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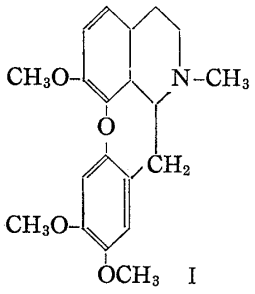
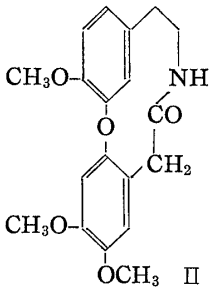
208. Tetsuji Kametani, Keiichiro Fukumoto, Shiroshi Shibuya, and Takuo Nakano : Cularine and Related Compounds. V.*2 Investigation of the Ullmann Reaction Products of Methyl (2-Bromo-4,5-dimethoxyphenyl)acetate with Phenolic Compounds, and an Approach to the Total Synthesis of Cularine.*3

(*Pharmaceutical Institute, School of Medicine, Tohoku University*[1])

In this paper will be described some results of synthetical experiments of the cyclic amide (II), which appeared to be the key intermediate for the total synthesis of the alkaloid cularine (I).

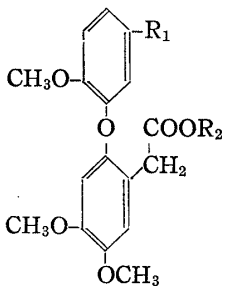


I

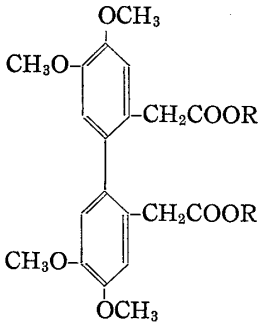


II

For the present purpose, recourse was taken chiefly of the Ullmann condensation reaction of methyl (2-bromo-4,5-dimethoxyphenyl)acetate with appropriately substituted phenolic compounds. First, isovanillin was treated with this acetate at 160~190° in presence of copper powder and potassium carbonate. Four compounds from the reaction mixture, were isolated and characterized.



III : R_1=CHO, R_2=CH_3
V : R_1=CHO, R_2=H
VII : R_1=CH=$CHNO_2$



IV : R=CH_3
VI : R=H

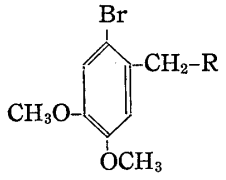
The acid (V) was esterified by the conventional method to III but the total yield of III was rather low. The esteraldehyde (III) thus obtained was further condensed with nitromethane to the corresponding β-nitrostyrene (VII), which was reduced catalytically according to Grundon and Perry's method.[1] During work up, the basic reduction product yielded some neutral material. Therefore, the whole was dissolved in a large amount

*1 No. 85, Kita-4-bancho, Sendai (亀谷哲治, 福本圭一郎, 渋谷 皓, 中野卓雄).
*2 Part IV : This Bulletin, **11**, 1322 (1963).
*3 This forms Part LXXXIV of "Studies on the Syntheses of Heterocyclic Compounds" by Tetsuji Kametani.
1) M. F. Grundon, H. J. H. Perry : J. Chem. Soc., **1954**, 3531.

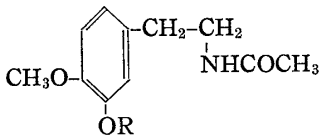
of benzene and refluxed for a long period of time to ensure complete conversion into a neutral substance, which remained oily. Though not thoroughly characterized due to scarcity of the material, the fact that this substance is a crude II was supported from its infrared absorption band ascribable to amide-CO group, which also exists in the spectrum of pure II prepared by an alternate method to be described later.

Another attempt to cyclize III or V with polyphosphoric acid failed to give the cyclic ketone.

