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158. Naoto Yoneda : Synthesis of 12-Methyl-1,2,3,4,6,7,12,12*b*-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine.*1

(*Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.**2)

This paper is concerned with the synthesis of the title compound (I), which represents the fundamental skeleton of sarpagine type of alkaloid.

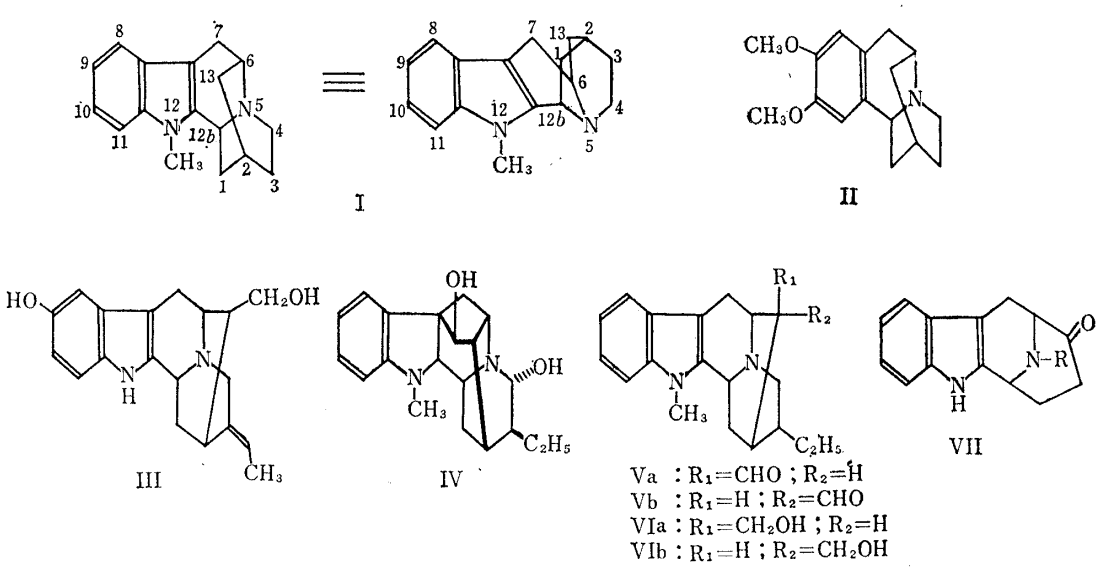

Chart 1.

Sarpagine (Ⅲ)[1,2] and its congeners are indole derivatives having a characteristic pentacyclic ring-system containing quinuclidine ring. They belong to Rauwolfia alkaloid and are considered to form precursors of ajmaline (Ⅳ)[1~3] and its congeners from biogenetic view-point.[3]

Recently Bartlett, *et al.*[4] have succeeded to convert deoxyajmalal-A (Va)[2] of sarpagine-type into deoxyajmaline having ajmaline skeleton by reducing the former in acidic solution, making feasible the synthesis of ajmaline type of base *via* an appropriate sarpagine type compound.

In the author's knowledge synthesis of any one of the natural sarpagine and ajmaline alkaloids, including their skeletal compound such as I hitherto has not been described in the literature. The synthesis of Ⅶ by Hobson, *et al.*[5] may be considered as the first paper describing a synthetical approach to these bases. The author's synthesis of Ⅱ, reported[6] in the first paper of this series, was the preliminary to the present synthesis.

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*1 For preliminary communications, see This Bulletin, **13**, 622 (1965).

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

1) J. E. Saxton : "The Alkaloids," Ed. by Manske, Ⅶ, p. 103 (1960). Academic Press, Inc., New York.
2) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, E. Wenkert : J. Am. Chem. Soc., **84**, 622 (1962).
3) R. B. Woodward : Angew. Chem., **68**, 13 (1956).
4) M. F. Bartlett, B. F. Lambert, H. M. Werblood, W. I. Taylor : J. Am. Chem. Soc., **85**, 475 (1963).
5) J. D. Hobson, J. Raines, R. J. Whiteoak : J. Chem. Soc., **1963**, 3495.
6) N. Yoneda : This Bulletin, **12**, 1478 (1964).

