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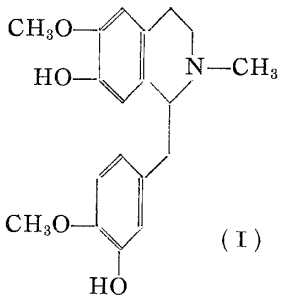
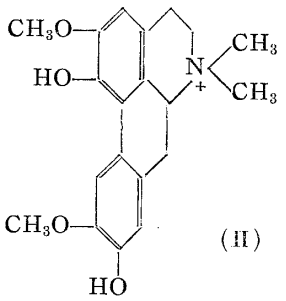
44. Masao Tomita and Ikuo Kikkawa : Studies on the Alkaloids of Menispermaceous Plants. CXXXIV.[1] Alkaloids of *Cocculus laurifolius* DC.(Suppl. 8).[1] Syntheses of *dl*-Coclanoline and *dl*-Laurifoline.

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto**)

Among the several alkaloids isolated by Tomita and Kusuda[2] from *Cocculus laurifolius* DC.(Japanese name " Kohshu-uyaku "), there are two bases named *d*-coclanoline and *d*-laurifoline. One of these alkaloids, laurifoline, has been determined as having structure (II), and for coclanoline formula (I) was assigned by these investigators. The proposed structure of the latter base, however, lacks confirmatory evidence as to the locations of its methoxyl and phenolic hydroxyl groups.

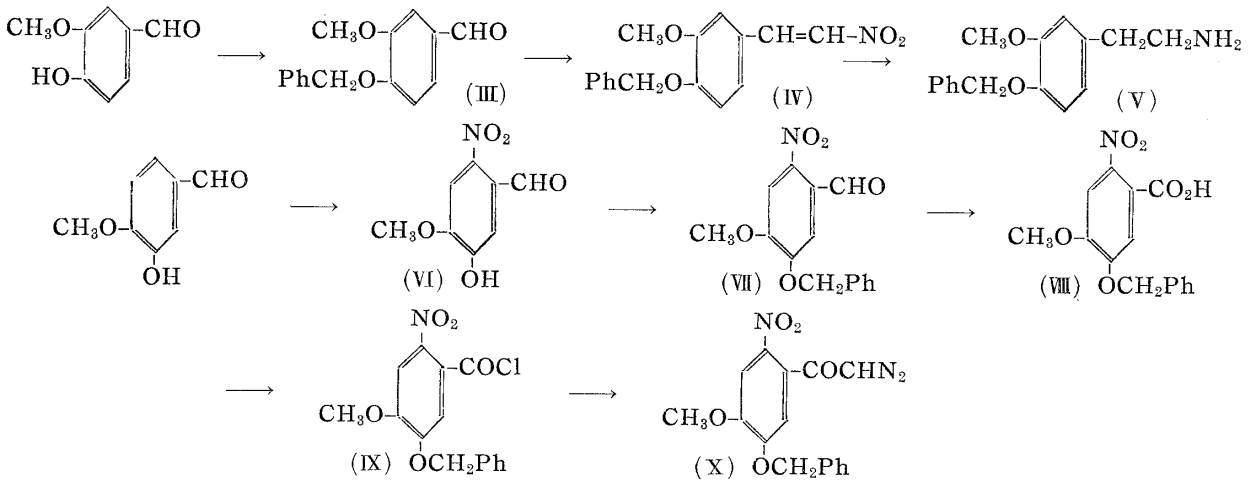


(I)



(II)

In view of the fact that one of these alkaloids, laurifoline, exhibits a significant pharmacological activity,[3,4] we have attempted to synthesize *dl*-compound of laurifoline, and in this projected synthesis, *dl*-compound of coclanoline was also produced besides that of laurifoline. Numerous methods for the synthesis of compounds of analogous structure have so far been reported in the literature,[5] and this synthesis was achieved in the following manner, employing such an easily removable blocking group as benzyl.