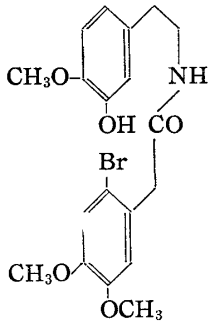
As was described above, the intermediate compoud (II) was obtained, and the yield of the Ullmann condensation product (III) at the preceding stage was so poor, that this method was abandoned and an alternative process was sought. (2-Bromo-4,5-dimethoxyphenyl)acetyl chloride was condensed with 3-hydroxy-4-methoxyphenethylamine, obtainable by the known methods,[2~6] to furnish the corresponding amide (XIII), which was then heated with copper and potassium carbonate, either in the presence or absence of pyridine or dimethylformamide. In none of the cases, however, the desired lactam was obtained even in a small amount in the reaction product and a dark intractable powdery solid melting at round 95° was formed.



XI : R=COOH
XXIII : R=CHO



XII : R=H
XIV : R=COCH3



XIII

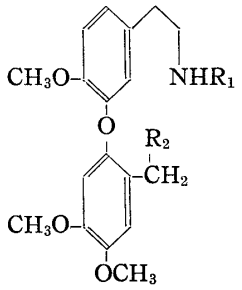
N-(3-Hydroxy-4-methoxyphenethyl)acetamide (XII) was prepared by partial hydrolysis of the diacethyl derivative (XIV) and condensed with methyl 6-bromohomoveratrate (cf. XI) under Ullmann conditions in the presence of pyridine. The reaction proceeded at 170~180° with copious evolution of carbon dioxide. From the reaction mixture the desired diphenyl ether derivatives (XV and XVI) were isolated, together with the biphenyl derivatives (IV and VI) as by-products, the latter being identified with the ones described above.

These four compounds were separated from each other as described in the experimental section and the compounds (XV and XVI) thus exhibited an infrared absorption bands characteristic to amino acid. During the above work up, some neutral substance was also formed, which was distilled *in vacuo* and identified through its infrared spectrum with the lactam (II) already mentioned. Simplified method of preparation of XVII is also described in the experimental section.

Since the amino acid thus prepared was not induced to crystallize, this was heated in benzene or toluene for a long period of time and furnished the lactam (II). This lactam now submitted to the Bischler-Napieralski cyclization reaction and from the reaction mixture, a basic substance was isolated.

2) K.E. Hamlin, F.E. Fischer : J. Am. Chem. Soc., **75**, 5119 (1953).
3) A. Chatterjee, N. Adityachaudhury : J. Org. Chem., **27**, 309 (1962).
4) G. Hahn, F. Rumpf : Ber., **71**, 2141 (1938).
5) F.A. Ramirez, A. Burger : J. Am. Chem. Soc., **72**, 2781 (1950).
6) D. Beke, Cs. Szántay : Acta. Chim. Acad. Sci. Hung., **14**, 325 (1958).

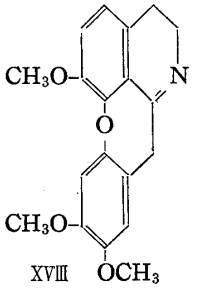
The infrared absorption spectrum of NH group was not recognized and one of C=N group was found at 1630 cm^{-1} (KBr). Accordingly, this compound was considered to be 6,9,10-trimethoxy-2,3-dihydro-12*H*-benz[2,3]oxepino[7,6,5-*ij*]isoquinoline (XVIII). All attempts to crystallize it or its derivatives failed, but after being purified through alumina chromatography an oil was obtained, which formed a crystalline picrate of m.p. 193~194°. Infrared spectrum of this picrate exhibited an absorption band at 1730 cm^{-1} ascribable to ketone CO-group,*4 suggesting the formation of the compound (XIX) from (XVIII) through oxidation. In contrast to XVIII which is readily soluble both in alcohol and acetone, this compound is sparingly soluble in these solvents.



