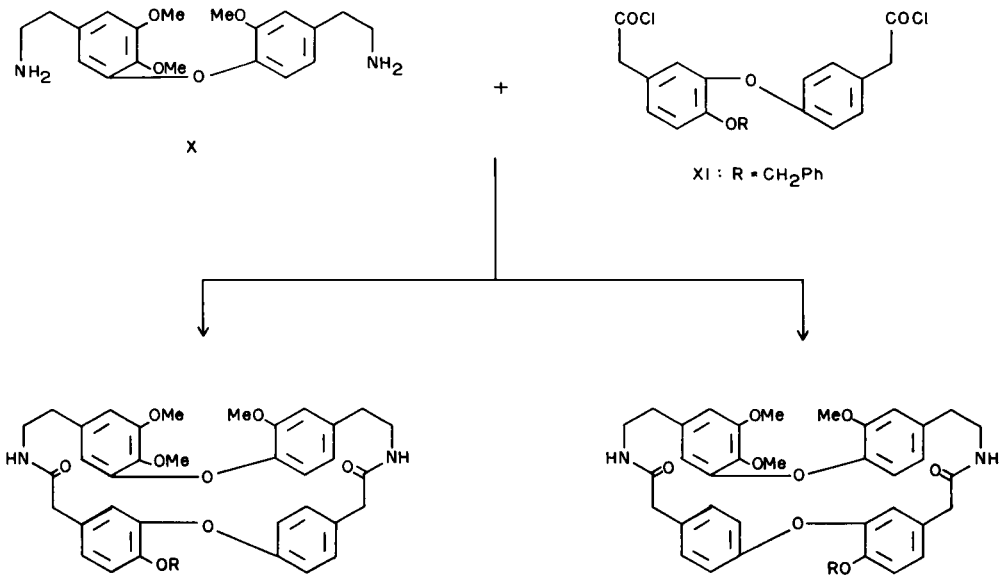
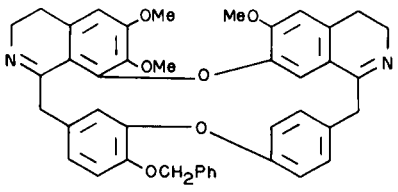
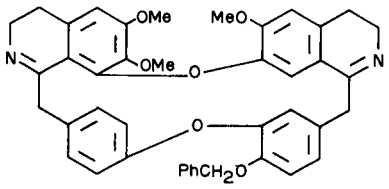


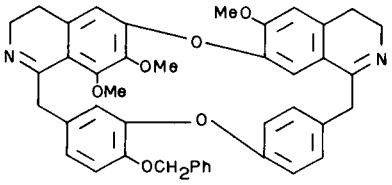
Chart 4



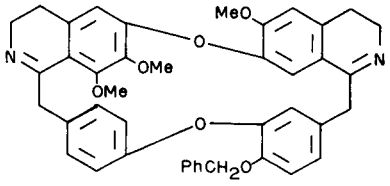
XIIIa



XIIIb

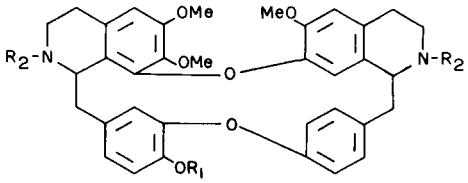


XIIIc



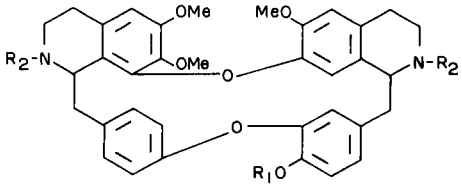
XIIId

Chart 5



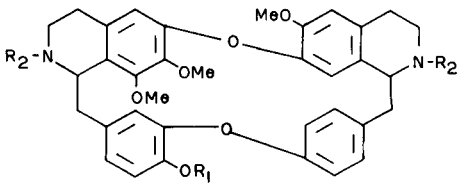
Ia: R_1 = H; R_2 = Me

XIVa: R_1 = CH_2Ph; R_2 = H



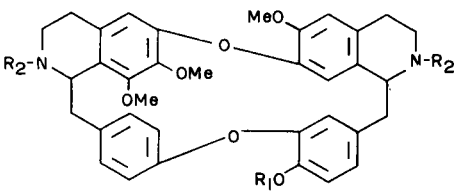
Ib: R_1 = H; R_2 = Me

XIVb: R_1 = CH_2Ph; R_2 = H



Ic: R_1 = H; R_2 = Me

IIIc: R_1 = CH_2Ph; R_2 = Me



Id: R_1 = H; R_2 = Me

IIId: R_1 = CH_2Ph; R_2 = Me

Figure 1. The Infrared Spectrum of Natural Berbamine in $CHCl_3$.