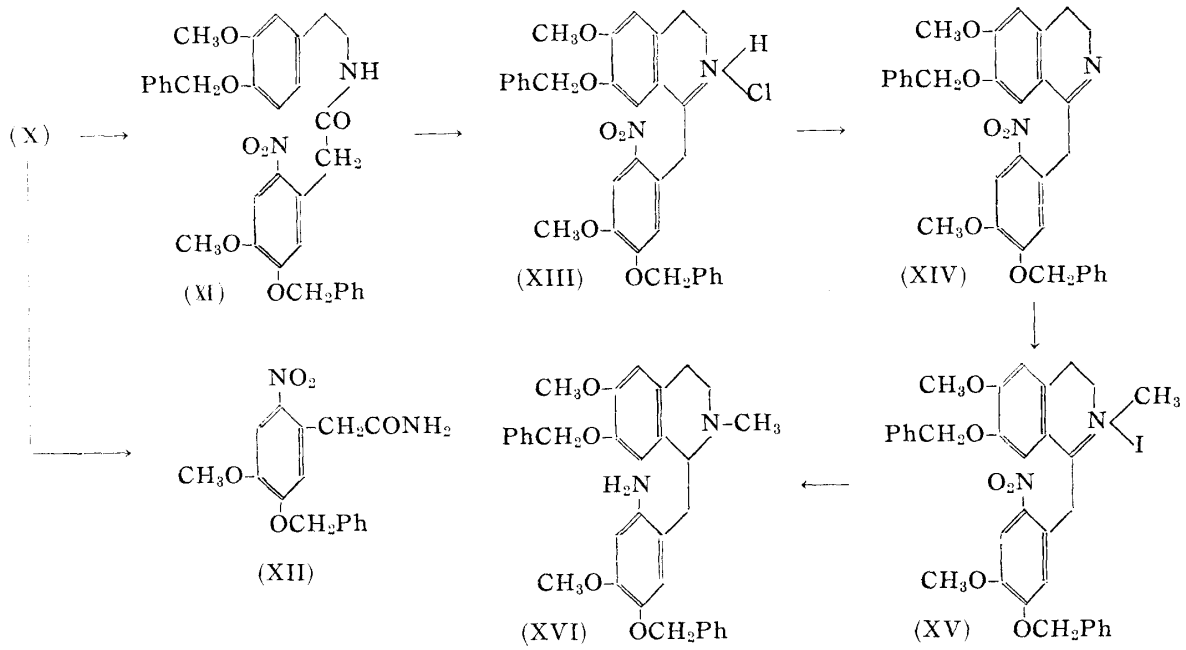


* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 橘川郁男).

1) Part. CXXXIII. Suppl. 7. M. Tomita, H. Yamaguchi : This Bulletin, **4**, 225(1956).
2) M. Tomita, F. Kusuda : J. Pharm. Soc. Japan, **72**, 280, 793(1952); F. Kusuda : This Bulletin, **1**, 1, 5, 55, 189(1953).
3) K. Ogiu, H. Takagi, M. Morita : Folia Pharmacol. Japon., **51**, 209(1955).
4) T. Maeda : *Ibid.*, **51**, 595(1955).
5) D. H. Hey, L. C. Lobs : J. Chem. Soc., **1954**, 2246.

The reduction of the nitrostyrene (IV) with lithium aluminum hydride to the phenylethylamine (V) was effected in a comparatively good yield than with the hitherto reported method[6] of catalytic reduction. 3-Benzyloxy-4-methoxy-6-nitrobenzaldehyde (VII) was oxidized with 5% aqueous potassium permanganate to the acid (VIII) in a good yield. This method of oxidation may serve as a substitute for that of employing silver oxide in an alkaline medium. (VIII) thus obtained was allowed to react with phosphorus pentachloride at room temperature to form the acid chloride (IX), which, because of its unstability in the air, was led directly to the ω-diazoketone (X) by treatment with diazomethane.

The condensation of 3-methoxy-4-benzyloxyphenylethylamine (V) with 3-benzyloxy-4-methoxy-6-nitro-ω-diazoacetophenone (X) was effected by Arndt-Eistert synthesis in benzene in the presence of silver oxide, giving the corresponding acid amide, viz., 3-benzyloxy-4-methoxy-6-nitrophenyl-N-2-(3′-methoxy-4′-benzyloxyphenyl)-ethylacetamide (XI) in a satisfactory yield. On the other hand, when (X) was treated with silver nitrate in the presence of ammonia in a dioxane solution, 3-benzyloxy-4-methoxy-6-nitrophenylacetamide (XII) was formed. The acid amide (XI) was then treated with phosphorus pentachloride by the procedure of Bischler-Napieralski and the dihydroisoquinoline (XIII) was isolated as its hydrochloride. The free base (XIV) liberated from the hydrochloride was converted by methyl iodide into the methiodide (XV), which in turn was reduced with hydrochloric acid and zinc dust to form the amine (XVI). Because of its unstability, however, (XVI) was isolated as its picrate.