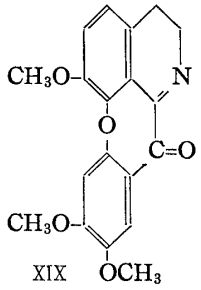
VIII : R_1=H, R_2=$COOCH_3$
XV : R_1=$COCH_3$, R_2=$COOCH_3$
XVI : R_1=$COCH_3$, R_2=COOH
XVII : R_1=H, R_2=COOH
XXIV : R_1=$COCH_3$, R_2=CHO

Such a phenomenon is not without precedence. Papaverine and its 3,4-dihydro derivative, especially so in the presence of alumina as was observed by our own experiment.[7]

Chemistry of ushinsunine reported by Yang[8] provides another example to support our view. For further confirmation, reduction and dehydrogenation of XIX were carried out but without effect.

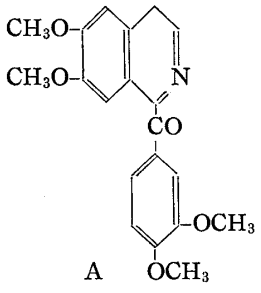


XVIII

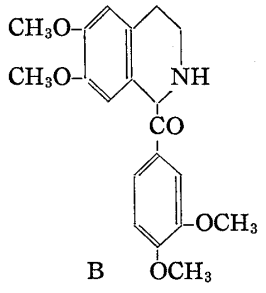


XIX

*4 Position of the absorption band of this CO, though doubly conjugated with two $\alpha,\beta:\alpha',\beta'$-unsaturation, is considered to be reasonable, because the aromatic ring, CO and C=N groups cannot exist coplanar in XIX. Otherwise such CO-group should absorb at lower frequency (around 1655 cm^{-1}). For instance, it is known that C=O group of dihydropapaveraldine (A) synthesized by us[7] was shown at 1659 cm^{-1}, but that of tetrahydropapaveraldine (B) was recognized at 1680 cm^{-1}. Therefore, the



A



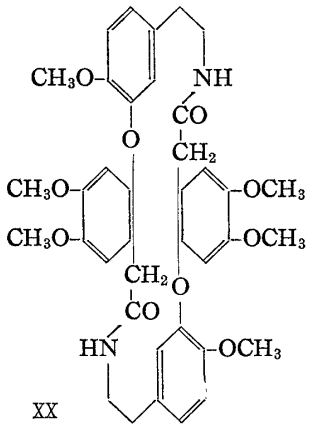
B

increase of double bond conjugation by O=C—C=N— does not seem to exercise so great influence over the existence of the absorption band of C=O group in XIX at higher frequency. Futhermore, XIX gave a reddish precipitate with 2,4-dinitrophenylhydrazine and the presence of CO group was thought to be proved.

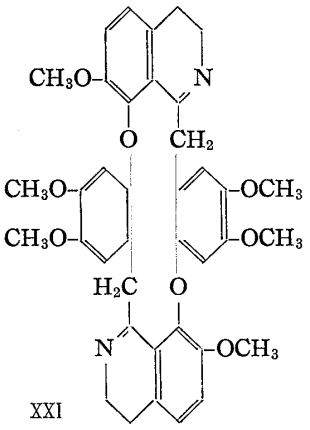
7) T. Kametani, K. Fukumoto : Yakugaku Zasshi, 83, to be published (1963).
8) T. Yang : *Ibid.*, 82, 797, 798, 804 (1962).

Application of the simplified method of isoquinoline synthesis by Sugasawa, *et al.*[9] ended in very much different result. The amino acid (XVII) was treated directly with phosphoryl chloride and afforded a syrupy basic substance*[6] insoluble in common organic solvents except chloroform. Its methiodide was reduced under Clemmensen conditions, the base obtained was dissolved in chloroform, and precipitated by adding hexane. The base was separated with water of crystallization and melted at 75°, which gradually became higher by drying, at last to reach 185°. Though the infrared and ultraviolet absorption spectrum of this base were similar to those of cularine, its decreased solubility (soluble only in chloroform) and higher melting point, together with the data of analysis and of molecular weight determination, suggested the structure XXII for it. The above-mentioned compound of tetrahydrate, m.p. 180~182° gave satisfactory analyses and molecular weight determination for $C_{40}H_{46}O_8N_2 \cdot 4H_2O$. During the cyclization reaction the starting amino acid (XVII) must have undergone intermolecular rather than intramolecular coupling to yield the double lactam (XX), which further suffered cyclization with a loss of two molar equivalents of water, and formed (XXI), which was characterized as chloroplatinate.

