Summary

A new synthetic method of pyrimidine and purine ribosides was introduced. Condensation of tribenzoylribofuranosyl chloride with trimethylsilyl derivatives of pyrimidines and purines and then deacylation furnished natural ribose nucleosides in good yields. In the syntheses of uridine and ribofuranosylthymine, α-isomers were also isolated and the determinations of the structures were described.

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202. **Naoto Yoneda**: Synthesis of 9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-2,6-methano-11*bH*-benzo[*a*]quinolizine.

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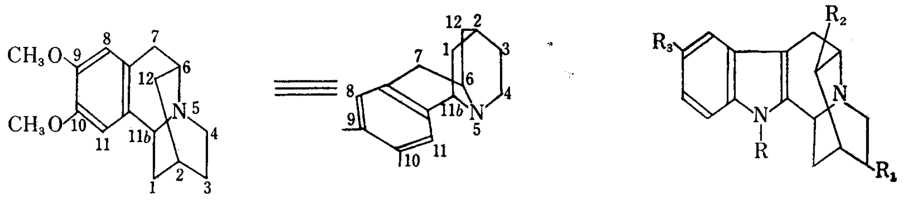
In this paper is described a synthesis of the title compound (I), as a preliminary to the synthesis of 2,6-methano-indolo[2,3-*a*]quinolizine derivative (II), which forms the fundamental skeleton of sarpagine (II) ($R=H$; $R_1=\rangle CH-CH_3$; $R_2=CH_2OH$; $R_3=OH$) and cognate Rauwolfia bases.



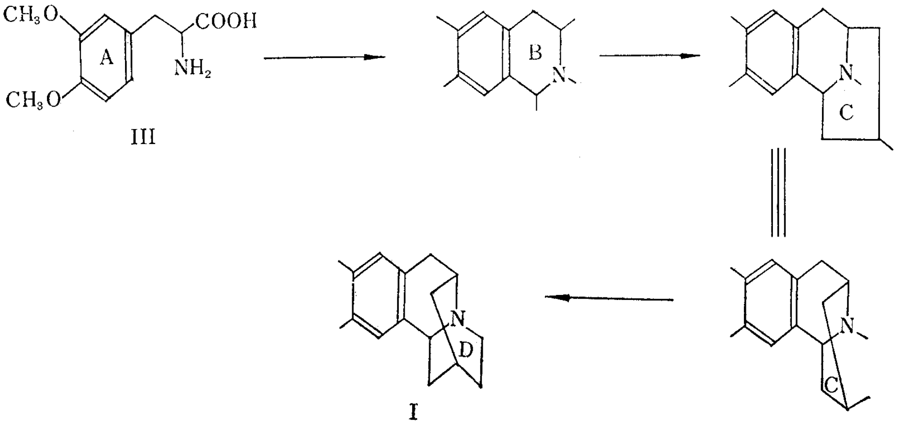
I

II

Chart 1.

An unsuccessful attempt of I has already been described by Arata and Sugasawa.[1]

The scheme of the present synthesis starting from *dl*-3-(3,4-dimethoxyphenyl)alanine (III) is outlined in the following Chart 2.



I

Chart 2.

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*1 Toda-machi, Kita-adachi-gun, Saitama-ken (米田直人).

[1] Y. Arata, S. Sugasawa: This Bulletin, 9, 104 (1961).

Thus ethyl ester (Ⅳ) of Ⅲ was condensed with benzaldehyde to form the Schiff base (V), which was reduced with sodium borohydride-methanol to give N-benzylester (Ⅵ) as a colorless viscous oil in an excellent yield.

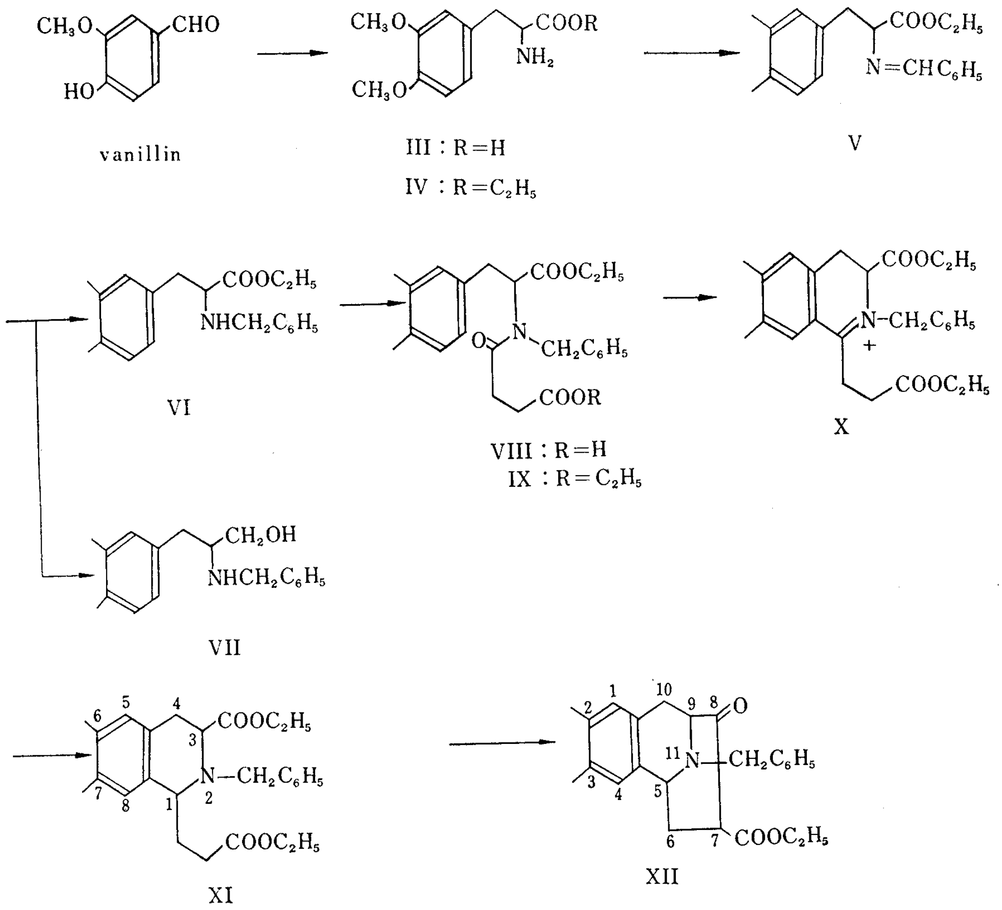

Chart 3.

Minor amount (ca. 5%) of alcohol (Ⅶ), colorless silky crystals, was also obtained as a by-product. The yield of Ⅶ increased when an excess of sodium borohydride was used, especially in ethanol. Similar reduction of α-amino acid ester to form the corresponding alcohol was also reported by Yamada, *et al.*[2]

Ⅵ was now heated with succinic anhydride in benzene to give the amido-acid (Ⅷ), whose ethyl ester (Ⅸ) was obtained in colorless plates, m.p. 68～69°, in a good yield.

The Bischler-Napieralski cyclization of Ⅸ to form the B-ring presented some difficulty. The convensional procedure using phosphoryl chloride in benzene hydrocarbons was not effective, the starting amide being completely recovered. A combination of phosphoryl chloride and phosphorus pentoxide met also with little success, yielding the cyclization product only in ca. 5% yield isolated as iodide. The best result so far obtained was achieved by treating the amide with phosphoryl chloride under reflux for 10 hours to give 54% yield of the iodide (X) once crystallized from methanol-ether. Further purification of this iodide from the same solvent gave two kinds of crystals : (a) yellowish orange plates and (b) faint yellow prisms. Both of them melted with decomposition at 155～156° and gave the same analytical values conforming to X and showed the same ultraviolet absorption spectra. Though their infrared spectra were not identical in Nujol mull, those in chloroform were found to be completely superimposable.

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[2] S. Yamada, K. Koga, H. Matsuo : This Bulletin, **11**, 1140 (1963).

Moreover the fact that their interconversion was observed in the recrystallization procedure in methanol-ether, and they gave one and the same chloride, proved them to be dimorphous.

On being reduced with sodium borohydride[3]-methanol both (X) iodides yielded the same reduction product (XI) in a good yield as a mixture of α- and β-diastereoisomers at position 1 and 3 of the reduced B-ring in a ratio of ca. 5:1. The α-isomer, the main reduction product, formed a syrup readily soluble in dil. hydrochloric acid and more basic, while the β-isomer was a solid almost insoluble in dil. hydrochloric acid.

These isomers manifested different aptitude toward the Dieckmann cyclization reaction to form the ring-C.

Thus when treated with sodium hydride in boiling toluene, both isomers furnished one and the same ketoester (XII), but the α-isomer reacted easier and gave a higher yield of the product than did the β-isomer. The ketoester (XII) gave reddish purple color test with ferric chloride, but was not soluble in sodium hydroxide solution. Even after repeated recrystallization it melted over a range of 101~112°, but the analyses of it and its picrate, and infrared data[4] (1650, 1610 cm^{-1} conjugated chelate enolic form of β-ketoester) provided support for XII. From the above mentioned fact the α-isomer was assumed to be *cis*, which directly entered into the cyclization reaction, while the *trans* β-isomer had to undergo epimerization at position 3 prior to cyclization.