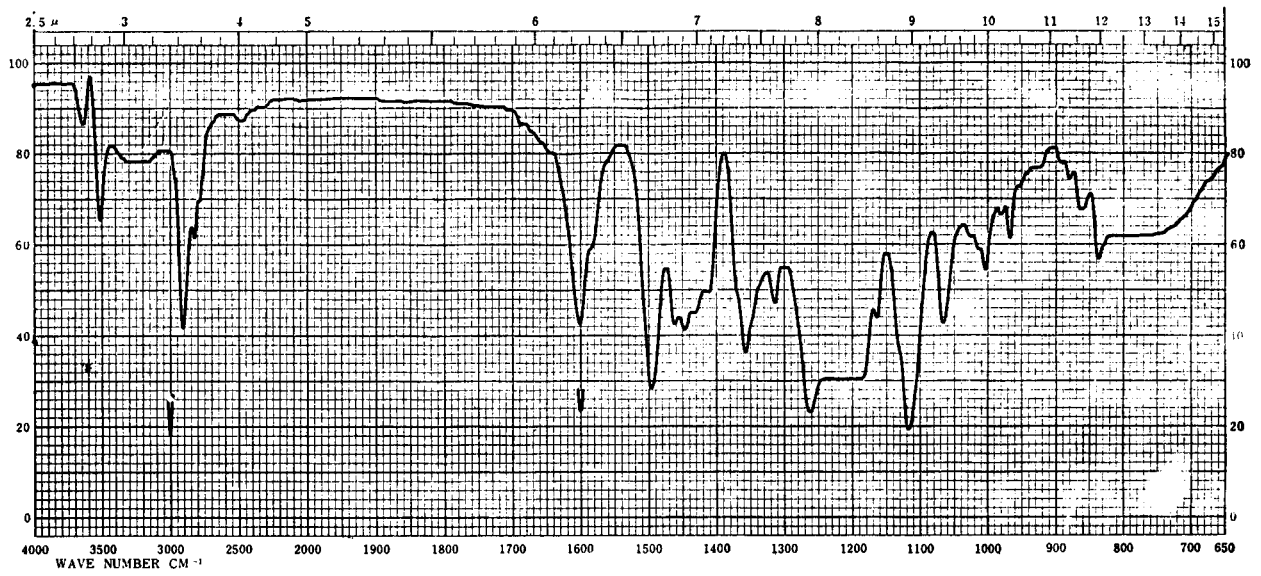


Figure 2. The Infrared Spectrum of Natural Oxyacanthine in $CHCl_3$.

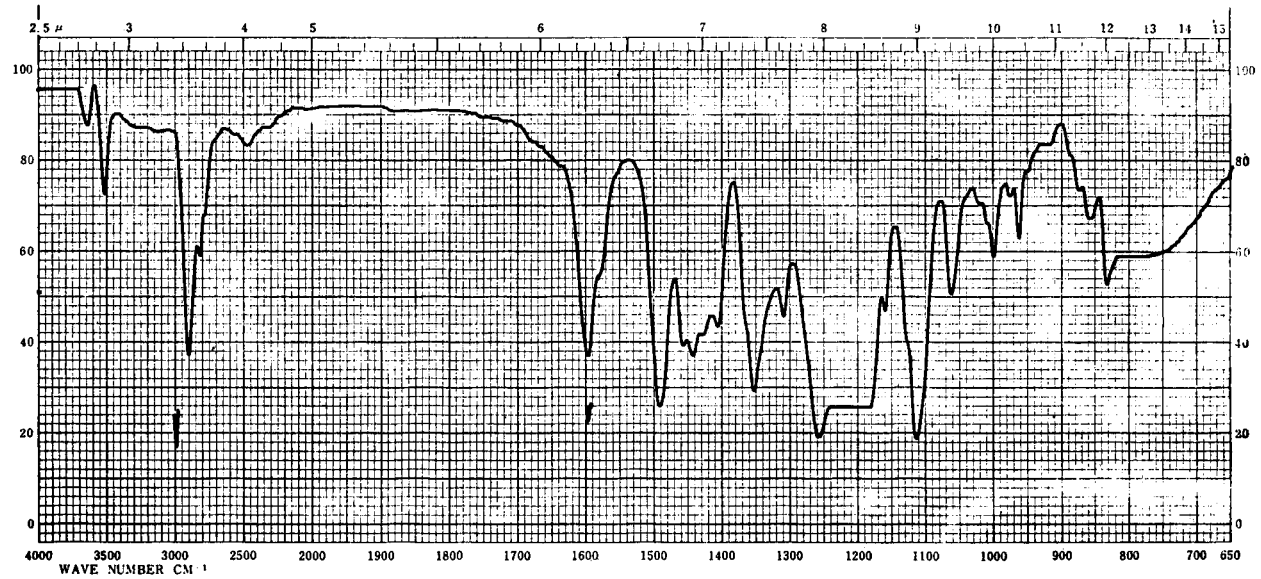


Figure 3. The Infrared Spectrum of Compound A_5 in $CHCl_3$.