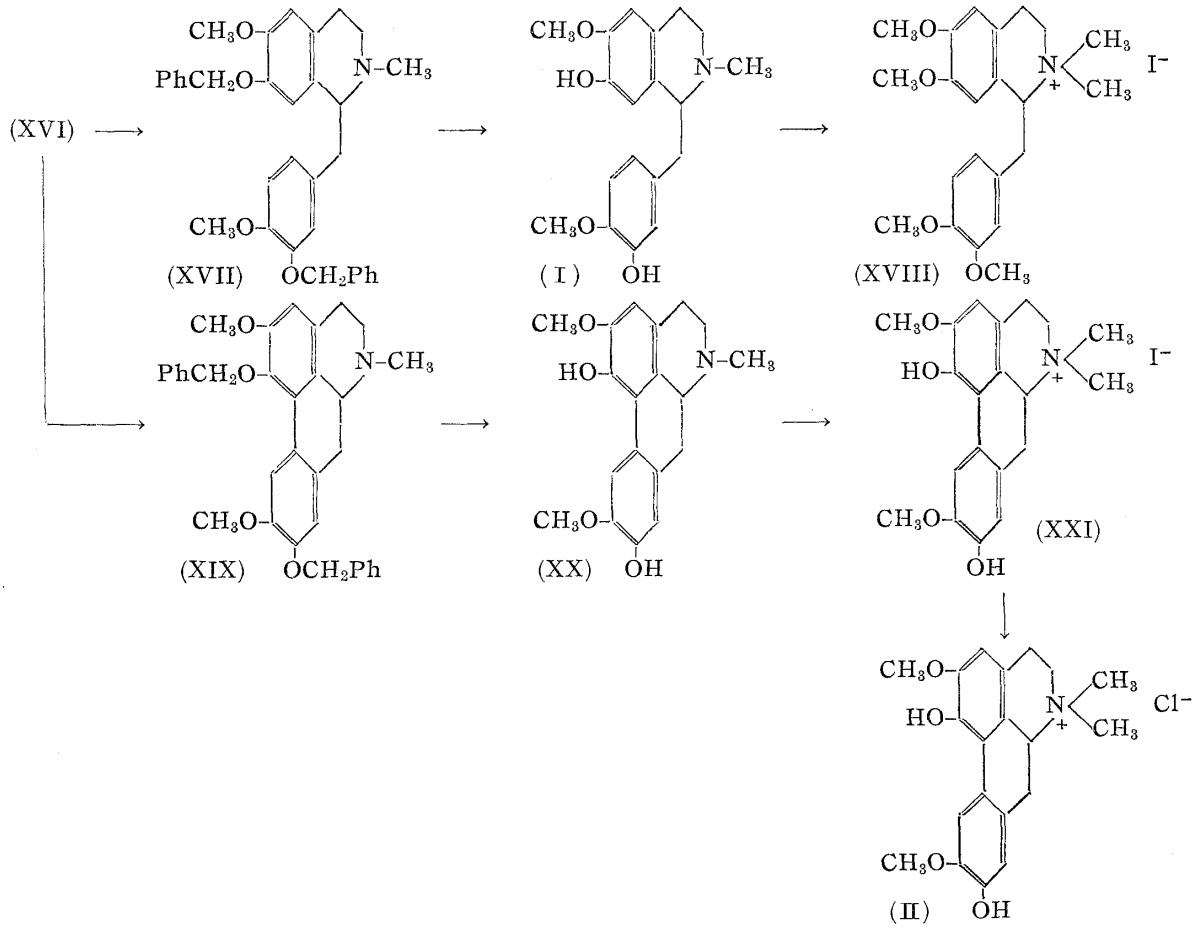


For the diazotization of 1-(3′-benzyloxy-4′-methoxy-6′-aminobenzyl)-6-methoxy-7-benzyloxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XVI), the Pschorr synthesis of phenanthrene was followed. (XVI) was dissolved in methanolic sulfuric acid, diazotized at low temperature with sodium nitrite, and then treated with copper powder, whereby deamination took place and a product (picrate, m.p. 149~150°) was obtained. This product was shown by ultraviolet absorption spectrum to be 1-(3′-benzyloxy-4′-methoxybenzyl)-6-methoxy-7-benzyloxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XVII). Subsequent debenzylation of (XVII) with 20% hydrochloric acid gave rise to the compound (I) whose oxalate showed m.p. 120~122°. The color reactions of (I) with Gibbs

6) M. Tomita, H. Watanabe : J. Pharm. Soc. Japan, **58**, 786(1938).

reagent, ferric chloride, and conc. sulfuric acid agreed well with those of natural *d*-coclanoline. Its oxalate and that of *d*-coclanoline also gave identical Rf values in the paper chromatography. Thus the synthesis of *dl*-coclanoline (I) gave support to the proposed structure of natural coclanoline. *dl*-Coclanoline (I) so obtained was then converted with methanolic potash and methyl iodide into *dl*-laudanosine methiodide (XVIII), which was confirmed to be identical with the methiodide derived from *dl*-laudanosine.