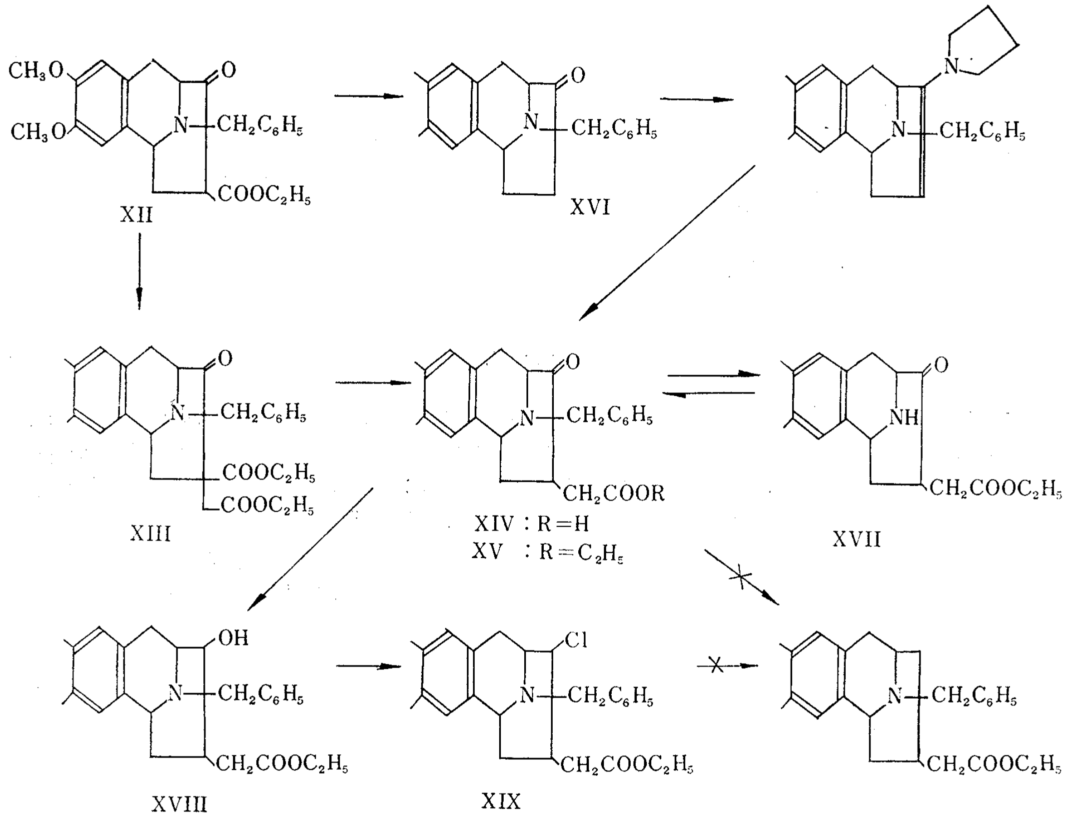

Chart 4.

XII was now converted to XIII whose ketone fission presented again some difficulty. The fission with acid ended abortive, giving back the starting material. XIII was, therefore, refluxed with dil. aqueous alcoholic solution of potassium hydroxide and then

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[3] B. Witkop, J. S. Patrick: J. Am. Chem. Soc., **75**, 4474 (1953).
[4] N. J. Leonard, H. S. Gutowsky, W. J. Middleton, E. M. Petersen: *Ibid.*, **74**, 4070 (1952).

treated with hydrochloric acid to ensure decarboxylation to separate XIV as hydrochloride salt. The corresponding ester (XV) was obtained in 25% overall yield from XII.

An alternative method was also investigated. Thus XII was acid-cleaved in a smooth reaction to give XVI, which was then carbethoxymethylated according to the Stork's method.[5] The product (XV) was, however, difficult to purify and in author's hand it was only possible to have it in crystalline state by de- and re-benzylation *via* XVII. The overall yield of XV from XII by this route was 20%. XV thus obtained formed colorless plates from ethanol, m.p. 138~140°, and gave correct analysis and molecular weight by the Rast method.

Since various attempts of direct conversion of CO group in XV to CH_2 were unsuccessful, it was reduced with sodium borohydride-ethanol to the corresponding alcohol (XVIII), which was obtained in 79% yield as hydrochloride salt. Tosylation and mesylation experiments under a variety of conditions gave invariably the same compound, in which S was absent, but Cl was present. This was identical with chloride (XIX) prepared from XVIII with thionyl chloride-pyridine in 77% yield.

Since dechlorination of XIX by catalytic hydrogenation ended fruitless, this was treated with lithium aluminum hydride-THF to afford a colorless caramel-like substance

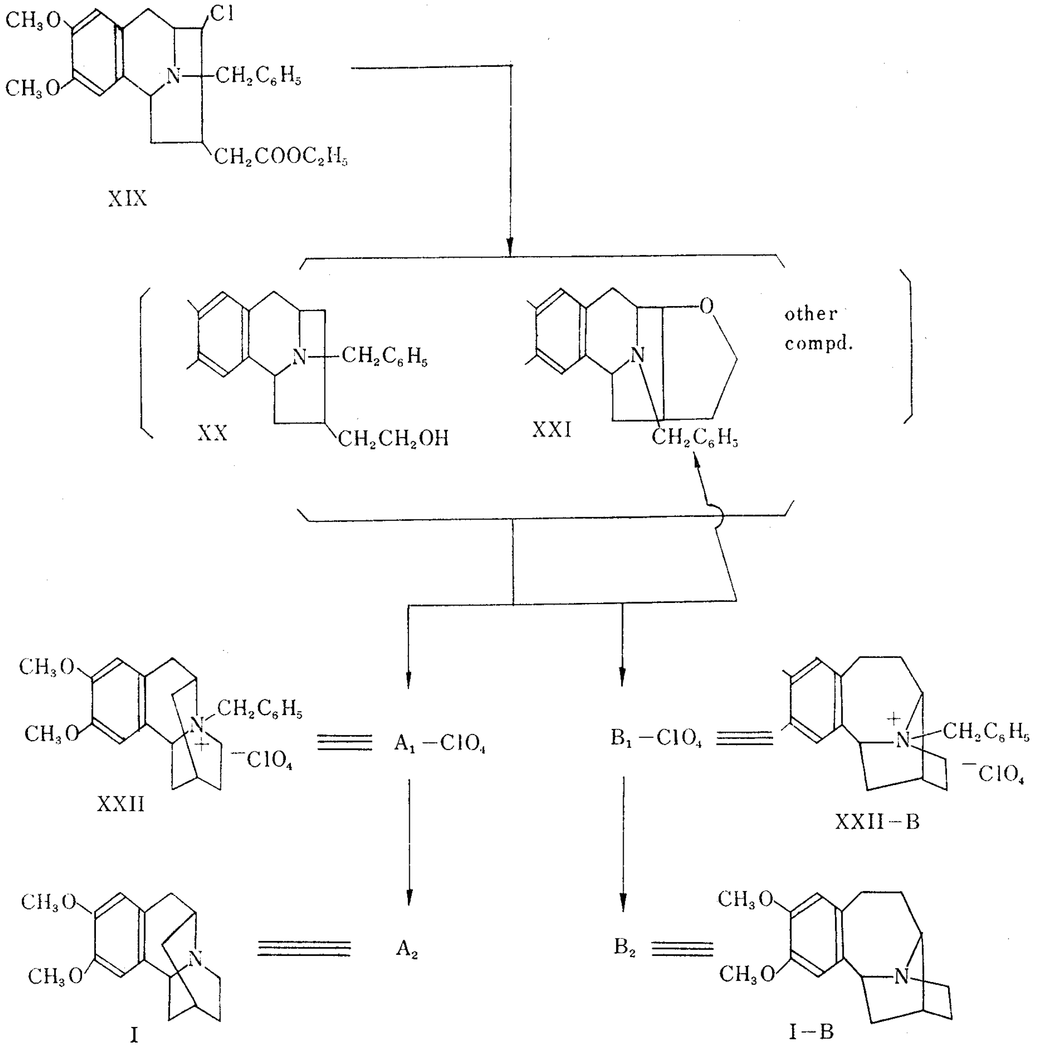

Chart 5.

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[5] A. R. Surrey: "Name Reactions in Org. Chemistry," 2nd Ed. p. 231 (1961), Academic Press Inc., New York.

devoid of both halogen and ester group, and this substance was found to comprise mainly the objective alcohol (XX) and a by-product (XXI) (***vide infra***). Since their separation was not successful, the above obtained product was directly tosylated in the presence of pyridine in the cold. The reaction product was freed from pyridine and thoroughly washed with ether, and the residue was extracted with water. By adding sodium perchlorate to the aqueous solution there separated a solid, which was purified from ethanol to give colorless minute needles, m.p. 238~239° with decomposition, in less amount and was tentatively called B_1-perchlorate.

The syrupy residue which was insoluble in water was dissolved in benzene and refluxed for some time to ensure the cyclization to form ring-D. The solvent was then removed and the residue was extracted with warm water. Addition of sodium perchlorate to the aqueous solution caused a solid to separate which was purified from ethanol to form colorless prisms, m.p. 210~211°, as the main product and was called A_1-perchlorate. The residual syrup was again dissolved in benzene and was purified through an alumina column to furnish a colorless syrup which was assumed to be the ether (XXI) based upon the following evidence, that this could not be acylated, conforming to the absence of OH absorption band in its infrared spectrum, and bands at 920 and 1090 cm^{-1} are ascribable to 5-membered ether linkage.⁶⁾ The hydrochloride and perchlorate salt were also analyzed correctly as XXI.