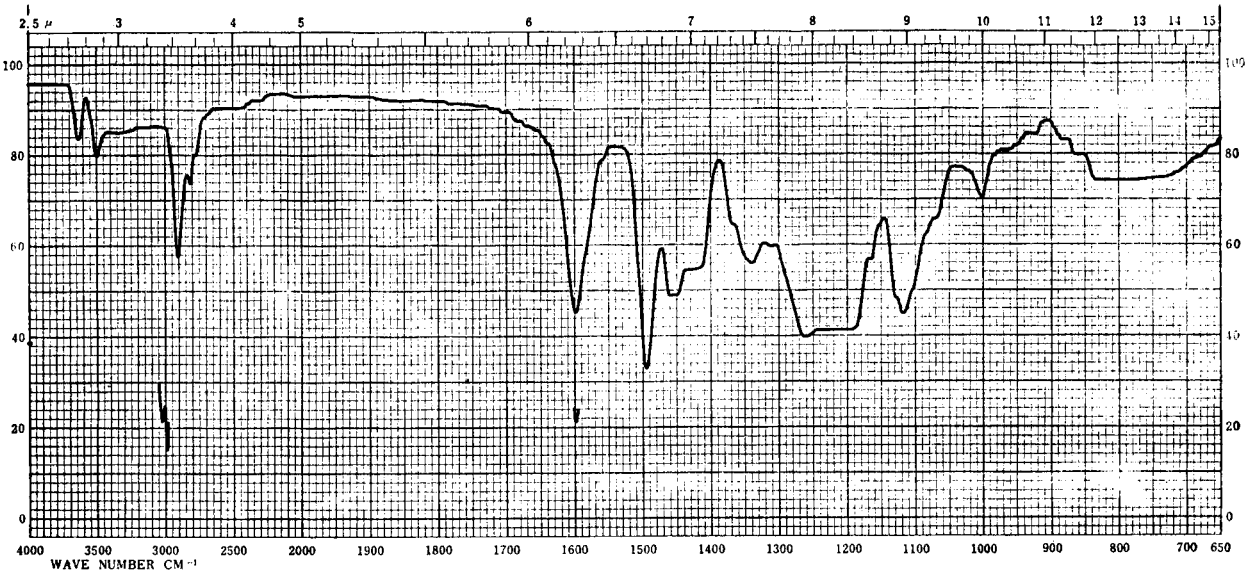
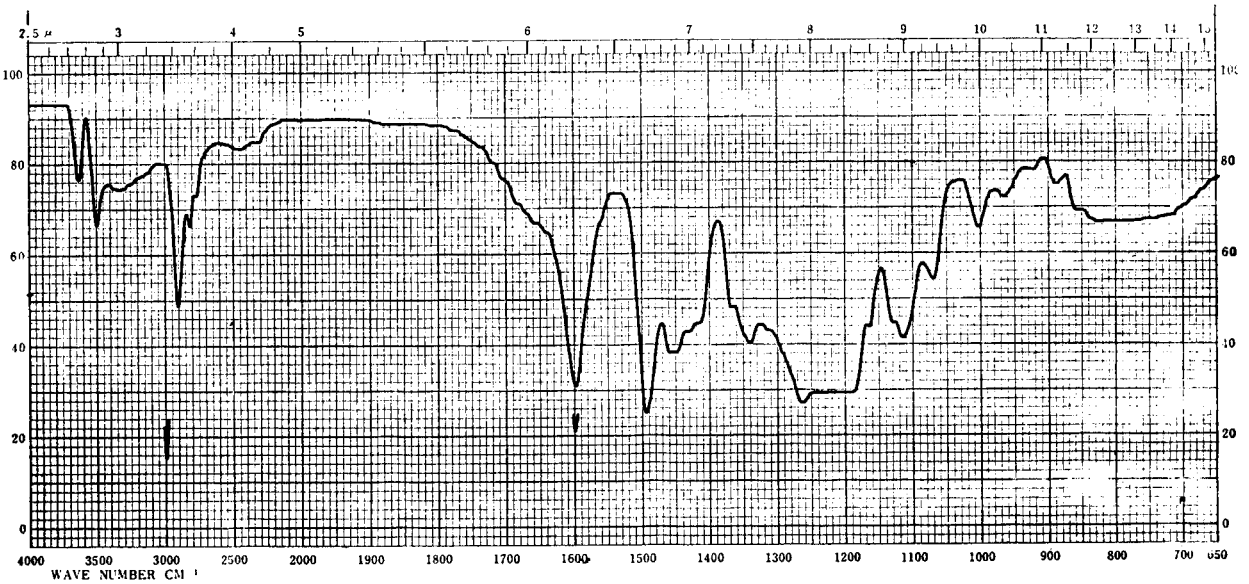


Figure 4. The Infrared Spectrum of Compound B_5 in $CHCl_3$.