It was already mentioned that in the above Pschorr synthesis of phenanthrene with copper powder, deamination occurred and coclanoline of the benzylisoquinoline type was formed. However, when the reaction was modified by employing zinc dust[7] instead of copper powder and the reaction products were purified in benzene by chromatography on alumina, 2,5-dibenzyloxy-3,6-dimethoxyaporphine (XIX) was obtained, together with the benzylisoquinoline (XVII), in a poor yield, whose ultraviolet absorption spectrum suggested its similarity to the aporphine series. From the acetone eluate fraction through the alumina column, there was obtained another product forming yellow plates, m.p. 201~202°, as the picrate, but its amount was too small to allow further investigations. On debenzylation, (XIX) yielded 2,5-dihydroxy-3,6-dimethoxyaporphine (XX) which, due to its unstability, was isolated as its hydrochloride. The methiodide (XXI) was also labile and was led to the methochloride (m.p. 233°) by treatment with silver chloride. The ultraviolet absorption spectrum of this methochloride was also found to be in good accord with that of natural *d*-laurifoline chloride.[2]



7) E. Schlittler, G. Barger : Helv. Chim. Acta, **15**, 381(1932).

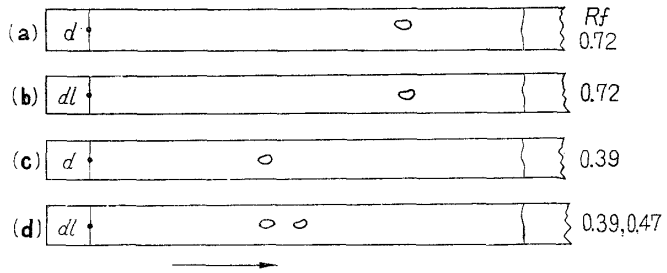


Fig. 1.

The paper partition chromagrams of *d*-coclanoline oxalate (a) and *dl*-coclanoline oxalate (b) are shown in Fig. 1, along with those of *d*-laurifoline chloride (c) and *dl*-laurifoline chloride (d). Toyo filter paper No. 50 was used and development was effected by the ascending technique with the solvent mixture of butanol, acetic acid, and water. For the detection of alkaloidal spots, Dragendorff reagent was employed. As shown in Fig. 1, both *d*- and *dl*-coclanoline oxalates gave a single spot at the same position (Rf 0.72), whereas *dl*-laurifoline chloride produced two spots at different positions (Rf 0.39 and 0.47), one of which was situated at identical position (Rf=0.39) with *d*-laurifoline chloride. Since these two spots were of the same size and concentration, it seems almost inconceivable that this synthetic *dl*-laurifoline chloride had originally been contaminated with impurities. It seems instead that *dl*-laurifoline chloride underwent racemic resolution by the paper chromatography, although because of its small amount, it was impossible to investigate this further. Such an example may be rare, but similar phenomena have been reported by Kotake, Sakan, and Nakamura[8] with some of amino acids.

We are indebted to Dr. Hiraizumi, Director of Takasago Perfume Industries, and Dr. Okuda of the Research Laboratory of the same firm for the generous gift of materials of vanillin and isovanillin used in this experiment, and to Dr. Takeda, Director of the Research Laboratory, Shionogi & Co., Ltd., for his interest in this work. This work has been supported partly by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which we are also grateful.

Experimental[9]

3-Methoxy-4-benzyloxyphenylethylamine (V)—1.5 g. of $LiAlH_4$ was suspended in 250 cc. of dehyd. ether. While stirring, a solution of 5 g. of 3-methoxy-4-benzyloxy-ω-nitrostyrene (IV), prepared from vanillin, in 50 cc. of dehyd. tetrahydrofuran, previously dried, was added dropwise at room temperature. After the addition, the reaction was completed by heating on a water bath for an additional 2 hrs. Then, while cooling, approximately 20 cc. of 30% aq. NaOH was slowly added with stirring to decompose the excess reagent. The ether and tetrahydrofuran layer was decanted and the residual oil was extracted twice with 100 cc. of ether. The combined organic layer was dried over anhyd. K_2CO_3, and the solvent removed, leaving a yellowish oil. This was induced to crystallize as the oxalate. After recrystallization from dehyd. EtOH, 5 g. of colorless pillars, m.p. 163~164°, were obtained. *Anal.* Calcd. for $C_{18}H_{27}O_6N$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.11; H, 6.08; N, 4.16.