A_1- and B_1-perchlorate, both of which gave correct analysis as XXII, were then treated with hydrogen activated over palladium-carbon to yield the debenzylated product

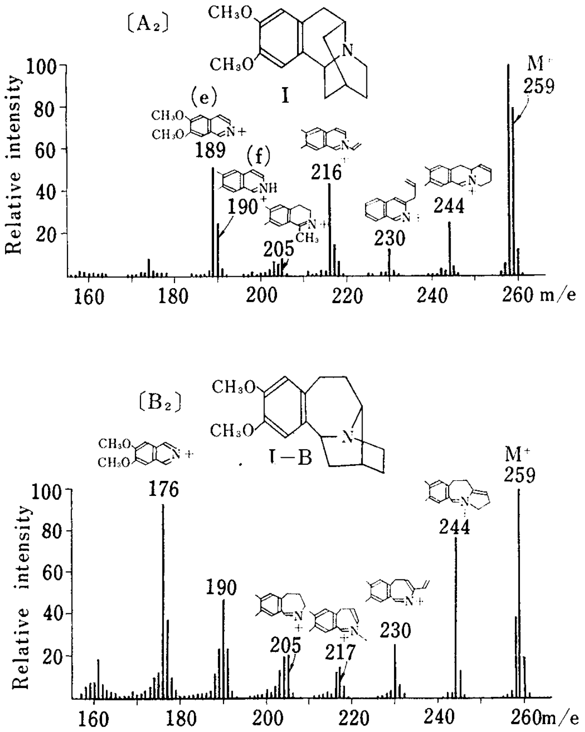

Fig. 1. Mass spectra of A_2 and B_2. CEC 21-103C (heated inlet system)

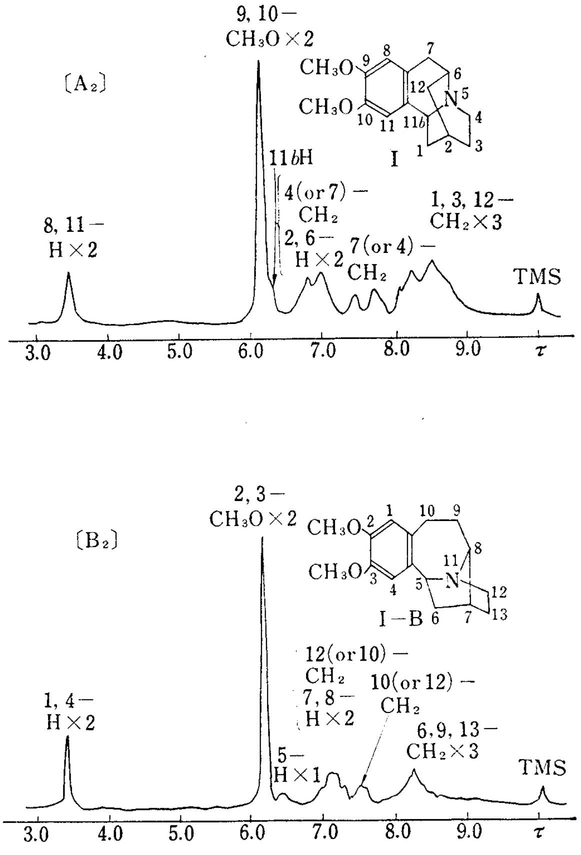

Fig. 2. Nuclear Magnetic Resonance Spectra of A_2 and B_2. ($CDCl_3$) (Varian A-60)

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6) R.N. Jones, C. Sandorfy: "The Application of Infrared and Raman Spectrometry to the Elucidation of Molecular Structure," Ed. by W. West, p. 436 (1961), Interscience Publishers, Inc., New York.

A_2 and B_2 as perchlorate salts respectively. When purified from hexane A_2 separated in colorless prisms of m.p. 106.5~108° and B_2 came in colorless plates of m.p. 96.5~99°. They and their derivatives analyzed correctly for I and its derivatives. Since there can exist no stereoisomers in I, they must be regarded as structural isomers.

Structure of A_2. Micro Rast-determination of A_2 gave a value of 267 (mean of 3 determinations), which is fairly close to the theoretical value of I, 259.35. The mass spectrum analysis, giving molecular ion peak at m/e 259 as shown in Fig. 1, also supported the Rast determination. Moreover the spectrum is similar to those of sarpagine derivative (c) and ajmaline derivative (d),⁷⁾ which have common skeleton in saturated ring as I.

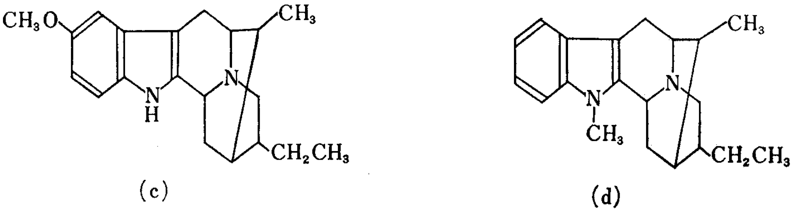

Chart 6.

Fragments at m/e 189 and 190 are understandable as dimethoxyisoquinoline ions (e) and (f) respectively, which supports A_2 as a dimethoxyisoquinoline derivative having a similar skeleton in the saturated ring as found in (c) and (d). Based on the abovesaid evidence and nuclear magnetic resonance data*² (Fig. 2) structure (I) was ascribed to A_2.

Structure of B_2. At first the author assumed the intermolecular condensation product (a) shown in Chart 7 as a possible structure of B_2, which became, however, untenable, when its molecular weight was found to be the same as A_2 by mass spectrum analysis. The second possibility (b) was also rejected, because no methyl signal was observed in its nuclear magnetic resonance spectrum. At present the seven-membered

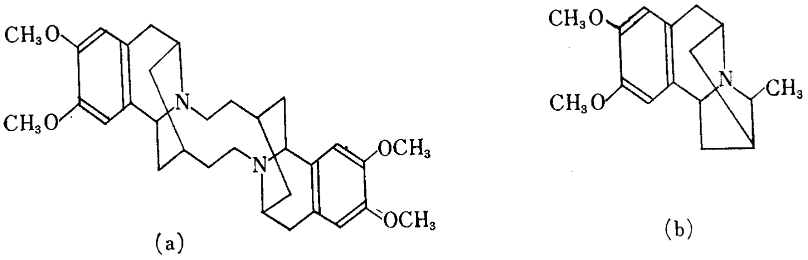

Chart 7.

structure (I-B) appears plausible on the following ground. There are recognized several differences in the fragmentation pattern in mass spetra of A_2 and B_2. Especially remarkable is the difference in m/e 176 peak, whose relative intensity in A_2 is only 2% while in B_2 it is as strong as 93% of the base peak as can been seen in Fig. 1. This may be construed as due to isoindole ion which may be formed through fission of the seven-membered B-ring followed by recyclization. The Chart 8 is presented to show the formation mechanism*³ of I-B based on an abnormal reaction ensued on the reductive dechlorination of XIX with lithium aluminum hydride.

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*² Although clear spectra could not be obtained because of too small quantities of the samples, these spectra agreed with the formula (I) and (I-B) as shown in Fig. 2.

*³ The author thanks Prof. Rinehart for this suggestion.

7) K. Biemann: J. Am. Chem. Soc., 83, 4801 (1961).

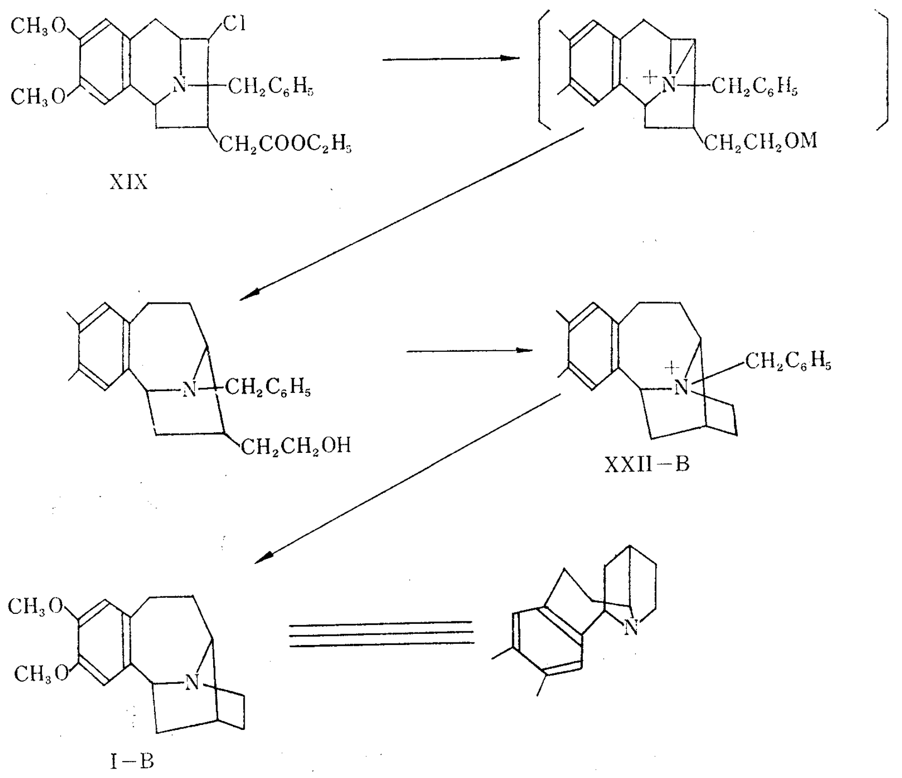

Chart 8.