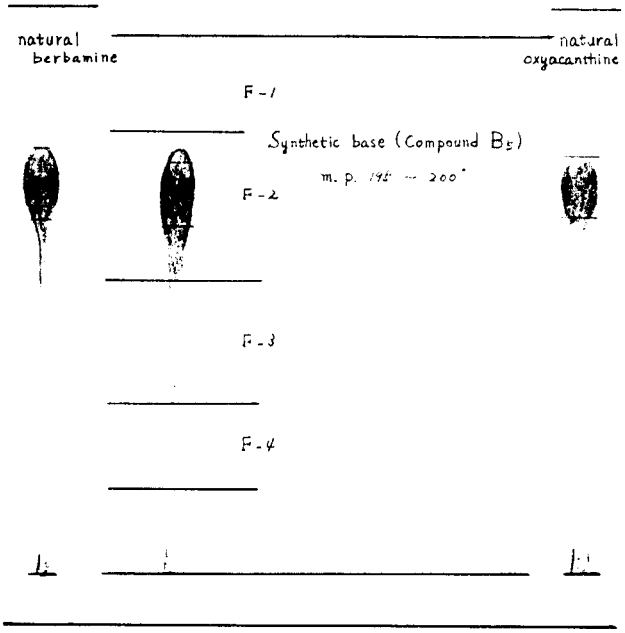


Figure 5. Preparative Thin-layer Chromatography of Synthetic Compound B_5.

among them. Tomita, *et al.*, (19) have recently reported that cyclization of the amide was carried out to give a mixture of tetrahydroisoquinoline in the case of the total synthesis of cycleanine. Therefore, four possible compounds (Ia, Ib, Ic and Id) appeared to be obtained in our case. It is possible that both compounds (A_5 and B_5) have the same composition as Ic and Id differing only slightly in infrared spectra of the synthetic and natural substance. The NMR spectrum (100 Mc) of natural berbamine could be measured in deuteriochloroform, however our synthetic samples (A_5 and B_5) could not be dissolved in deuterochloroform, therefore NMR spectral comparison was not possible. Unfortunately the structures have not been completely elucidated, therefore work on the structures of these two compounds is still in progress.

EXPERIMENTAL (27)

Acetylvanillin Acetal (V).

A mixture of 92 g. of acetylvanillin (IV) (20), 92 g. of ethyl orthoformate, 2.0 g. of ammonium chloride, and 50 ml. of dry ethanol was heated under reflux in an oil-bath at 105-110° for 4 hours. After the reaction mixture had been distilled under reduced pressure, the resultant residue was mixed with 150 ml. of ice-water and then extracted with ether. The extract was dried over potassium carbonate and distilled to give 92 g. (93%) of compound V as a colorless oil, b.p. 165-168.8°/8 mm.; ν max 1772 cm^{-1} (C=O) ($CHCl_3$).

Anal. Calcd. for $C_{14}H_{20}O_6$: C, 62.67; H, 7.51. Found: C, 62.37; H, 7.13.

4-(5-Formyl-2,3-dimethoxyphenoxy)-3-methoxybenzaldehyde Diethyl Acetal (VII).

A mixture of 20 g. of compound V, 20 g. of 5-bromo-3,4-dimethoxybenzaldehyde diethyl acetal (21) (VI), 30 g. of potassium carbonate, 2.0 g. of copper powder, 2.0 g. of cupric oxide, and 20 ml. of pyridine was heated under reflux in an oil-bath at 145-155° for 45 hours with stirring.

After the reaction, an insoluble substance was removed by filtration and washed with chloroform on a filter. The solvent layer and washings were combined. The total solvent was removed by distillation and the resultant residue was dissolved in ether. The ethereal extract was washed with 10% aqueous potassium hydroxide, dried over potassium carbonate and distilled to give 25 g. of a dark reddish oil, which upon distillation *in vacuo* gave 15.5 g. (53%) of a pale yellow viscous oil, b.p. 185-187°/0.001 mm. The IR spectrum showed no absorption band for the carbonyl group.

Anal. Calcd. for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81. Found: C, 64.39; H, 7.60.

4-(5-Formyl-2,3-dimethoxyphenoxy)-3-methoxybenzaldehyde (VIII).