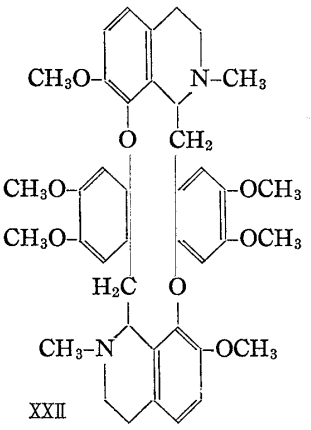
(2-Bromo-4,5-dimethoxyphenyl)acetaldehyde (XXIII) was also prepared and condensed with the amide (XII) in an attempt to prepare XXIV, but without success.



XX



XXI



XXII

Experimental

Ullmann Reaction of Methyl (2-Bromo-4,5-dimethoxyphenyl)acetate with Isovanillin——A mixture of 30 g. of isovanillin and 54 g. of methyl (2-bromo-4,5-dimethoxyphenyl)acetate to which 18 g. of Cu powder and 24.6 g. of K_2CO_3 were added, was fused by heating in an oil bath. The whole was heated to 160° (bath) and brisk evolution of CO_2 was observed. After the effervescence had almost ceased, the reaction mixture was gradually heated up to 190° and kept there for 2.5 hr. The reaction product was extracted with Me_2CO while warm, inorganic substances were removed by filtration, and removal of the solvent from the filtrate gave a resinous oil, to which H_2O was added and extracted with benzene. The benzene extract, which was separated from an alkaline solution (A), was washed with 10% NaOH and H_2O, dried $(Na_2SO)_4$, and the solvent was evaporated, yielding a brown oil. Distillation of the residue *in vacuo* yielded dimethyl 4,4',5,5'-tetramethoxy-2,2'-biphenyldiacetate (IV), $b.p_{0.17}$ 110° (*Anal.* Calcd. for $C_{20}H_{26}O_8$: C, 63.15; H, 6.26. Found : C,63.13; H, 6.42.) and methyl [2-(2-methoxy-5-formylphenoxy)-4,5-dimethoxyphenyl]acetate (III), $b.p_{0.1}$ 203°. The latter solidified on standing and recrystallization from EtOH afforded the ester (III) as colorless needles, m.p. 103~104°. Yield, 1.9 g. *Anal.* Calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found : C, 63.38; H, 5.83. IR ν_{max}^{KBr} cm^{-1} : 1730 (ester C=O), 1690 (aldehyde C=O.).

The alkaline solution (A) was acidified with HCl and extracted with $CHCl_3$. After being washed, $CHCl_3$ was evaporated to ca. 50 ml. and exhaustively extracted with saturated $NaHSO_3$ solution. The aqueous layer, separated from the $CHCl_3$ layer (B), was washed with benzene, mixed with about 2

*5 In the infrared spectrum of XXI, NH band was not recognized.

9) S. Sugasawa, S. Toda, H. Tomisawa : Yakugaku Zasshi, **72**, 252 (1952).

volumes of 20% HCl, and heated with $CHCl_3$, which was washed with H_2O and dried on Na_2SO_4. Evaporation of the solvent and recrystallization of the residue from EtOH afforded 1.8 g. of [2-(2-methoxy-5-formylphenoxy)-4,5-dimethyoxyphenyl]acetic acid as a grayish white powder, m.p. 173~174°. *Anal.* Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found : C, 62.39; H, 5.46. IR ν_{max}^{KBr} cm^{-1} : 1710, 1675.