The compound (I) may form a key intermediate for the synthesis of sarpagine and of certain degradation products of ajmaline, *e.g.*, deoxyajmalal-A and -B (Va, b),[2,3] and deoxyajmalol-A and -B (Ⅵa, b).[2] Hence its synthesis was attempted.

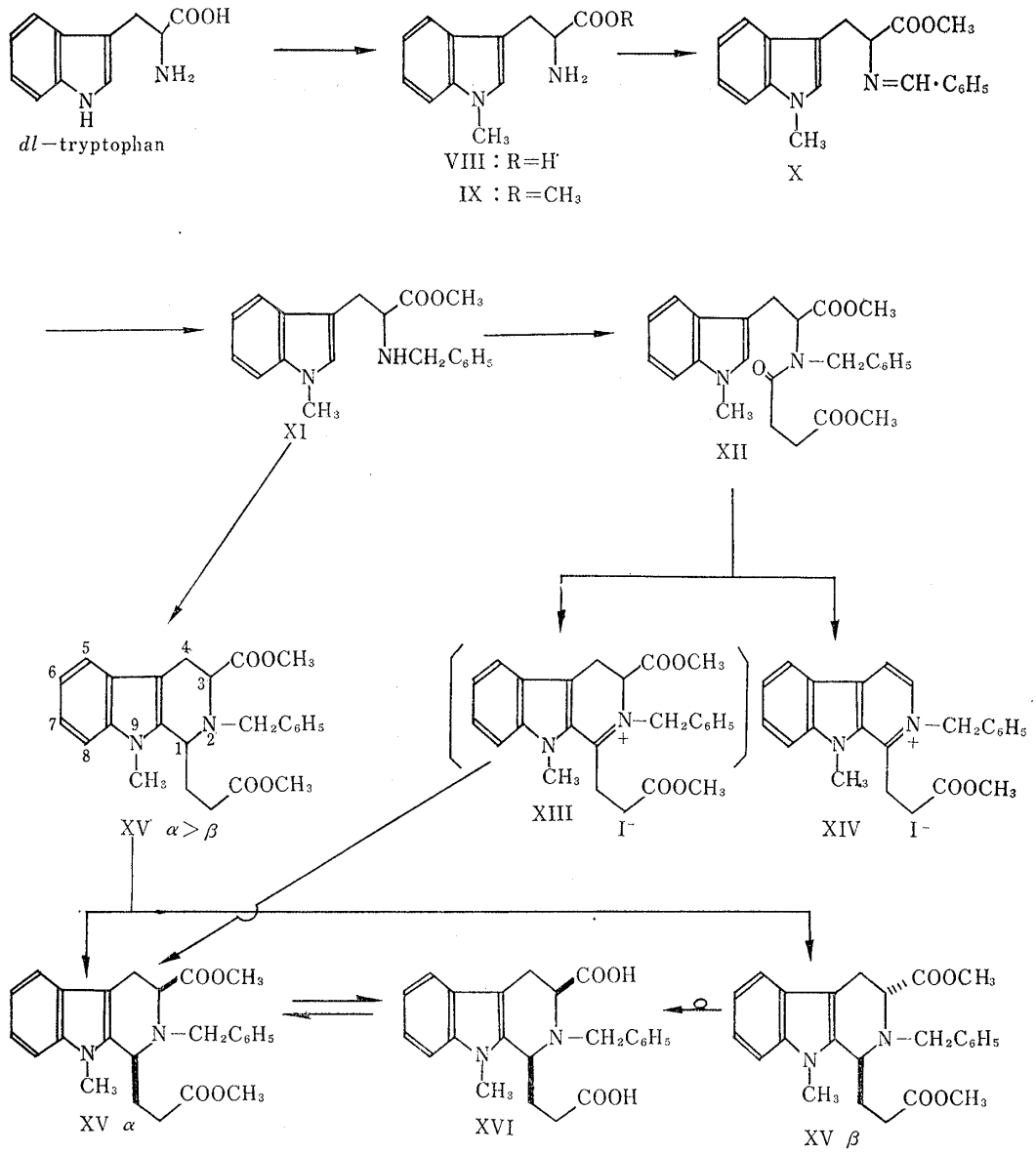


Chart 2.