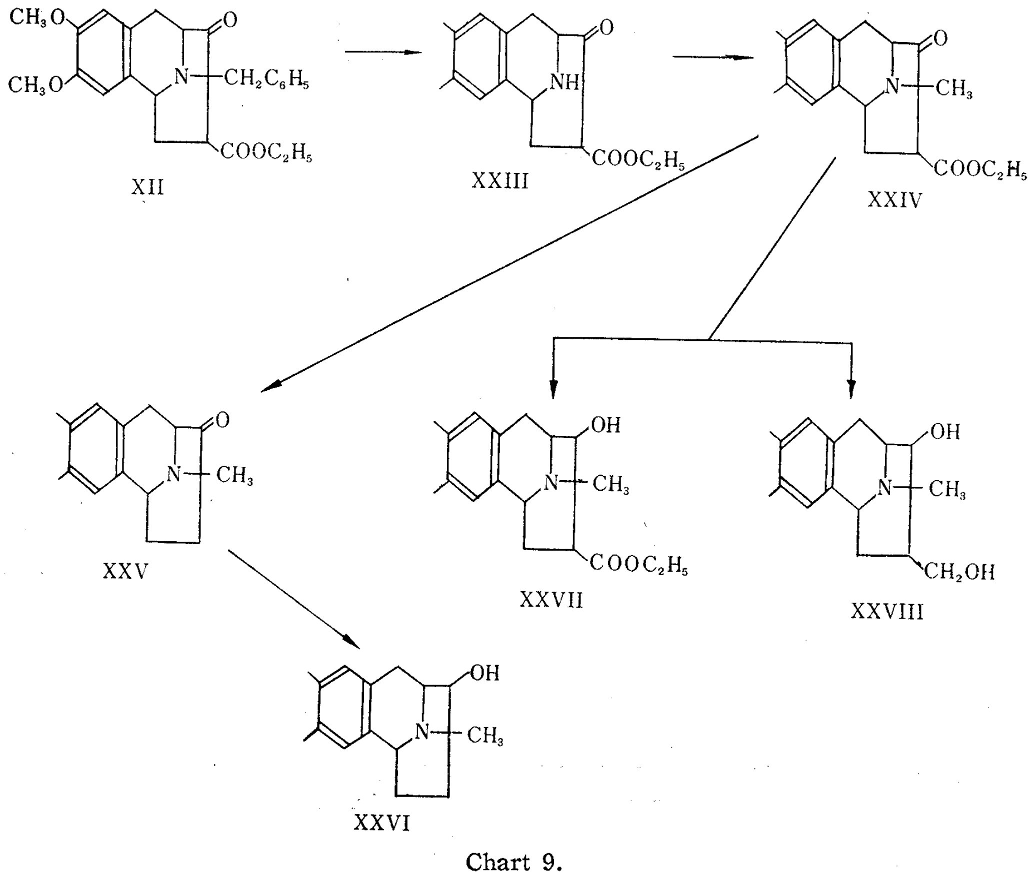

Chart 9.

From pharmacological view point it appeared of interest to synthesize several 5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene derivatives readily accessible from Ⅻ.

Thus, as shown in Chart 9, Ⅻ was reductively debenzylated to give XXⅢ, colorless plates of m.p. 152~153°, whose N-CH_3 derivative (XXIV) was prepared by the Eschweiler-Clarke's method.[8] Acid cleavage of the latter yielded the ketone (XXV), colorless grains of m.p. 114~115°, in a smooth reaction, which was reduced with sodium borohydride-methanol, yielding the corresponding alcohol (XXVI) as colorless pillars of m.p. 156~157°. Its benzoate was prepared.

When XXIV was treated with sodium borohydride-ethanol until ferric chloride color test became negative, there were produced colorless syrupy hydroxyester (XXVⅡ) and diol (XXVⅢ), colorless grains of m.p. 168~169.5°, nearly in the same amount, whose benzoyl derivatives were also prepared.

All of the above-mentioned compounds were obtained as a single entity and formation of stereoisomers was observed in none of the cases.

Experimental

3-(3,4-Dimethoxyphenyl)alanine Ethyl Ester (IV)——*dl*-3-(3,4-dimethoxyphenyl)alanine (Ⅲ) was prepared from 3,4-dimethoxybenzyl chloride by the acetamidomalonate method or from veratrum aldehyde *via* azlactone. Ⅲ was esterified to give the ethyl ester (Ⅳ) as a colorless oil, b.p_{20} 170~177°.
Hydrochloride : Colorless sandy crystals (from EtOH-Et_2O). m.p. 161~162°.[*4] *Anal.* Calcd. for $C_{13}H_{20}O_4NCl$: C, 53.89; H, 6.96; N, 4.83; Cl, 12.24. Found : C, 53.60; H, 6.83; N, 4.96; Cl, 12.26.

N-Benzyl-3-(3,4-dimethoxyphenyl)alanine Ethyl Ester (VI) and N-Benzyl-α-hydroxymethyl-3,4-dimethoxyphenethylamine (VII)——Ⅳ and benzaldehyde were condensed in the usual manner to produce the benzylidene derivative (V) in a quantitative yield as a faint yellow viscous oil [IR $\nu_{\max}^{\text{capil.}}$ cm^{-1} : 1730 (ester), 1640 (C=N)], which could not be obtained crystalline and was directly reduced. Thus, to a MeOH (600 ml.) solution of V (320 g.) was added $NaBH_4$ (21 g.) in small portions during 4 hr. with stirring at 0~5° and stirring was continued for additional 1 hr. at the same temperature. AcOH (50 ml.) was then added cautiously to the reaction mixture. MeOH was removed *in vacuo*, the resultant residue was made alkaline with $NaHCO_3$ and extracted with benzene. The benzene extract was washed, dried and evaporated to leave an oily product, which on distillation gave a faint yellow viscous oil of Ⅵ, b. $p_{0.01}$ 210~217°, (285 g., 89%). IR $\nu_{\max}^{\text{capil.}}$ cm^{-1} : 3300 (N-H), 1730 (ester).
Hydrochloride : Colorless prisms (from EtOH-Et_2O), m.p. 154~156°. *Anal.* Calcd. for $C_{20}H_{26}O_4NCl$: C, 63.23; H, 6.90; N, 3.69; Cl, 9.33. Found : C, 62.90; H, 6.90; N, 3.89; Cl, 9.40.

A by-product (Ⅶ) was obtained from the distillation residue of Ⅵ, and it was recrystallized from EtOH to form colorless silky needles, m.p. 114.5~115.5°. This compound was sparingly soluble in common organic solvents. Occasionaly, a small amount of white crystals of Ⅶ separated from the benzene extract of Ⅵ on standing. Yield of Ⅶ was about 5% based on Ⅲ. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3280 (N-H), 3100 broad (OH). *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found : C, 71.68; H, 7.77; N, 4.44.
Picrate : Oronge-yellow plates (from EtOH), m.p. 141~142°. *Anal.* Calcd. for $C_{24}H_{26}O_{10}N_4$: C, 54.34; H, 4.94; N, 10.56. Found : C, 54.24; H, 4.83; N, 10.65.

Ethyl N-Benzyl-N-(α-ethoxycarbonyl-3,4-dimethoxyphenethyl)succinamate (IX)——A mixture of Ⅵ (120 g.), succinic anhydride (36 g.) and benzene (150 ml.) was refluxed for 4 hr. After cooling, the condensation product (Ⅷ) was extracted thoroughly with Na_2CO_3 solution (Na_2CO_3(40 g.) in H_2O (700 ml.)), washed with benzene, filtered and the filtrate was made congo-red acid with HCl. A pasty mass thus separated was immediately extracted with AcOEt and the AcOEt solution was washed, dried and evaporated, leaving a clear yellow syrup of Ⅷ, which was not induced to solidify. The amido-acid (Ⅷ) was esterified by the usual method to yield a yellowish orange viscous syrup of Ⅸ (141 g., 85.5%), which gradually solidified on standing for several days in a refrigerator. For analysis a small portion of the crude amide was purified from iso-Pr_2O to form colorless plates, m.p. 68~69°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1730 (ester), 1660 (amide). *Anal.* Calcd. for $C_{26}H_{33}O_7N$: C, 66.22; H, 7.05; N, 2.97. Found : C, 65.95; H, 7.02; N, 3.24.

1-(2-Ethoxycarbonylethyl)-2-benzyl-3-ethoxycarbonyl-6,7-dimethoxy-3,4-dihydroisoquinolinium (X) Iodide——A mixture of the above-mentioned amide (Ⅸ) (133 g.) and $POCl_3$ (665 ml.) was gently refluxed for

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[*4] N. Sugimoto [Yakugaku Zasshi, **65**, 108 (1943)] reported that Ⅳ·HCl melted at 124~127° with decomposition.

[8] M.L. Moore : "The Leuckart Reaction," Org. Reactions, **5**, p. 323.

10 hr. From the dark reaction mixture excess of $POCl_3$ was removed *in vacuo*, and the tarry residue was cautiously decomposed with ice-water and repeatedly extracted with hot water (total about 3 L.). The combined aqueous solution was washed twice with benzene, filtered together with charcoal and the fluorescecent filtrate was evaporated to dryness *in vacuo*. Anhyd. EtOH (800 ml.) was then added to the residue and the whole was saturated with dry HCl gas with ice-cooling. After standing overnight, EtOH was evaporated to leave a dark reddish tarry residue, which was dissolved in ice-water and to this solution was added NaI solution (NaI (60 g.) in H_2O (300 ml.)). The separated syrup was thoroughly extracted with $CHCl_3$, washed once with satd. NaCl solution, dried and evaporated to leave a dark reddish residue, which was dissolved in warm anhyd. MeOH. After being treated with charcoal, anhyd. Et_2O was added to the filtrate until the solution became slightly turbid. On standing in a refrigerator overnight, a mixture of yellowish orange plates (a) and faint yellow prisms (b) separated out, which were collected and dried. Total yield of (a) and (b) was 89 g. (54.3%).