The $CHCl_3$ layer (B)was washed with H_2O, dried Na_2SO_4 and the solvent was evaporated. Distillation of the residue *in vacuo* gave a reddish brown, resinous oil, $b.p_{0.03}$ 219~219.5°. Recrystallization from benzene afforded 4,4'5,5'-tetramethoxy-2,2'-biphenyldiacetic acid (VI) as colorless needles, m.p. 150~151°. *Anal.* Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found : C, 61.66; H, 5.68.

Esterification of the Carboxylic Acid (V)——Into a stirred and refluxed solution of 1.094 g. of V in 60 ml. of MeOH, dry HCl was introduced. After the solvent was distilled off, the residue obtained was extracted with $CHCl_3$, washed with H_2O and 5% $NaHCO_3$, dried, and the solvent was evaporated. Distillation of the residue *in vacuo* gave 0.428 g. (37.6%) of the ester (III) asr a colorless oil, which solidified on standing. Recrystallization from EtOH afforded colorless cubes, m.p. 103~104°, which was proved by mixed melting point test to be identical with the ester obtained above.

Methyl {2-[2-Methoxy-5-(2-nitrovinyl)phenoxy]-4,5-dimethoxyphenyl}acetate (VII)——One g. of the aldehyde (III) was dissolved in 30 ml. of EtOH by warming and cooled, 0.2 g. of $MeNO_2$ was then added, followed by 1.9 g. of $MeNH_2 \cdot HCl$ and 1.5 g. of Na_2CO_3. The mixture was allowed to stand for 2 days and 0.6 g. (53.6%) of ω-nitrostyrene derivative separated. Recrystallization from EtOH afforded yellow needles, m.p. 135~136°. *Anal.* Calcd. for $C_{20}H_{21}O_8N$: C, 59.55; H, 5.25; N, 3.47. Found : C, 59.88; H, 5.48; N, 3.56.

Catalytic Hydrogenation of the Nitrostyrene Derivative (VII)——One g. of the above VII dissolved in 70 ml. of AcOEt was hydrogenated over a catalyst, prepared from 0.5 g. of PtO_2, suspended in a mixture of 10 ml. of 10% H_2SO_4 and 10 ml. of AcOEt, and 265 ml. of H_2 was taken up in 4 hr. After the usual work up, the residue was mixed with H_2O and basified, and a basic substance was extracted with benzene. Removal of the solvent gave 0.48 g. of methyl {2-[2-methoxy-5-(2-aminoethyl) phenoxy]-4,5-dimethoxypenyl}acetate. This was dissolved in a large amount of benzene and heated on a water bath under reflux for 5 hr. The resultant solution was washed with 10% HCl and H_2O, and the solvent was removed. The oily residue was purified through chromatography, but could not be induced to crystallize. The IR spectrum of this almost colorless oil, however, was identical with that of the cyclic amide (II) to be described later.

(2-Bromo-4,5-dimethoxyphenyl)acetic Acid (XI)——One g. of methyl (2-bromo-4,5-dimethoxyphenyl)-acetate was hydrolyzed by refluxing with 5% MeOH-KOH for 2 hr. The acid (XI) formed colorless plates, m.p. 116~117°, from ligroin, identical with that reported.[10] Yield, 0.65 g.

N-(3-Hydroxy-4-methoxyphenethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (XIII)——A mixture of 0.55 g. of the above acid (XI) with 2.4 g. of $SOCl_2$ was warmed for 1 hr. and the excess of $SOCl_2$ was removed. The residual acid chloride was extracted with dry Et_2O and was directly reacted with 3-hydroxy-4-methoxyphenethylamine (0.5 g.) in Et_2O and aqueous Na_2CO_3 during 0.5 hr. while being cooled and stirred. After the reaction mixture was allowed to stand overnight, it was extracted with AcOEt. The combined extract was washed successively with aqueous $NaHCO_3$, H_2O, 10% HCl, and H_2O, dried on Na_2SO_4, and the solvent was evaporated *in vacuo* to give 0.85 g. of the solid amide (XIII). Recrystallisation from EtOH afforded 0.3 g. of an amorphous powder, m.p. 165°. *Anal.* Calcd. for $C_{19}H_{22}O_5NBr \cdot \frac{1}{2}H_2O$: C, 50.55; N, 5.54; N, 3.11. Found : C, 50.92; H, 5.43; N, 3.41.