3-Benzyloxy-4-methoxy-6-nitrobenzaldehyde (VII)—According to the procedure of Pschorr and Stöhrer,[10] isovanillin was nitrated and the resultant 6-nitro compound was separated from 2-nitro compound. After benzylation of the 6-nitro compound by the procedure of Hey and Lobs,[5] 3-benzyloxy-4-methoxy-6-nitrobenzaldehyde was obtained as yellow needles, m.p. 134°, from EtOH (reported m.p. 133~134°).

3-Benzyloxy-4-methoxy-6-nitrobenzoic Acid (VIII)—To a solution of 10 g. of 3-benzyloxy-4-methoxy-6-nitrobenzaldehyde (VII) in 200 cc. of acetone was added dropwise with stirring a solution

8) M. Kotake, T. Sakan, N. Nakamura: J. Am. Chem. Soc., **73**, 2973(1951).
9) All melting points are uncorrected. We are indebted to Messrs. Miyahara, Ieki, Morita, and Nakai of the Microanalytical Laboratory of Shionogi & Co., Ltd., for the microanalytical data.
10) R. Pschorr, W. Stöhrer: Ber., **35**, 4394(1902).

of 5% aq. $KMnO_4$, during which period the temperature of the solution was kept below 40°. After the addition, stirring was continued for some time until the solution was decolorized. After filtration of MnO_2, solvent was removed, and the residue was acidified with HCl, depositing crystals. They were filtered with suction, washed with water, and extracted with warm 5% aq. Na_2CO_3. The aq. alkaline solution was acidified with 5% HCl, and the deposited crystals were recrystallized from hydrated EtOH, yielding 6 g. of slightly yellowish needles, m.p. 197~198°. *Anal.* Calcd. for $C_{15}H_{13}O_6N$: C, 59.37; H, 4.32; N, 4.61. Found : C, 59.29; H, 4.36; N, 4.64. From the alkali-insoluble portion, 5 g. of unreacted material was recovered.

3-Benzyloxy-4-methoxy-6-nitrobenzoyl Chloride (IX)—3 g. of PCl_5 was suspended in 30 cc. of dehyd. $CHCl_3$, and 4 g. of the acid(Ⅷ) was added in small portions with stirring at room temperature. After the whole had dissolved, the mixture was kept standing for a further 1 hr. and then filtered. The solvent was distilled off below 30° and 10 cc. of cooled dehyd. ether was then added to the residue, whereby crystals deposited. After being filtered and washed with cooled dehyd. ether, 3.5 g. of colorless needles, m.p. 124~125°, were obtained.

3-Benzyloxy-4-methoxy-6-nitro-ω-diazoacetophenone (X)—A solution of 5 g. of the acid chloride (IX) in 15 cc. of dehyd. benzene was added dropwise, with stirring at between 0° and 3°, to an ethereal solution of diazomethane (from 6 g. of nitrosomethylurea). After 3 hrs., the deposited crystals were filtered and washed well with cooled ether. 4.4 g. of colorless needless, m.p. 130~133°, was obtained. *Anal.* Calcd. for $C_{16}H_{13}O_5N_3$: C, 58.80; H, 4.00. Found : C, 58.87; H, 4.03.

3-Benzyloxy-4-methoxy-6-nitrophenyl-N-(3′-methoxy-4′-benzyloxyphenyl)ethylacetamide (XI)—To a stirred solution of 4.4 g. of the diazoketone (X) in 100 cc. of benzene, 0.4 g. of freshly prepared Ag_2O and a solution of 3-methoxy-4-benzyloxyphenylethylamine (liberated from 4.7 g. of the oxalate) in benzene were added at 60~63°. After 3 hrs., further 0.4 g. of Ag_2O was added and the reaction mixture was boiled for 30 mins. After treatment with charcoal, the reaction mixture was filtered and the solvent removed, leaving an oil. Crystallization from hot EtOH yielded 4.6 g. of slightly yellowish needles, m.p. 168.5~169.5°. *Anal.* Calcd. for $C_{32}H_{32}O_7N_2$: C, 69.05; H, 5.80; N, 5.03. Found : C, 68.66; H, 5.50; N, 5.16.