The iodide (a) and (b) could be separated manually but when each iodide was recrystallized from MeOH-Et_2O a mixture of (a) and (b) again was obtained. (a) : Yellowish orange plates (from MeOH-Et_2O), m.p. 155~156°(decomp.). (b) : Faint yellow prisms (from MeOH-Et_2O), m.p. 155~156°(decomp.). *Anal.* Calcd. for $C_{26}H_{32}O_6NI$: C, 53.71; H, 5.55; N, 2.41; I, 21.83. Found : (a); C, 54.03; H, 5.20; N, 2.58; I, 21.25. (b); C, 53.90; H, 5.54; N, 2.39; I, 21.88. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : (a); 253 (4.23), 317 (3.99). (b); 253 (4.22), 317 (3.98).

X·chloride : The mixture of the above iodide [mixture of (a) and (b)] (583 mg.), freshly prepared AgCl (from $AgNO_3$ (500 mg.)) and EtOH (25 ml.) was worked up as usual to form X-chloride (421 mg.) as pale yellow plates from MeOH-Et_2O, m.p. 160~161°(decomp.). *Anal.* Calcd. for $C_{26}H_{32}O_6NCl\cdot\frac{1}{2}H_2O$: C, 62.58; H, 6.67; N, 2.81; Cl, 7.11. Found : C, 62.70; H, 6.55; N, 2.95; Cl, 6.98. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : 254 (4.19), 310 (3.92).

Ethyl 2-Benzyl-3-ethoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinepropionate (XI)——To a suspension of X·iodide (a, b mixture) (54.6 g.) in anhyd. MeOH (400 ml.) was added $NaBH_4$ in small portions during 3 hr., with ice-cooling and stirring. Stirring was continued for additional 2 hr. with ice-cooling and the reaction mixture was allowed to stand overnight. The solvent was evaporated *in vacuo*, ice-water was added to the residue and the product was thoroughly extracted with Et_2O. After washing once with satd. NaCl solution, the Et_2O extract was shaken with 3.5% HCl (50 ml. × 8). The combined HCl solution was filtered and the filtrate was basified with solid K_2CO_3. The liberated base was extracted with Et_2O, washed, dried and evaporated to yield crude α-isomer (XI) as a clear yellow viscous oil (32.8 g.). Since this did not solidify, it was purified as hydrochloride. By recrystallization from EtOH-Et_2O, α-hydrochloride (XI) was obtained as colorless prisms, m.p. 169~171° (decomp.), in a yield of 30 g. or 65%. On further recrystallization, the melting point was raised to 172~173° (decomp.). *Anal.* Calcd. for $C_{26}H_{34}O_6NCl$: C, 63.47; H, 6.97; N, 2.85; Cl, 7.21. Found : C, 63.58; H, 6.71; N, 3.02; Cl, 7.23.

The foregoing ethereal mother solution was washed with H_2O, dried and evaporated to leave pale yellow crystalline residue of β-isomer (XI) (8.3 g.). This was recrystallized from benzene-hexane to form colorless prisms, m.p. 103~105°, which was raised to m.p. 104.5~105.5° on further purification. Yield was 5.6 g. (13%). *Anal.* Calcd. for $C_{26}H_{33}O_6N$: C, 68.55; H, 7.30; N, 3.08. Found : C, 68.72; H, 7.35; N, 3.37.

Hydrochloride : Colorless prisms (from EtOH), m.p. 147~148°. *Anal.* Calcd. for $C_{26}H_{34}O_6NCl$: C, 63.47; H, 6.97; N, 2.85; Cl, 7.21. Found : C, 63.49; H, 6.63; N, 2.61; Cl, 6.67.

Picrate : Yellow granular crystals (from EtOH), m.p. 122~123.5°. *Anal.* Calcd. for $C_{32}H_{36}O_{13}N_4$: C, 56.14; H, 5.30; N, 8.18. Found : C, 56.20; H, 5.27; N, 8.36.

Ethyl 8-Oxo-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-carboxylate (XII). i) Dieckmann Cyclization of α-Isomer (XI)——α-isomer (XI) (11.1 g.) was dissolved in dehyd. toluene (15 ml.) and the solution was added dropwise during 20 min. to a suspension of NaH (51.4% oil dispersion) (2.7 g.) in dehyd. toluene (15 ml.) at 125~130°. During this addition, a yellowish orange Na-salt of the cyclization product began to separate, generating H_2 gas, and the whole was gently refluxed for 1 hr. to complete the reaction. After cooling, the reaction mixture was decomposed cautiously by adding AcOH (5 ml.) in benzene (40 ml.), and then besified with satd. $NaHCO_3$ solution, extracted with benzene repeatedly. The benzene solution was washed, dried and evaporated to afford an orange viscous residue which was dissolved in hot EtOH (12 ml.) and allowed to stand overnight. The crude β-ketoester (XII) was separated as a colorless powder, which was collected and washed with a small amount of cold EtOH, yielding 6.8 g. (68%), m.p. 90~103°. It was insoluble in NaOH solution, but gave a reddish violet $FeCl_3$-test.

ii) β-Isomer (XI)——The Dieckmann cyclization was carried out with the β-isomer (11.1 g.) in the same manner as for α-isomer to yield crude β-ketoester (XII) as a colorless powder, m.p. 92~107°, 5.3 g., 53%. In this case the reaction appeared to start more slowly than with α-isomer. Both β-ketoesters prepared from α- and β-isomers (XI) showed a broad melting range but they were identified by the mixed melting point test and the IR spectra (Nujol).

iii) Mixture of α- and β-Isomers(XI)——Since α- and β-isomers gave one and the same Dieckmann product, the mixture was directly submitted to cyclization. Thus, a mixture ((105 g.) was treated with NaH

(51.4%, 25 g.) in the above manner to yield the β-ketoester (XII), 49.3 g. (52.2%), m.p. 89~103°, which was raised to 101~112° after repeated recrystallization from EtOH (colorless plates). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1650, 1610 (enol-form of β-ketoester). *Anal.* Calcd. for $C_{24}H_{27}O_5N$: C, 70.40; H, 6.65; N, 3.42. Found : C, 70.15; H, 6.68; N, 3.42.

Picrate : Yellow cubic crystals separated from Et_2O solution decomposed at 165~169°, but after repeated recrystallization from EtOH it formed yellow minute needles and melted at 137~141° with decomposition. *Anal.* Calcd. for $C_{30}H_{30}O_{12}N_4$: C, 56.42; H, 4.74; N, 8.77. Found : C, 56.36; H, 4.92; N, 8.86.

Ethyl 7-Ethoxycarbonyl-8-oxo-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocyclooöctene-7-acetate (XIII)——A mixture of β-ketoester (XII) (49.2 g.), NaH (51.4%, 6.2 g.) and dehyd. toluene (150 ml.) was heated with stirring for 1.5 hr. in an oil-bath kept at about 130°. To the resulting yellow syrupy mixture was added ethyl bromoacetate (25 g.) in dehyd. toluene (20 ml.) and the whole was gently refluxed for additional 8.5 hr. with stirring. After standing overnight, the reaction mixture was mixed with ice-water and extracted with benzene. The benzene extract was washed, dried and evaporated to leave a faint yellow viscous syrup, which was dissolved in anhyd. Et_2O and saturated with dry HCl gas with ice-cooling. The separated hydrochloride of XIII was collected and recrystallized from EtOH-Et_2O as colorless minute needles (39.6 g., 60%), m.p. 199~201° (decomp.), which was raised to 202~203° (decomp.) on further recrystallization. *Anal.* Calcd. for $C_{28}H_{34}O_7NCl$: C, 63.21; H, 6.44; N, 2.63, Cl, 6.66. Found : C, 63.09; H, 6.54; N, 2.64; Cl, 6.56.

The free base of XIII was recovered from the above HCl salt as a faint yellow hard syrup. It was converted to semi-soild on standing in a refrigerator, but was difficult to purify through recrystallization.

Semicarbazone : Colorless needles (from EtOH), m.p. 197.5~199° (decomp.). *Anal.* Calcd. for $C_{29}H_{36}O_7N_4$: C, 63.03; H, 6.57; N, 10.01. Found : C, 62.78; H, 6.47; N, 10.29.

Picrate : Yellow prisms (from EtOH), m.p. 181.5~182.5°. *Anal.* Calcd. for $C_{34}H_{36}O_{14}N_4$: C, 56.32; H, 5.00; N, 7.73. Found : C, 56.39; H, 5.17; N, 7.53.

Ethyl 8-Oxo-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocyclooöctene-7-acetate (XV)——A mixture of XIII·HCl (19.6 g.) and KOH solution (KOH 9 g. in EtOH (360 ml.) and H_2O (90 ml.)) was heated in a water-bath for 10 hr. under reflux. The solvent was then evaporated *in vacuo* to leave a yellow-orange syrup, which was dissolved in H_2O (100 ml.). To this solution conc. HCl (100 ml.) was slowly added and the whole was gradually heated in an oil-bath, evolution of CO_2 being observed. After cessation of the gas evolution (refluxed for 1 hr.), the reaction mixture was treated with charcoal and filtered while hot. On chilling the filtrate with ice-water, colorless precipitates of 8-Oxo-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocyclooöctene-7-acetic acid (XIV) hydrochloride monohydrate separated out, which were collected and washed with a small volume of cold H_2O. A small portion of XIV·HCl was recrystallized from 5% HCl to form colorless plates, m.p. 175~180° (decomp.). *Anal.* Calcd. for $C_{23}H_{26}O_5NCl \cdot H_2O$: C, 61.40; H, 6.27; N, 3.11; Cl, 7.88. Found : C, 61.56; H, 6.36; N, 3.27; Cl, 7.94.