dl-Tryptophan was N(a)-methylated and esterified according to Yamada's method.[7] The compound (Ⅸ) thus obtained was condensed with benzaldehyde and the resultant N(b)-benzylidene derivative (X) was reduced with sodium borohydride in methanol to yield N(b)-benzyl derivative (Ⅺ). The latter was condensed with succinic anhydride and the product esterified to give amidediester (Ⅻ), which was submitted to Bischler-Napieralski type cyclization. The result was not satisfactory under a variety of working conditions so far tried. For instance, from the reaction product of Ⅻ with an excess of boiling phosphoryl chloride, there was isolated a small amount of crystalline iodide (yield ca. 5%), which was found to be XIV by analysis, infrared and ultraviolet[8] data. Uncrystallizable portion was recovered from the mother liquor of the

7) S. Yamada, T. Shioiri, T. Itaya, T. Hara, R. Matsueda : This Bulletin, **13**, 88 (1965).
8) I. D. Spenser : J. Chem. Soc., **1956**, 3659.

above iodide, which yielded a minute amount of α-isomer (*vide infra*) of the desired tetrahydro-β-carboline derivative (XV) after being reduced with sodium borohydride-methanol.

Pictet-Spengler type of reaction of XI was next investigated. Thus XI-hydrochloride salt dissolved in 50% aqueous methanol was reacted with methyl 3-formylpropionate for ca. 40 hr. under reflux to give about 60% yield of the aimed (XV) as a mixture of two (α and β) diastereoisomers separable through silicagel chromatography. α-Isomer was colorless prisms of m.p. 144~145° and formed the main constituent, whereas β-isomer separated in colorless plates of m.p. 195~196°(decomp.).

When hydrolyzed with sodium hydroxide the α-isomer gave the corresponding acid (XVI), which could be reconverted to the original ester on being treated with diazomethane, whereas the β-isomer yielded the same acid (XVI) through epimerization by alkaline hydrolysis, which furnished with diazomethane α-ester only. Based on the above fact the more stable 1,3-*cis* configuration was conjectured for α-isomer and hence β-isomer was considered to be 1,3-*trans* disposed.