Ullmann Reaction of N-(3-Hydroxy-4-methoxyphenethyl)acetamide (XII) with Methyl (2-Bromo-4,5-dimethoxyphenyl)acetate——a) Separation of Condensation Products : To a fused mixture of 10 g. of methyl (2-bromo-4,5-dimethoxyphenyl)acetate and 5 g. of the amide (XII), 6.5 g. of K_2CO_3, 6.5 g. of Cu powder, and 1.5 ml. of pyridine were added, and the mixture was heated at 160~170° for 2 hr. The reaction mixture was extracted with warm $CHCl_3$ and the $CHCl_3$ extract (A) was extracted with 10% Na_2CO_3 and then with 10% NaOH. From the carbonate extract solution, 7 g. of a mixture of XI and XVI was obtained by acidification with HCl and extraction with $CHCl_3$. From the NaOH extract, the starting material was recovered. In order to obtain only the acid (XVI), 7 g. of the above mixture was refluxed with 30 ml. of 10% HCl for 1 hr. and after being cooled, it was successively extracted with Et_2O, benzene, and AcOEt. Evaporation of the Et_2O extract gave 1.3 g. of dicarboxylic acid (VI), whose IR spectrum was identical with that of an authentic sample obtained as above. The precipitate, which formed at pH 4.0~4.2 by neutralization of the acid solution with 10% NaOH, was extracted with AcOEt and evaporation of the dried (Na_2SO_4) solvent gave 3.5 g. of a brown, viscous substance (II), $b.p_{0.02}$ 250° (bath temp.) (*Anal.* for $C_{19}H_{21}O_5N \cdot 1H_2O$: C, 61.90; H, 6.91; N, 3.97. Found: C, 61.60; H, 6.53; N, 3.77), whose infrared spectrum was identical with that of the amide (II) to be described later. IR ν_{max}^{liquid} cm^{-1} : 3333 (NH), 1634 (C=O), 3378 (OH of H_2O).

Evaporation of the $CHCl_3$ extract (A) yielded 10 g. of a viscous substance, which was also treated with 30 ml. of 10% HCl under reflux for 1 hr. and resultant solution (B) was successively extracted with

10) R.D. Haworth, W.H. Perkin : J. Chem. Soc., **127**, 1451 (1925); K. Goto, *et al.* : Bull. Chem. Soc. Japan, **4**, 167 (1929).

Et_2O, benzene, and AcOEt to remove non-basic compounds. Evaporation of Et_2O from the extract gave 4 g. of (2-bromo-4,5-dimethoxyphenyl)acetic acid (XI) as colorless needles, m.p. 65~67°, identified with an authentic specimen. By extracting the precipitate separated from the acid solution (B) at pH 4.0~4.2 with AcOEt, 1.3 g. of the amino acid (XVII) was collected.

b) Simple Procedure for Separation of Amino Acid (XVII) alone : A mixture of 6.9 g. of methyl (2-bromo-4,5-dimethoxyphenyl)acetate, 4.5 g. of the above amide (XII), 2.9 g. of Cu powder, and 2.9 g. of anhyd. K_2CO_3 was heated at 180~190° with frequent shaking in the presence of 0.2 ml. of pyridine. After several minutes, CO_2 began to evolve, the evolution gradually became vigorous, and ceased after 2 hr. The reaction mixture was extracted with $CHCl_3$ on cooling, inorganic substances were filtered off, and evaporation of the solvent under reduced pressure gave 10 g. of a brown viscous oil, which was mildly refluxed with 140 ml. of 18% HCl over a free flame for 3 hr. The mixture changed to a clear, reddish brown solution. After this reaction, a non-basic substance was removed by exhaustive extraction with $CHCl_3$ and the resultant acid solution was evaporated to dryness under reduced pressure to leave 3.2 g. of a reddish brown viscous oil. This base was dissolved in 50 ml. of H_2O, the aqueous solution was neutralized with 10% NaOH, and the precipitate formed at pH 4.0~4.2 was extracted with AcOEt. Evaporation of the dried (Na_2SO_4) solvent gave 1.7 g. of the amino acid (XVII) as a reddish brown viscous substance.