Twenty percent hydrochloric acid (100 ml.) was added to a stirred solution of 15 g. of compound VII in 15 ml. of acetic acid which was kept at 50° for 1 hour. After the addition, the mixture was heated with stirring for an additional 1 hour, giving a dark green precipitate, which was collected by filtration, washed with water and dried. Recrystallization from ether-acetone gave 10 g. (95%) of VIII as colorless needles, m.p. 101-102°. The IR spectrum (in potassium bromide) was superimposable on that of an authentic sample (lit., (16) m.p. 99-101°). The mixture melting point with an authentic specimen was not depressed.

4-[5-(2-Aminoethyl)-2,3-dimethoxyphenoxy]-3-methoxyphenethylamine (X).

To a suspension of 3 g. of compound VIII in 20 ml. of methanol was added 2.0 g. of nitromethane and a solution of 3 g. of potassium hydroxide in 50 ml. of methanol was added dropwise to the above cooled mixture with stirring. After stirring for an additional 1 hour, the reaction mixture was poured into 10% hydrochloric acid solution and a yellow precipitate was collected by filtration, washed with water and then a small amount of methanol and dried. Recrystallization from acetone-methanol afforded 2.5 g. of compound IX, yellow prisms, m.p. 180-182° (lit., (10) m.p. 180-183°).

A solution of 2.5 g. of IX in tetrahydrofuran was added dropwise to a solution of 2.5 g. of lithium aluminum hydride in tetrahydrofuran with stirring. The mixture was refluxed for 7 hours, then treated as usual, giving the amine (X), whose oxalate (1.0 g.) was obtained as colorless plates, m.p. 104-110° (lit., (10) m.p. 106-109°).

N,N'-(3,3',4-Trimethoxy-4',5-oxydiphenethyl)-2,2'-(4-benzyloxy-3,4'-oxydiphenyl)bisacetamide (XIIa) and *N,N'*-(3,3',4-Trimethoxy-4',5-oxydiphenethyl)-2,2'-(4'-benzyloxy-3',4-oxydiphenyl)bisacetamide (XIIb).

After a mixture of 2.0 g. of 4-benzyloxy-3,4'-oxydiphenyldiacetic acid (18), 3.5 g. of thionyl chloride, and one drop of pyridine had been allowed to stand at room temperature overnight, the excess of the reagent was removed by distillation under reduced pressure. After allowing the resultant acid chloride (XI) to stand overnight, it solidified to give yellow crystals, m.p. 105-110°, which was dissolved in 40 ml. of dry chloroform and used in the following reaction without purification.

On the other hand, 2.5 g. of the oxalate of the preceding diamine (X) was decomposed with 40 ml. of 5% potassium hydroxide solution and extracted with chloroform. To the chloroform extract of the amine (X) was added dropwise the solution of acid chloride (XI) prepared above with stirring, during which time the reaction mixture was kept alkaline by dropwise addition of 20 ml. of 5% potassium hydroxide solution with cooling.

After the reaction, the mixture was stirred for an additional 1 hour. The solvent layer (chloroform) was separated, washed with 5% potassium hydroxide solution, 5% hydrochloric acid solution and water, dried over potassium carbonate and distilled to give 3.0 g. of a yellow-brown syrup, which was dissolved in 10 ml. of chloroform. The resultant solution was chromatographed on 50 g. of alumina (22). After the first benzene eluate had been discarded, the second eluate (benzene:chloroform = 9:1; 500 ml.) and the third one (benzene:chloroform = 8:2; 500 ml.) were combined. Removal of the mixed solvents gave 1.1 g. of a pale brown syrup, which upon recrystallization from

chloroform–ether gave 0.3 g. of the bis-amide (XIIb) (named as compound B_1) (23) as colorless needles, m.p. 177-183°; ν max 3420 (NH), 1675 cm^{-1} (C=O) ($CHCl_3$).

Anal. Calcd. for $C_{42}H_{42}N_2O_8$: C, 74.78; H, 6.02; N, 3.99. Found: C, 74.48; H, 6.14; N, 3.91.

Furthermore, the fourth eluate (benzene:chloroform = 6:4; 100 ml.), the fifth eluate (benzene:chloroform = 5:5; 100 ml.), the sixth eluate (benzene:chloroform = 4:6; 300 ml.) and the seventh eluate (benzene:chloroform = 4:6; 300 ml.) and the eighth eluate (benzene:chloroform = 3:7; 500 ml.) were combined. Removal of all the solvents gave 0.4 g. of a pale brown syrup, which was recrystallized from chloroform-ether to give 0.15 g. of the bis-amide (24) (XIIa) (named as compound A_1) as a pale brown powder, m.p. 92° dec.; ν max 3420 (NH), 1673 cm^{-1} (C=O).