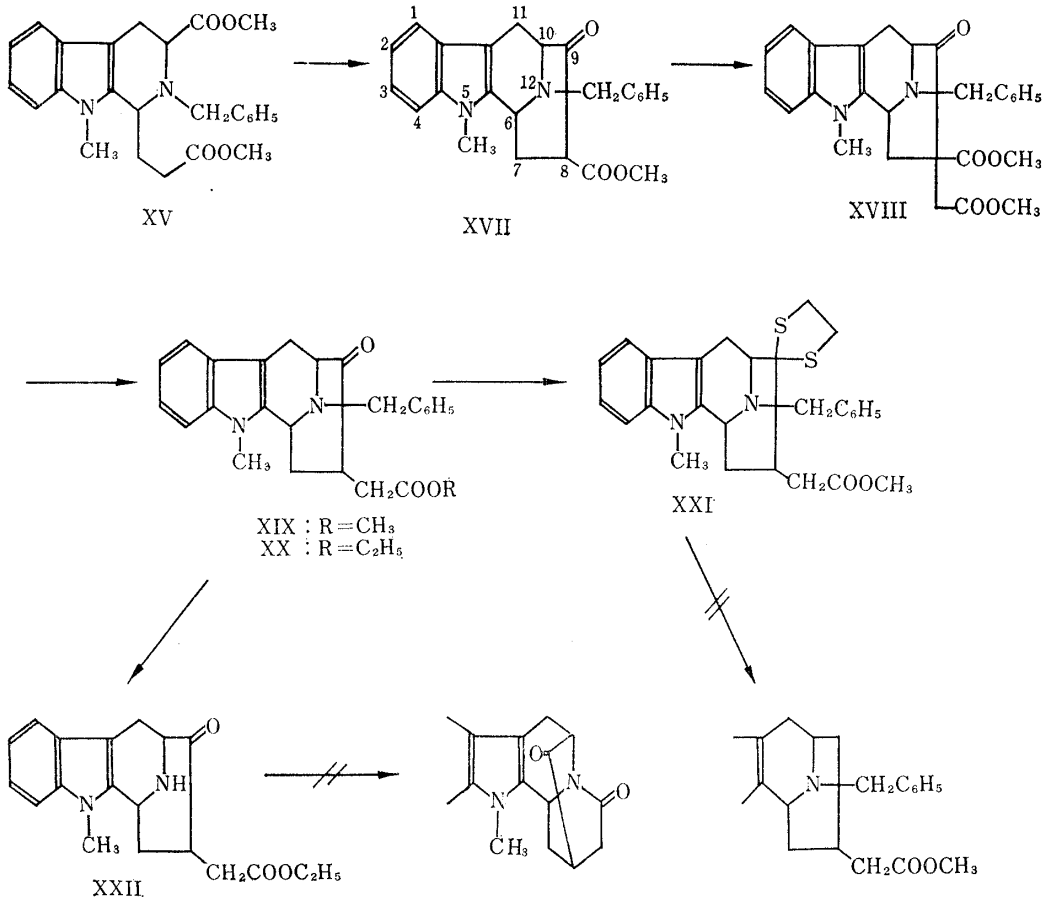


Chart 3.

The compound (XV : a mixture of isomers) was then treated with sodium hydride in boiling toluene containing a small amount of methanol to furnish the cyclization product, 6,10-imino-5*H*-cycloöct[*b*]indole (XVII), in 77% yield.*3 The latter is not soluble

*3 The Dieckmann cyclization of this ester did not proceed at all with sodium hydride-toluene or with sodium methylate-methanol. Potassium tertiary butylate-toluene gave only a little cyclization product. The yield by Hobson's method (ref. 5) using sodium hydride-tetrahydrofuran was ca. 30%, as compared with 77% in the present case.

in sodium hydroxide solution, but gives positive ferric chloride-color test as enol, which was also supported by its infrared absorption bands[9] at 1670 and 1625 cm^{-1}.

The above obtained (XVII) was condensed with methyl bromoacetate to give keto-diester (XVIII) in 70% yield, which was submitted to ketone fission reaction as was described in the previous paper.[6] Thus XVIII was hydrolyzed with potassium hydroxide in aqueous methanol and neutralized with acetic acid. The keto-acid separated was decarboxylated at 120~130° *in vacuo* (4 mm. Hg) and the product was esterified; both methyl (XIX) and ethyl ester (XX) were prepared. Reduction of the keto-group in these esters to methylene-group presented a difficult problem. For instance, the ethylene dithioketal of XX, prepared by treating the latter with ethane dithiol in the presence of boron trifluoride-etherate according to Fieser's method,[10] was submitted to the conventional desulfurization reaction with Raney nickel.[11] The product was an uncrystallizable syrup devoid of S and was a mixture of several substances as was revealed by its thin-layer chromatography, probably as a reductive debenzylation reaction occurred simultaneously around N(b). Any one of these components could not be isolated in a state of purity.

Therefore the γ-ketoester (XX) was first reductively debenzylated forming imino-keto-ester (XXII), attempted lactamization of which under a variety of working condi-