Intramolecular Dehydration of Amino Acid (XVII)——Refluxing of 1.7 g. of the above amino acid (XVII) in 300 ml. of benzene for 6 hr. gave the cyclic amide (II) as neutral substance, which was used in the following reaction without purification. Infrared spectrum of this compound was identical with that of the amide (II) obtained by distillation.

Cyclization of the Amide (II)——A mixture of the cyclic amide (II) (prepared from 1.7 g. of the amino acid (XVII)), 3.5 ml. of $POCl_3$, and 40 ml. of benzene were refluxed for 4 hr. The solvent was evaporated under reduced pressure. After the residue was washed with a small amount of benzene, viscous residue was made alkaline with 10% NaOH and extracted with $CHCl_3$, evaporation of which yielded 0.6 g. of a brown resinous product. After it was purified by Al_2O_3 chromatography, the picrate*6 was recrystallized from hexane-EtOH to form yellow plates (XIX), m.p. 193~194°. *Anal.* Calcd. for $C_{19}H_{19}O_5N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 52.44; H, 4.22; N, 9.77; mol. wt.*7 588.47. Found : C, 52.83; H, 4.82; N, 9.69; mol. wt. 618.02. IR : ν_{max}^{KBr} 1730 cm^{-1}(C=O).

Reduction of this free base by $NaBH_4$ or dehydrogenation by Pd-black with or without cinnamic acid ended in failure.

Bischler-Napieralski Cyclization of the Amino Acid (XVII)——A mixture of 1.8 g. of the above amino acid (XVII), 50 ml. of dry benzene, and 4 ml. of $POCl_3$ was refluxed for 4 hr. until HCl no longer evolved. An excess of the condensing agent and solvent were evaporated under reduced pressure. The residue was washed with benzene and extracted with 10% HCl in the presence of 5 ml. of EtOH. The resultant acid solution was made alkaline and extracted with $CHCl_3$. Evaporation of the dried (Na_2SO_4) solvent afforded reddish brown, viscous substance, characterized as its chloroplatinate. Yield, 0.7 g. m.p. >240°. *Anal.* Calcd. for $C_{38}H_{38}O_4N_2 \cdot H_2PtCl_6 \cdot 3H_2O$*8 : C, 46.66; H, 4.67; N, 2.86; Pt, 13.31. Found : C, 46.65; H, 4.99; N, 3.02; Pt, 13.37.

One g. of the above free base (XXI) was refluxed with 5 ml. of MeI in 40 ml. of MeOH for 4 hr. and then the solvent was distilled off.

The residue was dissolved in a mixture of 50 ml. of dil. AcOH (1:1) and 25 ml. of conc. HCl, and Zn-Hg, prepared from 6.25 g. of Zn powder and 0.5 g. of $HgCl_2$, was added in small portions to the above mixture. This mixture was then heated and stirred at 60~70° for 3 hr. and the red solution turned pale yellow and gradually decolorized. The filtrate was made strongly alkaline with conc. NaOH and extracted with $CHCl_3$. Evaporation of the dried (Na_2SO_4) solvent gave 0.5 g. of the dimer (XXII) as an amorphous product, which was triturated with hexane and crystallized, m.p. 70~72°. Recrystallization from hexane-$CHCl_3$ afforded a white amorphous powder,*9 m.p. 140~143°.[12] *Anal.* Calcd. for $C_{40}H_{46}O_8N_2 \cdot 6H_2O$: C, 60.74; H, 7.32; N, 3.54. Found : C, 60.85; H, 7.04; N, 3.41.