3-Benzyloxy-4-methoxy-6-nitrophenylacetic Amide (XII)—2.5 g. of the ω-diazoketone (X) was dissolved in 50 cc. of dioxane, and 9 cc. of 10% aq. $AgNO_3$ and 5 cc. of 28% aq. NH_4OH were added. While stirring, the mixture was heated gradually to 70°, and after the evolution of nitrogen had ceased, heating was continued at 80° for 2 hrs. Then the reaction mixture was filtered with charcoal while hot and the filtrate was evaporated. Upon recrystallization of the residue, 1.9 g. of slightly yellowish needles, m.p. 227~229°(decomp.), were obtained. *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$: C, 60.75; H, 5.10; N, 8.85. Found : C, 60.84; H, 5.00; N, 8.86.

1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline Hydrochloride (XIII)—A mixture of 3.5 g. of the acetamide (XI), 5.8 g. of PCl_5, and 18 cc. of $CHCl_3$ was kept in a sealed flask at room temperature for 100 hrs. Then the lid was removed and the mixture was kept standing for a further 20 hrs. 200 g. of ice was then added, and after all had dissolved, $CHCl_3$ was distilled off below 30°, depositing crystals. They were collected and washed with cool water. The crude crystals were heated with 2 cc. of conc. HCl and 30 cc. of MeOH for 10 mins., the solution was filtered with charcoal, and the filtrate concentrated. The deposited crystals were recrystallized from MeOH, yielding 2.6 g. of slightly yellowith needles, m.p. 212~212.5°. *Anal.* Calcd. for $C_{32}H_{30}O_6N_2 \cdot HCl$: C, 66.84; H, 5.43; N, 4.87. Found : C, 67.02; H, 5.32; N, 4.73.

1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline (XIV)—0.3 g. of the above hydrochloride (XIII) was dissolved in 30 cc. of MeOH, and while hot, made alkaline with 10% aq. NH_4OH, depositing crystals. Recrystallization from MeOH containing dichloroethane yielded 0.27 g. of slightly yellowith pillars, m.p. 168.5~169.5°. *Anal.* Calcd. for $C_{32}H_{30}O_6N_2$: C, 71.36; H, 5.61; N, 5.32. Found : C, 71.73; H, 5.57; N, 5.30.

1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline Methiodide (XV)—The free base (XIV) was refluxed with MeI for 6 hrs. and after removal of the excess MeI, the residue was recrystallized from $CHCl_3$-benzene to yellow plates, m.p. 193~194.5°. The yield was quantitative. *Anal.* Calcd. for $C_{32}H_{30}O_6N_2 \cdot CH_3I$: C, 58.02; H, 4.81. Found : C, 58.24; H, 4.88.

1-(3′-Benzyloxy-4′-methoxy-6′-aminobenzyl)-6-methoxy-7-benzyloxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XVI)—1 g. of the methiodide (XV) was dissolved in 40 cc. of glacial AcOH and 14 cc. of conc. HCl was added followed by 4.4 g. of Zn powder, in small portions with stirring, between −1° and 3°. The stirring was continued at this temperature for 4 hrs. until the solution became colorless. The reaction mixture was filtered, the filtrate was diluted with 20 cc. of water, and after being alkalized with 10% aq. NH_4OH, extracted with 40 cc. of ether. The aq. layer was again extracted with ether and the combined ether extract was dried over anhyd. K_2CO_3. Removal of the ether left a slightly yellow, reddish viscous oil. Addition of picric acid to its

EtOH solution gave a precipitate of the picrate which, on recrystallization from acetone-MeOH, formed yellow needles, m.p. 144~145°. Yield, 1 g. *Anal.* Calcd. for $C_{33}H_{36}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 55.00; H, 4.30; N, 11.40 Found : C, 55.28; H, 4.12; N, 11.40.