Anal. Calcd. for $C_{42}H_{42}N_2O_8 \cdot 1/2CHCl_3$: C, 66.94; H, 5.62; N, 3.67. Found: C, 66.58, 66.58; H, 5.62, 5.77; N, 3.67, 3.73. The Beilstein halogen test was positive.

1,1'-(4-Benzyloxy-3,4'-oxydibenzyl)-3,3',4,4'-tetrahydro-6,6',7-trimethoxy-7',8-oxydiisoquinoline (XIIIa) or (XIIIb, XIIIc, XIIId) (compound A_2).

A mixture of 110 mg. of the preceding amide (compound A_1) (m.p. 92° dec.), 5 ml. of phosphoryl chloride, and 110 ml. of dry chloroform was mildly heated on a water-bath for 10 hours. After the reaction, removal of the yellowish-orange reaction mixture at 30-40° under reduced pressure gave an orange oil, to which was added an excess of *n*-hexane and allowed to stand in a refrigerator overnight. The resultant upper layer was removed by decantation to give the residue, which was dissolved in 2 ml. of methanol. To the resultant solution was added 60% perchloric acid solution, and a pale brown precipitate was separated. Collection by filtration and recrystallization from methanol-ether afforded 83 mg. of the compound A_2 as a pale brown powder, m.p. 193-195°; ν max 1645 (C=N), 739, 695 cm^{-1} (monosubstituted benzene).

Anal. Calcd. for $C_{42}H_{38}N_2O_8 \cdot 2HClO_4$: C, 58.14; H, 4.64. Found: C, 58.63; H, 4.57.

1,1'-(4-Benzyloxy-3,4'-oxydibenzyl)-1,1',2,2',3,3',4,4'-octahydro-6,6',7-trimethoxy-2,2'-dimethyl-7',8-oxydiisoquinoline (IIIa) or (IIIb, IIIc or IIId) (compound A_4).

The perchlorate (70 mg.) of the above compound A_2 was made alkaline with 50% potassium hydroxide solution and extracted with chloroform. The extract was dried over potassium carbonate and distilled to give the free base as a yellow viscous syrup, which was admixed with 2 ml. of methyl iodide and allowed to stand overnight under cooling. After the excess of methyl iodide had been removed by distillation under reduced pressure and the resultant residue had been washed with ether, the dimethiodide (compound A_3) was obtained as a reddish-brown syrup, which could not be purified and therefore used in the following reaction without purification.

The preceding dimethiodide (A_3) was dissolved in 50 ml. of a mixture of methanol-chloroform (3:1) containing 1 ml. of water, and 0.3 g. of sodium borohydride was gradually added to the above mixture with stirring. After the addition, the mixture was stirred for an additional 1 hour and the excess of the reagent was then decomposed with 10% acetic acid solution and extracted with chloroform. The extract was dried on potassium carbonate and distilled to give the residue, which was chromatographed on 2.0 g. of alumina using chloroform as solvent.

Removal of the chloroform eluate and recrystallization from chloroform-*n*-hexane gave 45 mg. of the compound A_4 as a pale brown powder (25), which was recrystallized from chloroform-*n*-hexane to give a grayish white powder, m.p. 152-155°. Beilstein test was positive.

Anal. Calcd. for $C_{44}H_{46}N_2O_8 \cdot 4/5CHCl_3$: C, 67.73; H, 5.93. Found: C, 67.33; H, 6.46.

1,1'-(4-Hydroxy-3,4'-oxydibenzyl)-1,1',2,2',3,3',4,4'-octahydro-6,6',7-trimethoxy-2,2'-dimethyl-7',8-oxydiisoquinoline (Ia) or (Ib, Ic or Id) (compound A_5).

A mixture of 45 mg. of the above compound (A_4) and 20 ml. of ethanol-concentrated hydrochloric acid solution (1:1) was refluxed on a water-bath for 10 hours. After the reaction, removal of the solvent under reduced pressure gave the residue, which was basified with 10% ammonium hydroxide solution and extracted with chloroform. The extract was dried over sodium sulfate and distilled to give a brown syrup, which was chromatographed on 0.3 g. of silica gel using chloroform as solvent. Removal of the eluate ($CHCl_3$:MeOH = 20:1) and recrystallization from chloroform-*n*-hexane gave 15 mg. of compound A_5 as a grayish-white powder, m.p. 190-195°; ν max 3500 cm^{-1} (OH) (chloroform).

Anal. Calcd. for $C_{37}H_{40}N_2O_8 \cdot 1/2H_2O$: C, 71.94; H, 6.69. Found: C, 72.14; H, 6.91.

1,1'-(4'-Benzyloxy-3',4-oxydibenzyl)-3,3',4,4'-tetrahydro-6,6',7-trimethoxy-7',8-oxydiisoquinoline (XIIIb) or (XIIIa, XIIIc or XIIId) (compound B_2).