*6 During the purification by chromatography of the free base (XVIII), it tended to be converted into 6,9,10-trimethoxy-2,3-dihydro-12*H*-benz[2,3]oxepino[7,6,5-*ij*]isoquinolin-12-one (XIX) by oxidation. Another such example will be given in a subsequent paper.

*7 Molecular weight determination was done by Rast's method.[7]

*8 This was dried over P_2O_5 at room temp. (8 mm.) for 24 hr.

*9 As this substance did not dissolve in almost any solvent except AcOH and could not be fused with camphor, its molecular weight was determined by cryoscopic method in AcOH. Calcd : mol. wt., 790.78. Found : 803.1. Although this method is not suitable for molecular weight determination in this case, the analytical and UV data[12] supported its similarity to cularine (I), but its melting point was different from that of the synthesized cularine.[11] Therefore, we thought it would be the dimer (XXII).

11) T. Kametani, K. Fukumoto : Chem. & Ind. (London), **1963**, 291.

12) UV data of cularine, cf. T. Kametani, K. Fukumoto : J. Chem. Soc., **1963**, 4289.

The above powder, when dried at 50~60°/7 mm. for 24 hr. gave a tetrahydrate, m.p. 180~182°.*10 *Anal.* Calcd. for $C_{40}H_{46}O_8N_2 \cdot 4H_2O$: C, 63.64; H, 7.21; N, 3.71. Found : C, 63.73; H, 6.59; N, 3.41. UV λ_{max}^{EtOH} mμ (log ε) : 222 (4.727), 282 (4.282).

(2-Bromo-4,5-dimethoxyphenyl)acetaldehyde (XXIII)——To a suspension of 2 g. of homoveratraldehyde in AcOH (10 ml. added with 1 g. of NaOAc), a solution of 2 g. of Br_2 in AcOH was added dropwise while being cooled and stirred. Br_2 was soon docolorized and the mixture was stirred for 1 hr. with continuous cooling. The reaction mixture was poured into 120 ml. of H_2O, basified with 10% Na_2CO_3, and extracted with Et_2O, which was washed with H_2O and dried on Na_2SO_4. Evaporation of the solvent gave 2.8 g. (97.9%) of white solid, m.p. 58~62°. Recrystallization from petr. ether afforded 1.6 g. of colorless prisms, m.p. 68~69°. *Anal.* Calcd. for $C_{10}H_{11}O_3Br$: C, 46.33; H, 4.25. Found : C, 46.35; H, 4.38.

On standing, this aldehyde turned pale orange and became viscous. In order to determine the position of Br, a solution of 0.1 g. of $KMnO_4$ in 10 ml. of H_2O was gradually added to the stirred suspension of 0.2 g. of the above aldehyde in 20 ml. of H_2O at 70°, MnO_2 being separated, giving a brown solution. The mixture was stirred for additional 1.5 hr. at 75° and then 10 ml. of NaOH was added. After the insoluble substance was filtered off, the filtrate was acidified with 10% HCl. The resultant solution was allowed to stand to separate yellow needles, which were collected by filtration, and recrystallized from petr. benzin, giving 0.1 g. of (2-bromo-4,5-dimethoxyphenyl)acetic acid (XI) as colorless needles, m.p. 116°, identified with an authentic sample by mixed melting point test.

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Summary

Preparation of the cyclic amide (II) as the key intermediate for the synthesis of cularine was elaborated. Bischler-Napieralski cyclization of this amide appeared to proceed as expected to give the desired isoquinoline derivative, didehydronorcularine, in a crude state, which, however, was readily oxidized and turned during purification into the corresponding ketone derivative, which was characterized as its picrate.

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*10 Further desication of the above powder yielded the product of $C_{40}H_{46}O_8N_2 \cdot 3H_2O$, m.p. 185° (Calcd : H_2O, 2.12. Found : H_2O, 2.36).