The above-obtained XIV·HCl was dissolved in dehyd. EtOH (300 ml.) and esterified by the usual method to give a faint yellow glassy residue (10 g.) of γ-ketoester (XV), which solidified by trituration with Et_2O, and was purified from EtOH to yield colorless plates, m.p. 135~137° (6.2 g, 40%). On further recrystallization from EtOH, the melting point was raised to 138~140°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1735 (ester), 1705 (ketone). *Anal.* Calcd. for $C_{25}H_{29}O_5N$: C, 70.90; H, 6.90; N, 3.11; mol. wt., 423.52. Found : C, 70.77; H, 6.64; N, 3.30; mol. wt., 429 (Rast).

Picrate : Yellow prisms (from EtOH), m.p. 183~184° (decomp.). *Anal.* Calcd. for $C_{31}H_{32}O_{12}N_4$: C, 57.05; H, 4.94; N, 8.59. Found : C, 56.95; H, 5.09; N, 8.44.

Hydrochloride : Colorless prisms (from EtOH-Et_2O), m.p. 202.5~203.5° (decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_5NCl$: C, 65.28; H, 6.57; N, 3.05; Cl, 7.71. Found : C, 65.09; H, 6.10; N, 3.15; Cl, 7.89.

11-Benzyl-2,3-dimethoxy-5,6,9,10-tetrahydro-5,9-iminobenzocyclooöcten-8(7*H*)-one (XVI)——A mixture of β-ketoester (XII) (5.0 g.) and 17% HCl (100 ml.) was refluxed for 2.5 hr., evolution of CO_2 being observed. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in hot H_2O, treated with carbon and filtered while hot. On ice-chilling the filtrate there separated colorless prisms of the ketone (XVI) hydrochloride (probably as its hydrate), which was collected (about 4.5 g.) and again dissolved in H_2O, strongly basified with 10% NaOH solution, and the base liberated was collected in benzene. The benzene solution was washed, dried and evaporated to leave ketone (3.5 g. 85%) as a colorless caramel-like residue, which was treated with a small volume of iso-Pr_2O to form a crystalline solid, m.p. 84~87°. On recrystallization from benzene-hexane, it formed colorless prisms, m.p. 85~87.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1710 (ketone). *Anal.* Calcd. for $C_{21}H_{23}O_3N$: C, 74.75; H, 6.87; N, 4.15. Found : C, 75.29; H, 7.04, N, 4.07.

The free base of ketone seemed to be considerably unstable and slowly resinified on standing.

Oxime : Colorless sandy crystals (from EtOH), m.p. 180.5~182°. *Anal.* Calcd. for $C_{21}H_{24}O_3N_2$: C, 71.57; H, 6.86; N, 7.95. Found : C, 71.27; H, 7.03; N, 8.25.

Hydrochloride dihydrate : Colorless prisms (from 5% HCl), m.p. ca. 80~120° (decomp.), dried in a desiccator over P_2O_5 at 60° for 10 hr. under reduced pressure. *Anal.* Calcd. for $C_{21}H_{24}O_3NCl \cdot 2H_2O$: C, 61.53; H, 6.89; N, 3.42; Cl, 8.65. Found : C, 61.87; H, 6.50; N, 3.44; Cl, 8.96. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3200~3300 (OH), no C=O.

Hydrochloride : Colorless crystalline powder, m.p. 199.5~200.5°(decomp.), dried in a desiccator over P_2O_5 at 80~85° for 90 hr. under reduced pressure. IR ν_{max}^{Nujol} cm^{-1} : 2300~2350 ($\geqslant\underset{+}{N}$-H), 1720 (ketone), no OH. *Anal.* Calcd. for $C_{21}H_{24}O_3NCl$: C, 67.46; H, 6.47; N, 3.75; Cl, 9.48. Found : C, 67.92; H, 6.10; N, 3.54; Cl, 9.49.

Ethyl 8-Oxo-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-acetate (XVII). i) **Pyrrolidine Enamine of Ketone (XVI)**——A mixture of the above-obtained ketone (XVI) (5.0 g.), freshly distilled pyrrolidine (4.0 g.) and dehyd. benzene (30 ml.) was refluxed for 6.5 hr. with a Cope's constant water separator. Excess of pyrrolidine and benzene were removed, leaving a yellow-orange caramel-like residue (5.7 g.), which was considered to be an expected enamine containing a small amount of the starting ketone based on its IR spectrum ($CHCl_3$) (1640 cm^{-1} enamine >N-C=C-; 1710 cm^{-1} C=O v.w.). A small portion of the above crude enamine was dissolved in dehyd. benzene, to which dehyd. hexane was added and the whole was allowed to stand in a refrigerator. A small amount of white crystals separated out, m.p. 114~120°, whose IR spectrum was almost identical with that of the above crude enamine. This could not be purified by further recrystallization, because it was easily hydrolyzed even by moisture and was directly used for the next reaction.

ii) **Condensation of Enamine with Ethyl Bromoacetate**——A mixture of the foregoing crude enamine (5.7 g.), ethyl bromoacetate (3.2 g.) and dehyd. dioxane*[5] (30 ml.) was heated under reflux for 24 hr. After cooling, H_2O (10 ml.) was added to the reaction mixture and the whole was allowed to stand overnight at room temperature in order to complete the decomposition of the reacted enamine. The resultant reaction mixture was concentrated *in vacuo*, leaving a orange-brown viscous syrup, which was made alkaline with satd. $NaHCO_3$ solution and repeatedly extracted with benzene. The benzene extract was washed, dried and evaporated to leave a brownish orange syrupy residue, which was redissolved in dehyd. benzene and purified by filtration through an Al_2O_3-column. The syrupy product was dissolved in a mixture of benzene and Et_2O and saturated with dry HCl gas under ice-cooling to give an orange-yellow powder of crude hydrochloride (XV) (6.3 g.). Since recrystallization of this hydrochloride was difficult, it was directly debenzylated by catalytic hydrogenation for purification.

iii) **Debenzylation of Crude Product**——A solution of the above-obtained hydrochloride (3.6 g.) in EtOH (100 ml.) was reduced over 10% Pd-C catalyst (4.5 g.) at room temperature, absorbing 440 ml. of H_2 in about 8 hr. The catalyst was removed by filtration and the filtrate was evaporated, leaving a faint yellow crystalline residue, which was purified by recrystallization from benzene-hexane to give XV as a colorless crystalline powder, m.p. 140~146°, 2.0 g., 45% from XVI. On further recrystallization from benzene-hexane, colorless prisms, m.p. 147~148°, were obtained. IR ν_{max}^{Nujol} cm^{-1} : 3280 (NH), 1735 (ester), 1705 (ketone). *Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.85; H, 6.95; N, 4.20. Found : C, 64.88; H, 6.63; N, 4.23. Picrate : Faint yellow minute needles (from EtOH), m.p. 216.5~217°(decomp.). *Anal.* Calcd. for $C_{24}H_{26}O_{12}N_4$: C, 51.25; H, 4.66; N, 9.96. Found : C, 50.62; H, 4.71; N, 9.57.

Ethyl 8-Oxo-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-acetate (XV) Benzylation of XVII——A mixture of the above-obtained (XVII) (0.40 g.), benzylchloride (0.18 g.), dehyd. K_2CO_3 (0.20 g.) and dehyd. toluene (10 ml.) was refluxed for 25 hr. After cooling, the reaction mixture was mixed with ice-water and extracted with benzene. The benzene extract was washed successively with satd. $NaHCO_3$ solution and satd. NaCl solution, dried and evaporated to leave an orange-yellow syrup (0.51 g.). A part of this surup was solidified by trituration with Et_2O. This solid was proved to be the starting material (XVII) (0.14 g., 35%) by the mixed melting point test and IR spectrum. The Et_2O filtrate was purified through an Al_2O_3-column, and the effluent was evaporated to give a yellow syrup (0.29 g.), which soon solidified. On further recrystallization from EtOH, the above product gave colorless prisms, m.p. 134~136°.

This product was identical with the specimen of XV obtained by the above ketone-fission method based on the mixed melting point test and IR spectrum.

Ethyl 8-Hydroxy-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-acetate (XVIII)——To a suspension of XV (4.2 g.) in EtOH (60 ml.) was added $NaBH_4$ (0.12 g.) in small portions during 30 min. with ice-cooling and stirring, and stirring was continued for additional 30 min. at room temperature and further for 1.5 hr. on a water-bath kept at 45~50°. On working up as usual, a colorless caramel-like product (4.1 g.) was obtained, which was dissolved in anhyd. Et_2O and saturated with dry HCl gas with ice-cooling. The separated hydrochloride of XVIII was collected and recrystallized from EtOH-Et_2O to form colorless plates (3.65 g., 79%), m.p. 217~219°(decomp.). *Anal.* Calcd. for $C_{25}H_{32}O_5NCl$: C, 65.00; H, 6.98; N, 3.03; Cl, 7.67. Found : C, 64.90; H, 7.19; N, 2.98; Cl, 7.34.

The free base of XVIII was obtained from the above hydrochloride as a colorless syrup which could not be crystallized.