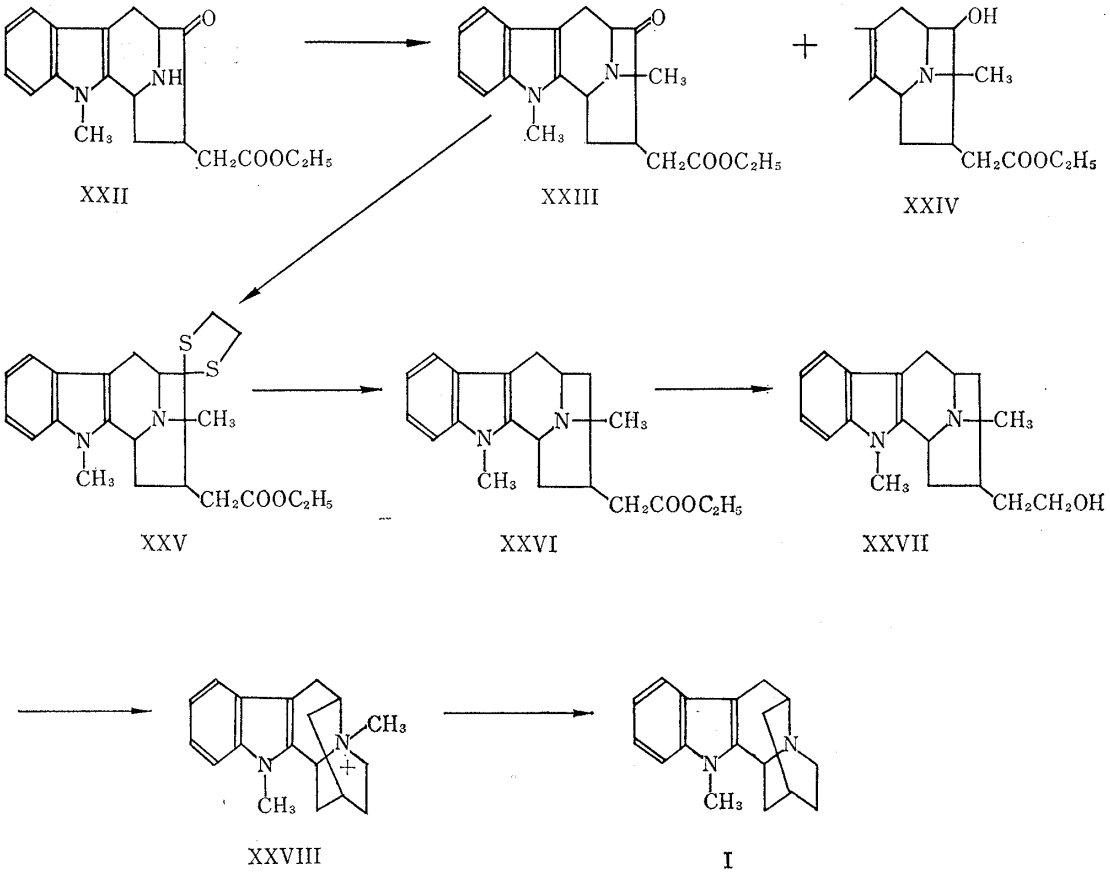


Chart 4.

9) N. J. Leonard, H. S. Gutowsky, W. J. Middleton, E. M. Petersen : J. Am. Chem. Soc., **74**, 4070 (1952).
10) L. F. Fieser : J. Am. Chem. Soc., **76**, 1945 (1954).
11) E. E. van Tamelen : "Desulfurization with Raney Nickel." Org. Reactions, **12**, 356 (1962). John Wiley & Sons Inc. N. Y.

tions was unsuccessful. This failure may be ascribed to bridgehead amide interdict. A couple of similar precedents are cited.[12,13]

N(b)-Methylation of XXII was effected by treating it with formalin under reducing conditions over palladium-carbon to yield XXIII, concomitant formation of some alcohol (XXIV) was also observed. XXIII was now converted to the corresponding thioketal (XXV) as above and the latter was desulfurized by the usual method to furnish XXVI in a smooth reaction, which was again reduced with lithium aluminum hydride to give the corresponding alcohol (XXVII) in good yield. This remained syrupy and was characterized as crystalline methiodide.

The alcohol (XXVII) was tosylated by allowing to stand it with tosyl chloride in pyridine in the cold, when simultaneous quaternization ensued to give the quaternary base (XXVIII), which was extracted with water. The corresponding perchlorate, iodide and chloride were also prepared, all of which were crystalline suitable for characterization.

The quarternary nature of these salts, which are readily soluble in chloroform, was evidenced from i) nothing was transferred to organic solvent layer after the aqueous solution of the salt was basified with sodium hydrogen carbonate and shaken, ii) in infrared spectra no absorption band ascribable to $\overset{+}{\geqslant}$N-H is present and finally, iii) analytical data.

The ultimate step of the synthesis consisted in the thermal decomposition of the above-mentioned methochloride salt (XXVIII), which proceeded neatly *in vacuo* (10^{-3} mm. Hg).