A mixture of 102 mg. of the preceding bis-amide (compound B_1) (m.p. 177-183°), 3 ml. of phosphoryl chloride, and 50 ml. of dry chloroform was heated under reflux on a water-bath at 70-80° for 10 hours. The excess of the reagent was distilled off and a large amount of *n*-hexane was added to the residue. After the mixture had been allowed to stand overnight, an upper clear solution was removed by decantation to give a yellowish-orange syrup, which was washed with *n*-hexane several times. A solution of the resultant residue in methanol was added to 60% perchloric acid solution, 97 mg. of an orange powder, m.p. 200-210°, being separated. Recrystallization from methanol-ether gave the compound B_2 as an orange powder, m.p. 210-213°; ν max 1640 cm^{-1} (C=N-) (KBr).

Anal. Calcd. for $C_{42}H_{38}N_2O_8 \cdot 2HClO_4$: C, 58.14; H, 4.64; N, 3.23. Found: C, 58.44; H, 4.92; N, 3.43.

1,1'-(4'-Benzyloxy-3',4-oxydibenzyl)-1,1',2,2',3,3',4,4'-octahydro-6,6',7-trimethoxy-7',8-oxydiisoquinoline (XIVb) or (XIVa, XIVc or XIVd) (compound B_3).

To a solution of 147 mg. of the preceding compound B_2 in 50 ml. of methanol and 3 ml. of water was added portionwise 0.5 g. of sodium borohydride with cooling and stirring. After the addition, the mixture was stirred at room temperature for 1 hour then heated on a water-bath at 60° for 0.5 hour and distilled to give a colorless solid, which was admixed with 30 ml. of water and extracted with benzene. The extract was washed with water, dried over sodium sulfate and distilled to give a pale yellow glassy substance. Recrystallization from benzene-*n*-hexane afforded 65.5 mg. of a colorless powder, m.p. 147-150°; ν max 3410 (NH, broad), 738, 697 cm^{-1} (monosubstituted benzene).

Anal. Calcd. for $C_{42}H_{42}N_2O_8 \cdot H_2O$ (26): C, 73.23; H, 6.44; N, 4.07. Found: C, 73.26; H, 6.10; N, 3.95.

1,1'-(4'-Benzyloxy-3',4-oxydibenzyl)-1,1',2,2',3,3',4,4'-octahydro-6,6',7-trimethoxy-2,2'-dimethyl-7',8-oxydiisoquinoline (IIIb) or (IIIa, IIIc or IIId) (compound B_4).

A mixture of 105 mg. of the compound B_2, 1.5 ml. of 98% formic acid, and 0.7 ml. of 37% formalin was heated in an oil-bath at 100-110° for 4 hours. After the reaction, the solvent was distilled under reduced pressure to give a yellow syrup, to which was added 10% ammonium hydroxide solution and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Removal of the extract gave a pale brown syrup, which was recrystallized from chloroform-*n*-hexane to give 54 mg. of a pale brown powder, m.p. 175-180°; ν max 2820 cm^{-1} (N-Me) (chloroform). Recrystallization of the dipicrate from acetone-ether afforded a yellow powder, m.p. 181-184°.

Anal. Calcd. for $C_{44}H_{46}N_2O_8 \cdot 2C_6H_3N_3O_7 \cdot 2H_2O$: C, 56.37; H, 4.73. Found: C, 56.27; H, 5.00.

1,1'-(4'-Hydroxy-3',4-oxydibenzyl)-1,1',2,2',3,3',4,4'-octahydro-6,6',7-trimethoxy-2,2'-dimethyl-7',8-oxydiisoquinoline (Ib) or (Ia, Ic, Id) (compound B_5).

A mixture of 54 mg. of the preceding compound B_4, 7 ml. of concentrated hydrochloric acid, and 2 ml. of ethanol was heated under reflux on a water-bath for 10 hours and the pale brown reaction mixture changed to green. After the reaction, the solvent was removed from the reaction mixture by distillation under reduced pressure. The resultant residue was basified with concentrated ammonium hydroxide solution and extracted with chloroform. The solvent was again extracted with 5% potassium hydroxide solution. An excess of crystalline ammonium chloride was added to the above potassium hydroxide solution, and the resultant ammoniacal solution was extracted with chloroform. The extract was dried over sodium sulfate and distilled to give a brown syrup which was dissolved in chloroform and chromatographed on 0.3 g. of silica gel using a mixture of chloroform-methanol (20:15:1) as solvent. Removal of the above eluate and recrystallization from chloroform-*n*-hexane gave 15 mg. of compound B_5 as a pale yellow powder, m.p. 195-200°; ν max 3500 cm^{-1} (OH) (chloroform).

Anal. Calcd. for $C_{37}H_{40}N_2O_8 \cdot 1/2H_2O$: C, 71.94; H, 6.69. Found: C, 71.87; H, 6.78.