Ethyl 8-Chloro-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-acetate (XIX). i) **Chlorination with $SOCl_2$**——To a solution of XVIII·HCl (1.54 g.) in dehyd. $CHCl_3$ (20 ml.) containing

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*[5] When MeOH was used as the reaction solvent instead of dioxane, the objective product could not be obtained, recovering the starting ketone (XVI).

3 drops of pure pyridine was added $SOCl_2$ (1.6 ml.), and the whole was allowed to stand overnight at room temperature. The reaction mixture was then refluxed for 4 hr. and the excess of $SOCl_2$ and $CHCl_3$ was removed to leave a syrupy orange residue, to which ice-cold $NaHCO_3$ solution was added and the product was thoroughly extracted with benzene. The benzene solution was washed, dried and evaporated to leave a yellow-orange syrup, which was dissolved in boiling hexane. Charcoal was added to the above solution and filtered off together with a small amount of undissolved substance while hot. After standing in a refrigerator, chloride (XIX) (1.13 g. 76.5%) separated out as colorless prisms, m.p. 97~100°, which was raised to m.p. 102~103° on further purification. *Anal.* Calcd. for $C_{25}H_{30}O_4NCl$: C, 67.63; H, 6.81; N, 3.16; Cl, 7.99. Found : C, 68.05; N, 6.75; N, 3.31; Cl, 8.46.

ii) Treatment with Tosyl Chloride-Pyridine——To a solution of the free base of XVIII (244 mg.), liberated as a colorless caramel from its hydrochloride by treatment with K_2CO_3, in dry pyridine (0.15 ml.) pure tosyl chloride (132 mg.) was added with ice-cooling, and the whole was allowed to stand overnight at room temperature. The reaction mixture was warmed on a water-bath at 60~65° for 4 hr. and evaporated *in vacuo*. The residue was mixed with ice-cold $NaHCO_3$ solution and extracted with benzene repeatedly. The benzene solution was worked up as in above (i) to yield colorless prisms (0.10 g., 40%), m.p. 100~102°. This product was identical with the specimen obtained by the method (i) based on the mixed melting point test and IR spectrum.

iii) Treatment with Mesyl Chloride-Pyridine——Chlorination of the above (XVIII) (234 mg.) with mesyl chloride (90 mg.) and pyridine (0.5 ml.) gave the same chloride (XIX) (120 mg., 50%) as colorless prisms, m.p. 97.5~100°.

Reduction of Ethyl 8-Chloro-11-benzyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-acetate (XIX) with Lithium Aluminum Hydride in Tetrahydrofuran——To a suspension of $LiAlH_4$ (0.83 g.) in anhyd. THF (25 ml.) was added gradually a solution of the chloride (XIX) (1.13 g.) in the same solvent (25 ml.) with stirring at room temperature, then stirring was continued under reflux for 7 hr. After cooling, the reaction mixture was cautiously decomposed with a small volume of H_2O, then the inorganic material was filtered off. The filtered cake was treated with 10% NaOH solution and repeatedly extracted with Et_2O. The filtrate and the extract were combined and dried over K_2CO_3. After removal of the solvent, the residue was dissolved in 5% HCl solution, washed once with benzene and filtered. The filtrate was basified with 10% NaOH solution and the product was taken up in benzene. The benzene layer was washed, dried and evaporated to leave colorless caramel-like residue, 0.76 g., which was negative to the Beilstein's halogen test. Since all attempts to crystallize the above product were unsuccessful, this was used directly in the next step.

Reaction of the Lithium Aluminum Hydride-reduction Product with Tosyl Chloride-Pyridine——To a solution of the above product (0.76 g.) in dry pyridine (3.0 ml.) was added tosyl chloride (0.51 g.) and the whole was allowed to stand in a refrigerator for 2.5 days. After removal of pyridine *in vacuo*, the residue was washed with Et_2O, and extracted with H_2O. To the aqueous solution was added $NaClO_4$ solution and the precipitates were collected and recrystallized from EtOH to give B_1 (XXII-B)·perchlorate (0.09 g.) as colorless minute needles, m.p. 238~239° (decomp.). On the other hand, the residue insoluble in H_2O was dissolved in benzene and then heated for 4 hr. under reflux to complete cyclization. The residue from the benzene solution was repeatedly extracted with warm H_2O and the aqueous solution was worked up as above for B_1 (XXII-B)·perchlorate to yield A_1 (XXII)·perchlorate (0.20 g.) as colorless prisms, m.p. 210~211°. Finally, the residue insoluble in warm H_2O was redissolved in benzene and passed through an alumina column to give the ether compound (XXI) as colorless syrup (0.25 g.).

A_1 (XXII)·perchlorate : Colorless prisms (from EtOH), m.p. 210~211°. *Anal.* Calcd. for $C_{23}H_{28}O_6NCl$: C, 61.40; H, 6.27; N, 3.11; Cl, 7.88. Found : C, 61.29; H, 6.27; N, 3.16; Cl, 7.86.

B_1 (XXII-B)·perchlorate : Colorless minute needles (from EtOH), m.p. 238~239° (decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_6NCl$: C, 61.40; H, 6.27; N, 3.11; Cl, 7.88. Found : C, 61.37; H, 6.59; N, 3.16; Cl, 7.92.

Ether[*6] compound (XXI) : Colorless syrup. IR $\nu_{\max}^{\text{capil.}}$ cm^{-1} : 1090, 920 (5-membered -O-).

$HClO_4$ salt : Colorless prisms (from EtOH-Et_2O), m.p. 230~231° (decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_7NCl$: C, 59.29; H, 6.06; N, 3.01; Cl, 7.61. Found : C, 59.04; H, 5.96; N, 2.93; Cl, 7.75.

Hydrochloride : Colorless prisms (from EtOH-Et_2O), m.p. 223~224° (decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_3NCl \cdot 1/2H_2O$: C, 67.22; N, 7.11; N, 3.41; Cl, 8.63. Found : C, 67.15; H, 7.06; N, 3.35; Cl, 8.25.

9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-2,6-methano-11*bH*-benzo[*a*]quinolizine (I): (A_2). Debenzylation of A_1 (XXII)·perchlorate——A_1 (XXII)·perchlorate (170 mg.) in 95% EtOH (35 ml.) was reduced over 10% Pd-C catalyst (0.10 g.), absorbing 11.5 ml. (1.35 mol. of theo. amt.) of H_2 at 30~32° in 5 min. After being

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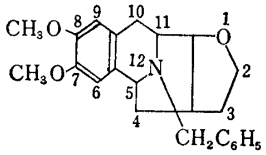
[*6] 

12-Benzyl-7,8-dimethoxy-2,3,3*a*,4,5,10,11,11*a*-octahydro-5,11-iminobenzo[5,6]-cycloöcta[*b*]furan was proposed to this compound.

shaken for 30 min., the catalyst was filtered off and washed with hot EtOH. The combined EtOH solution was evaporated to leave a colorless semi-solid residue (135 mg.), which was dissolved in H_2O and made alkaline with K_2CO_3. The liberated base was taken up in Et_2O and the Et_2O solution was washed with a small volume of satd. NaCl solution, dried over K_2CO_3 and evaporated to leave I (82 mg., 84%) in a crystalline form, m.p. 102～104°. This was readily soluble in most solvents. The product was recrystallized from a small volume of hexane to form colorless prisms, m.p. 106.5～108°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: N, 5.40. Found : N, 5.47.

a) m. p. 177.2°

Sample (mg.)	Camphor[a] (mg.)	mixed. m.p. (°C)	Δt (°C)	mol. wt.	
0.384	3.902	162.3	14.9	264	
0.276	1.434	147.7	29.5	261	
0.200	4.274	170.4	6.8	275	mean : 267

Molecular weight (micro Rast method). Calcd. mol. wt. of I : 259.35. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : 284 (3.59), 288 (3.59). UV $\lambda_{\min}^{\mathrm{EtOH}}$ mμ (log ε) : 253 (2.34) [286 (3.59)].

Perchlorate : Colorless prisms (from H_2O), m.p. 190～191.5° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_6NCl$: C, 53.49; H, 6.16; N, 3.89; Cl, 9.85. Found : C, 53.55; H, 6.07; N, 3.98; Cl, 9.95.

Picrate : Yellow prisms (from EtOH), m.p. 167～169° (decomp.). *Anal.* Calcd. for $C_{22}H_{24}O_9N_4$: C, 54.10; H, 4.95; N, 11.47. Found : C, 54.19; H, 4.98; N, 11.43.

(I-B) : (B_2).[7] **Debenzylation of B_1 (XXII-B)・perchlorate**——A suspension of the above-obtained B_1 (XXII-B)・perchlorate (190 mg.) in 95% EtOH (40 ml.) was reduced over 10% Pd-C catalyst (0.15 g.) at room temperature until a clear solution was obtained (about 1.5 days). On working up as above for I, a colorless crystalline solid (135 mg., m.p. 232～235° decomp.), was obtained, which was recrystallized from EtOH to give I-B・$HClO_4$ as colorless grains, m.p. 236～238° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_6NCl$: C, 53.49; H, 6.16; N, 3.89; Cl, 9.85. Found : C, 53.95; H, 5.82; N, 3.80; Cl, 9.93.

The base of I-B was recovered from the above $HClO_4$ salt by the usual method and purified by Al_2O_3-chromatography followed by recrystallization from hexane to form colorless plates, m.p. 96.5～99°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: N, 5.40. Found : N, 5.69.