***dl*-Coclanoline (I)**—1 g. of the dipicrate of the amine (XVI) was decomposed with 10% aq. NaOH and the liberated base was extracted several times with ether. The ether extracts were combined, dried over anhyd. K_2CO_3, and the solvent removed, leaving an oil. This was dissolved in 10 cc. of MeOH and 5 cc. of 20% H_2SO_4 added. To this solution, an aq. *N* $NaNO_2$ solution ($NaNO_2$=0.09 g.) was added with stirring between 0° and 2°. After 6 hrs., the solution became bluish green. At this point, 0.5 g. of freshly prepared copper powder was added at 0° and stirring was continued at room temperature for 30 mins. The reaction mixture was then boiled gently for 30 mins., during which period the vigorous evolution of nitrogen occurred. After filtration, the nearly colorless solution was obtained, from which the remaining MeOH was evaporated *in vacuo*. The residual solution was made alkaline with 10% aq. NaOH and extracted three times with ether. The combined ether extract was dried over anhyd. K_2CO_3 and evaporated, yielding 0.45 g. of reddish brown viscous oil. This was chromatographed in benzene on alumina, and the eluate furnished 0.15 g. of the picrate forming yellow plates, m.p. 149~150°, from benzene. The free base (XVII) was obtained as a nearly colorless oil, whose ultraviolet spectrum (λ_{max}^{EtOH} 282 mμ) suggested its similarity to the benzylisoquinoline series. *Anal.* Calcd. for $C_{33}H_{35}O_4N \cdot C_6H_3O_7N_3$: C, 63.40; H, 5.18. Found : C, 63.62; H, 4.98.

The free base (XVII) was boiled with 20% HCl on a water bath for 1 hr., after which the solution was evaporated *in vacuo* to dryness. The residue gave no crystalline chloride in spite of various attempts. Therefore, it was dissolved in a little water, made alkaline with $NaHCO_3$, and extracted three times with ether. The ether extract was dried over anhyd. Na_2SO_4, and the ether removed. The residue (coclanoline (I)[11]) was a slightly yellowish amorphous powder, m.p. 88~91°, and did not crystallize in spite of various treatments. Its oxalate, however, formed colorless short pillars, m.p. 120~122° (*dl*-coclanoline (I) oxalate) from MeOH-acetone. *Anal.* Calcd. for $2C_{19}H_{23}O_4N \cdot (COOH)_2 \cdot 2H_2O$: C, 61.20; H, 6.66. Found : C, 61.11; H, 7.15.

dl-Coclanoline (I) so obtained gave positive tests with Gibbs reagent and ferric chloride, and it produced pink color with conc. H_2SO_4. These color reactions agreed well with those given by natural *d*-coclanoline. The melting points of both synthetic and natural coclanoline oxalates are identical. The paper chromatography of these compounds were carried out according to the following procedure. Toyo Roshi No. 50 was used and development was effected by the ascending technique in a sealed tank with a 4:1:2 mixture of BuOH, AcOH, and H_2O. For the detection of alkaloidal spots, Dragendorff reagent was used with the result that both *dl*- and *d*-compounds gave identical Rf values (0.72) (see Fig. 1).

***dl*-Laudanosine Methiodide (XVIII)**—0.2 g. of *dl*-coclanoline (I) obtained above was refluxed with 5 cc. of 0.5*N* methanolic potash and 2 cc. of MeI for 3 hrs. Then, similar amounts of 0.5*N* methanolic potash and MeI were added and heating was continued for a further 3 hrs. After one more repetition of similar procedure, the reaction mixture was concentrated *in vacuo*, and the remainder was dissolved in $CHCl_3$, washed with 5% aq. NaOH, and the $CHCl_3$ distilled off. The oily residue was dissolved in a 1 : 1 mixture of acetone and benzene and the solution was passed through an alumina column. The chromatogram was developed with acetone and the eluate, after evaporation, left a colorless oil. This was induced to crystallize from MeOH-acetone, yielding 0.15 g. of colorless short plates, m.p. 212~213°. Admixture with *dl*-laudanosine methiodide, m.p. 212~213°, gave no depression. *Anal.* Calcd. for $C_{22}H_{30}O_4NI$: C, 52.91; H, 6.06; N, 2.81. Found : C, 53.15; H, 6.03; N, 2.73.