Preparative thin-layer chromatography of 10 mg. of the above base on Wakogel B-5 [15 plates (20 x 20 cm.) having a thickness of 0.75 mm. were used; a mixture of chloroform-methanol (5:4) was used as solvent; and the spots were detected by 5% iodine-chloroform solution or Dragendorf reagent] gave 3 mg. of phenolic base. In this case the layers of F-2 (Fig. 5) were collected by scratching and extracted with 200 ml. of chloroform-methanol (9:1). R_f (synthetic) 0.70, (natural oxyacanthine) 0.68, (natural berbamine), 0.68.

Since these racemic compounds (A_s and B_s) as above were so insoluble in various solvents suitable for NMR spectrum, the NMR spectra of both specimens could not be measured.

Acknowledgment.

We are grateful to Dr. M. C. Woods of Varian Associates for 100 Mc NMR spectrum measurements. We also thank President Dr. M. Terasaka of Tokyo College of Pharmacy for his grateful assistance.

REFERENCES

(1) Part CLXIII: *Yakugaku Zasshi*, 87, 316 (1967).
(2) O. Hesse, *Ber.*, 19, 3109 (1886).
(3) C. Rüdel, *Arch. Pharm.*, 229, 631 (1891); H. Pommerehne, *ibid.*, 233, 127 (1895).
(4) F. von Bruchhausen and H. Schultze, *ibid.*, 267, 617 (1924); F. von Bruchhausen and P. H. Gericke, *ibid.*, 269, 115 (1913).
(5) F. von Bruchhausen, H. Oberembt, and A. Feldhaus, *Ann. Chem.*, 507, 144 (1933).
(6) Y. Inubushi, *Yakugaku Zasshi*, 72, 220 (1952).
(7) E. Fujita, *ibid.*, 72, 217 (1952).
(8) M. Tomita, E. Fujita, and F. Murai, *ibid.*, 71, 1035 (1951).
(9) M. Tomita and J. Kunitomo, *ibid.*, 82, 741 (1962).
(10) F. von Bruchhausen, G. A. Santos, and C. Schäfer, *Arch. Pharm.*, 293, 785 (1960).
(11) F. von Bruchhausen, *ibid.*, 283, 44 (1950).
(12) E. Fujita and T. Saijo, *Yakugaku Zasshi*, 72, 1232 (1952).
(13a) H. Kondo, H. Kataoka, and Y. Baba, *Annual Report of ITSUU Lab.*, 5, 8 (1954); (b) H. Kondo, H. Kataoka, and K. Kigasawa, *ibid.*, 6, 13 (1955); (c) H. Kataoka, *ibid.*, 8, 1 (1957); (d) H. Kondo, Y. Hayashi, and T. Uchibori, *ibid.*, 9, 1 (1958).
(14) M. Tomita, K. Fujitani and T. Kishimoto, *Yakugaku Zasshi*, 82, 1148 (1962).
(15) W. M. Whaley and L. N. Starker, *J. Org. Chem.*, 19, 1019 (1954).
(16) M. Tomita, T. Kikuchi, K. Bessho, T. Hori, and Y. Inubushi, *Chem. Pharm. Bull.*, 11, 1484 (1963).
(17) K. Freudenberg, V. Jovanoric and F. Topfmeier, *Chem. Ber.*, 94, 3227 (1961).
(18) T. Kametani, S. Takano, R. Yanase, C. Kibayashi, H. Iida, S. Kano, and K. Sakurai, *Chem. Pharm. Bull.*, 14, 73 (1966).
(19) M. Tomita, K. Fujitani, and Y. Aoyagi, *Tetrahedron Letters*, 4243 (1966).
(20) I. J. Pisovschi, *Ber.*, 43, 2139 (1910).
(21) K. Fujitani, N. Matsumoto, K. Yoshioka, I. Yoshida, and Y. Inubushi, *Yakugaku Zasshi*, 84, 333 (1964).
(22) Aluminum oxide of 300 mesh was used.
(23) TLC:Silica gel (Wakogel D-5) (0.25 mm.) and chloroform-methanol (9:1) as solvent were used; R_f value (0.79) was detected as one spot by 50% sulfuric acid.
(24) TLC:Silica gel (0.25 mm.) and chloroform-methanol (9:1) as solvent were used; R_f value (0.87) was detected as one spot by 50% sulfuric acid.
(25) Thin layer chromatography with silica gel showed one spot.
(26) This was dried on phosphorus pentoxide at 100° under reduced pressure for 48 hours.
(27) Infrared spectra were measured on a Type EPI-2 Hitachi infrared spectrophotometer. Melting points are uncorrected.

Received December 3, 1966 Sendai, Japan