Ethyl 8-Oxo-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocyclooöctene-7-carboxylate (XXIII)——A solution of the β-ketoester (XII) (6.8 g.) in EtOH (68 ml.) was reduced over 10% Pd-C catalyst (3.4 g.), absorbing 410 ml. (1.1 mol. of the theo. amt.) of H_2 at room temperature in about 5 hr. On working up as usual, there was obtained a colorless syrup (4.5 g.) which was purified from benzene-hexane to form colorless plates, 4.1 g., 77.3%, m.p. 148～150°. This product also gave a reddish purple coloration with $FeCl_3$. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1} : 3230 (NH), 1655, 1605 (enol-form of β-ketoester). On further recrystallization from benzenehexane, the melting point was raised to 152～153°. *Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 63.94; H, 6.63; N, 4.39; mol. wt., 319.36. Found : C, 63.75; H, 6.61; N, 4.22; mol. wt., 311 (Rast). Picrate : Yellow orange minute needles (from EtOH), m.p. 212.5～213° (decomp.). *Anal.* Calcd. for $C_{23}H_{24}O_{12}N_4$: C, 50.37; H, 4.41; N, 10.22. Found : C, 50.00; H, 4.72; N, 10.06.

Ethyl 8-Oxo-11-methyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocyclooöctene-7-carboxylate (XXIV)——A mixture of the foregoing (XXIII) (1.0 g.), 80% formic acid (3.0 ml.), and 37% HCHO solution (0.36 g.) was warmed at 80～85° for 30 min., during which time the crystals went into solution and evolution of gas was observed. The temperature was then raised to 110～115° and maintained there for 2 hr. After cooling, the excess of formic acid and HCHO solution were evaporated *in vacuo* and the residue was dissolved in H_2O, basified with $NaHCO_3$ and extracted with benzene. The benzene extract was washed, dried and evaporated to leave a viscous syrupy product, which was triturated with Et_2O to form a reddish orange solid. When purified from a small amount of EtOH this formed colorless prisms, 0.83 g. (80%), m.p. 130～132°. This product also gave reddish purple color test to $FeCl_3$. On further purification, the melting point was raised to 133～134.5°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1} : 1660, 1610 (enol-form of β-ketoester). *Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.85; H, 6.95; N, 4.20. Found : C, 64.79; H, 6.64; N, 4.43.

11-Methyl-2,3-dimethoxy-5,6,9,10-tetrahydro-5,9-iminobenzocycelooöcten-8(*7H*)-one (XXV)——A mixture of XXIV (0.91 g.) and 17% HCl (18 ml.) was refluxed for 1 hr. until the evolution of CO_2 had ceased. The

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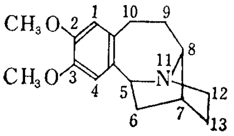
[7] 

The by-product (I-B) could be expressed as 2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,8-imino-7,11-ethanobenzocyclooöctene.

reaction mixture was worked up in the usual manner to yield a viscous syrup, which solidified on treatment with iso-Pr_2O-hexane as colorless granular crystals, 0.60 g., 83.3% m.p. 113～115°. $FeCl_3$ test was negative. IR ν_{max}^{Nujol} cm^{-1} : 1720 (ketone). For analysis a small portion of the above product was recrystallized from iso-Pr_2O to form colorless granular crystals, m.p. 114～115°. *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found : C, 68.65; H, 7.30; N, 5.41. Oxime : Colorless granular crystals (from H_2O-EtOH), m.p. 187.5～189° (decomp.). *Anal.* Calcd. for $C_{15}H_{20}O_3N_2$: N, 10.14. Found : N, 10.14. IR ν_{max}^{Nujol} cm^{-1} : 1645 ($\rangle$C=N-).

11-Methyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöcten-8-ol (XXVI)——A MeOH (10 ml.) solution of the ketone (XXV) (0.56 g.) was reduced with $NaBH_4$ (0.09 g.) and worked up as usual to yield a colorless caramel-like residue (0.52 g.), which was dissolved in dry Et_2O and saturated with dry HCl gas with ice-cooling. The hydrochloride of XXVI separated was collected and recrystallized from EtOH to form colorless minute needles, 0.48 g. (70%), m.p. 268～269° (decomp.). No trace of isomer was found in the alcoholic mother liquor. On further recrystallization from EtOH, this formed colorless needles, m.p. 272° (decomp.). *Anal.* Calcd. for $C_{15}H_{22}O_3NCl$: C, 60.09; H, 7.40; N, 4.64; Cl, 11.83. Found : C, 59.83; H, 7.44; N, 4.65; Cl, 11.46.

From the above hydrochloride (0.33 g.), the base of XXVI (0.24 g., m.p. 151～153°) was obtained by the usual method. On further purification from Et_2O, this formed colorless pillars, m.p. 156～157°. *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found : C, 68.07; H, 7.93; N, 5.38.
Picrate : Yellow prisms (from EtOH). m.p. 230～231° (decomp.). *Anal.* Calcd. for $C_{21}H_{24}O_{10}N_4 \cdot H_2O$: C, 49.41; H, 5.13; N, 10.98. Found : C, 49.53; H, 4.97; N, 11.25.
Benzoate (XXVI) : Benzoylation of XXVI (0.15 g.) with PhCOCl (0.1 g.) and pyridine (1 ml.) by the usual method afforded a yellow syrup (0.16 g.) which was converted to the hydrochloride and then purified from EtOH-Et_2O to form colorless minute plates, m.p. 232～233°. *Anal.* Calcd. for $C_{22}H_{26}O_4NCl \cdot \frac{1}{2}H_2O$: C, 63.99; H, 6.59; N, 3.39. Found : C, 63.96; H, 6.34; N, 3.62.

Ethyl 8-Hydroxy-11-methyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-carboxylate (XXVII) and 8-Hydroxy-11-methyl-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5,9-iminobenzocycloöctene-7-methanol (XXVIII)——To a solution of XXIV (0.73 g.) in EtOH (30 ml.) was added $NaBH_4$ (50 mg.) with stirring and stirring was continued for 1 hr. at room temperature and for 4 hr. at 60～70°. Since $FeCl_3$ test was still positive, further $NaBH_4$ (40 mg.) was added and stirring was continued at 60～70° until $FeCl_3$ coloration became nagative (about 2 hr.). After removing the solvent, the resultant residue was mixed with ice-water and thoroughly extracted with benzene. The aqueous mother liquor was repeatedly extracted with $CHCl_3$. The benzene and $CHCl_3$ extracts were separately worked up as usual. From the benzene extract, colorless caramel-like hydroxy ester (XXVII) (0.25 g.) was obtained, which was negative to $FeCl_3$ color test. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3450 (OH), 1730 (ester).
Picrate : Yellow minute plates (from EtOH-Et_2O), m.p. 202～204° (decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_{12}N_4$: C, 51.06; H, 5.00. Found : C, 51.34; H, 5.29.
Benzoate (XXVII) : Benzoylation of XXVII was carried out by the usual method and the resultant syrupy benzoate was converted to hydrochloride, colorless granular crystals (from EtOH-Et_2O), m.p. 241～243° (decomp.). *Anal.* Calcd. for $C_{25}H_{30}O_6NCl \cdot \frac{1}{2}H_2O$: C, 61.91; H, 6.44; N, 2.89; Cl, 7.31. Found : C, 61.87; H, 6.19; N, 2.84; Cl, 7.49.

On the other hand, from the $CHCl_3$ extract there was obtained a colorless syrup of XXVIII (0.26 g.) which solidified on treatment with benzene-hexane. On recrystallization from benzene it formed colorless granules (0.15 g.), m.p. 168～169.5°. The product was negative to $FeCl_3$ color test. IR ν_{max}^{Nujol} cm^{-1} : 3360, 2680. no $\rangle$C=O. *Anal.* Calcd. for $C_{16}H_{23}O_4N$: C, 65.61; H, 8.00; N, 4.77. Found : C, 65.51; H, 7.88; N, 4.82.
Dibenzoate hydrochloride XXVIII : Prepared by the same method for above XXVII, colorless prisms (from EtOH-Et_2O), m.p. 222～224° (decomp.). *Anal.* Calcd. for $C_{30}H_{32}O_6NCl$: C, 66.97; H, 6.00; N, 2.60; Cl, 6.59. Found : C, 66.69; H, 5.67; N, 2.77; Cl, 6.64.

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Summary

A synthesis of 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-2,6-methano-11b*H*-benzo[*a*]-

quinolizine having a new ring system was described. Thus, *dl*-N-benzyl-3-(3,4-dimethoxyphenyl)alanine ester (Ⅷ) was condensed with succinic anhydride followed by esterification to give amido-ester (Ⅸ), which on being cyclized with phosphoryl chloride under reflux furnished the corresponding dihydroisoquinoline derivative (X) isolated as iodide. When the latter was reduced with sodium borohydride-methanol, there were obtained α- and β-isomers of tetrahydroisoquinoline derivative (Ⅺ) ca. in a ratio of 5:1. On being cyclized with sodium hydride-toluene they gave one and the same cyclic β-ketoester (Ⅻ), which was condensed with ethyl bromoacetate followed by ketone fission to yield γ-ketoester (XV). An alternative route to XV was also discribed. XV was then reduced with sodium borohydride and the resultant alcohol (XVⅢ) was chlorinated to give the chloride (XIX), which was reduced with lithium aluminum hydride-tetrahydrofuran. The reduction product was directly tosylated and worked up properly furnishing the cyclized product, which was characterized as perchlorate. On being reduced catalytically the latter furnished the ultimate product (I). A smaller quantity of by-product was also obtained in the final cyclization step, to which structure (I-B) was postulated.

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