***dl*-Laurifoline Chloride (II)**—The free base from 1.8 g. of the dipicrate (XVI) was dissolved in 20 cc. of MeOH and 20 cc. of 2*N* H_2SO_4 added. To this solution, an aq. *N* $NaNO_2$ solution ($NaNO_2$=0.18 g.) was added dropwise at below 3°. After standing for 10 hrs., the solution was boiled on a water bath for 30 mins., whereafter the bluish green colored solution turned reddish brown. Then, 1.0 g. of Zn dust and 2.7 cc. conc. HCl were added and the mixture was heated for 15 mins. The nearly colorless solution was filtered while hot, the filtrate concentrated *in vacuo*, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 10% aq. NaOH, dried over anhyd. K_2CO_3, and the $CHCl_3$ removed, yielding 0.85 g. of reddish brown oily product. This was chromatographed in benzene on alumina and from the eluate, a nearly colorless viscous oil was obtained. This formed from EtOH-acetone two kinds of crystalline picrates consisting of 0.08 g. of yellow pillars (a) and 0.15 g. of yellow plates (b). The picrate (b), after recrystallization from EtOH-acetone, showed m.p. 149~150°, undepressed on admixture with 1-(3′-benzyloxy-4′-methoxybenzyl)-6-methoxy-7-benzyloxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XVII) picrate. On the other hand, the picrate (a), after recrystallization from EtOH-acetone, showed m.p. 189~190°,

11) Natural coclanoline was also difficult to crystallize.

identical with that of 2,5-dibenzyloxy-3,6-dimethoxyaporphine (XIX) picrate. *Anal.* Calcd. for $C_{33}H_{33}O_4N \cdot C_6H_3O_7N_3$: C, 63.85; H, 4.92; N, 7.60. Found : C, 63.40; H, 5.22; N, 7.69.

The free base of the picrate (a) formed from MeOH colorless needles, m.p. 140°. The ultraviolet absorption spectrum exhibits λ_{max}^{EtOH} mμ(log ε) : 282 (4.07) and 303 (4.06), resembling that of the aporphine-type alkaloids. *Anal.* Calcd. for $C_{33}H_{33}O_4N$: C, 78.08; H, 6.55; N, 2.76. Found : C, 78.31; H, 6.72; N, 3.04.

The acetone eluate fraction from the alumina column after development with benzene furnished 10 mg. of the picrate forming yellow plates, m.p. 201~202°, which, however, was not further examined.

70 mg. of the dibenzyl ether (XIX) was heated with 15 cc. of 20% HCl on a water bath for 1 hr., after which the reaction mixture was evaporated *in vacuo* to dryness. The residue was crystallized from EtOH to colorless short pillars, m.p. 249°(decomp.) (2,5-dihydroxy-3,6-dimethoxyaporphine (XX) hydrochloride). Yield, 40 mg. *Anal.* Calcd. for $C_{19}H_{22}O_4NCl \cdot {}^1/_2 H_2O$: C, 61.23; H, 6.21; N, 3.76 : Found : C, 61.19; H, 6.30; N, 3.97.

The hydrochloride was dissolved in a small portion of water, made alkaline with $NaHCO_3$, and extracted with ether. The combined ether extract was dried over anhyd. Na_2SO_4 and the solvent removed, leaving a colorless oil (2,5-dihydroxy-3,6-dimethoxyaporphine (XX)). Since this showed a great tendency to darken in air, it was converted into the methiodide by refluxing with MeI in MeOH for 1 hr. 2,5-Dihydroxy-3,6-dimethoxyaporphine methiodide (XXI) was obtained as colorless pillars, which, however, were liable to darken in air and separate as an oil at recrystallization. 40 mg. of (XXI) was then dissolved in hydrated MeOH, shaken with 50 mg. of freshly prepared silver chloride for 1 hr., and filtered. The filtrate was evaporated *in vacuo* to dryness and the residue was crystallized from MeOH-acetone to form colorless short pillars, m.p. 233°(decomp.) (*dl*-laurifoline chloride (II)). Yield, 30 mg. *Anal.* Calcd. for $C_{20}H_{24}O_4NCl \cdot {}^1/_2 H_2O$: C, 62.08; H, 6.51; N, 3.61. Found : C, 62.30; H, 6.47; N, 3.14. The literature records m.p. 239°(decomp.) for natural *d*-laurifoline chloride. The ultraviolet absorption spectrum of (II), $\lambda_{max}^{H_2O}$ mμ(log ε): 279 (4.05) and 304 (4.11) agreed with that givin for *d*-laurifoline chloride. Both these compounds were further submitted to paper chromatography. Toyo Roshi No. 50 was used and development was effected by the ascending technique with a 4 : 1 : 2 mixture of BuOH, AcOH, and H_2O. For the detection of alkaloidal spots, Dragendorff reagent was used. The *dl*-compound exhibited two spots at different positions (Rf 0.37 and 0.47), whereas the *d*-compound gave a single spot (Rf 0.37) (Fig. 1).

Summary

The *dl*-compound of coclanoline (I) and laurifoline (II), so far isolated from *Cocculus laurifolius* DC., were synthesized.

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