The product was purified by alumina chromatography and then crystallized from hexane to form colorless prisms of m.p. 142~143°, yield 80%. When allowed to stand with methyl iodide in ethereal solution, this base was again converted to the

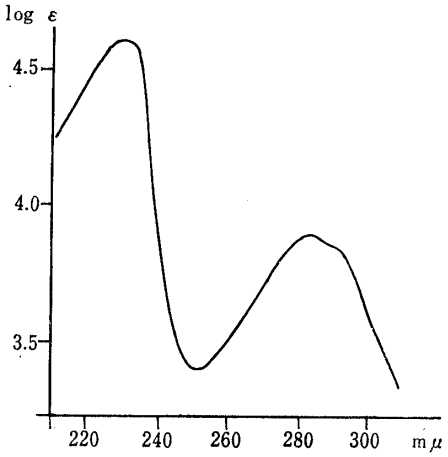


Fig. 1. Ultraviolet Absorption Spectrum of I in Ethanol

λ_{max}^{EtOH} mμ (log ε): 230(4.60), 285(3.90).
shld.: 278(3.86), 292(3.86).
λ_{min}: 251(3.40).
Deoxyajmalal-B (Vb)[2]
λ_{max}^{EtOH} mμ (ε): 226~229(38.960), 283(7.870).
shld.: 278(7.300), 292(6.700).
λ_{min}: 249~250(2.900).

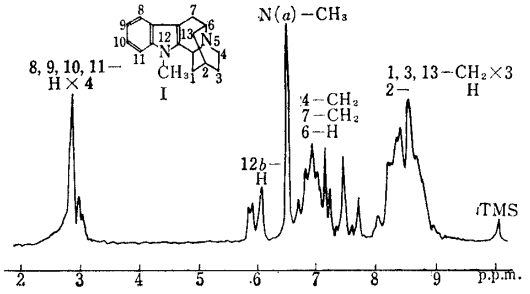


Fig. 2. Nuclear Magnetic Resonance Spectrum of I in Deuterochloroform, 60 Mc.

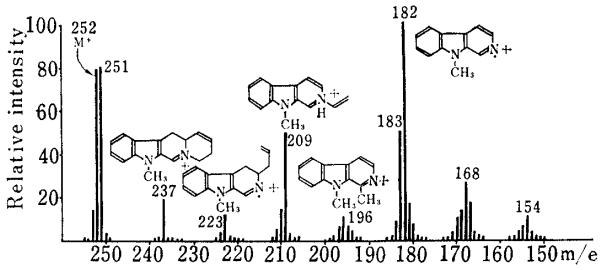
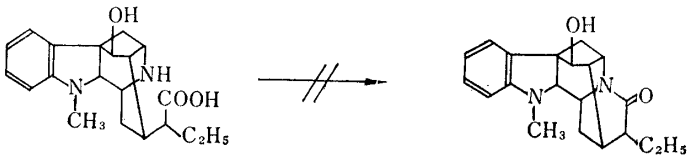
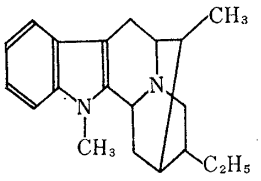


Fig. 3. Mass Spectrum of I (HITACHI RMU-6D)

12) R. Lukés: Collection Czechslov. Chem. Commun., **10**, 148 (1938).
13) F. A. L. Anet, D. Chakravarti, Sir R. Robinson, E. Schlittler: J. Chem. Soc., **1954**, 1242.





(A)

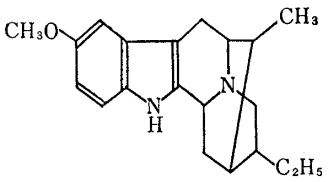


Chart 5.

original methiodide, showing that the ring system has suffered no change during pyrolysis reaction. The structure of I was supported by analysis, mass spectrum (Fig. 3: mol. wt. 252 calcd. and found), which is similar to spectra of ajmaline derivative (A) and sarpagine derivative (B) described by Biemann.[14]

The base (I) appears to be synthesized more conveniently by starting from ester of N(a, b)-dimethyltryptophan.

Work is being continued aiming at introducing such C-2 unit, ethyl or ethylidene group, at 3-position of I as is usual in natural sarpagine and ajmaline alkaloids. Grafting -CHO, $-CH_2OH$ or -COOR group at 13-position of I is also being attempted to secure a foot'hold for the synthesis of ajmaline ring.

Experimental*4

***dl*-1-Methyltryptophan Methyl Ester (IX)**——*dl*-1-Methyltryptophan methyl ester (IX) prepared from *dl*-tryptophan *via* 1-methyltryptophan (VIII)[7,15] according to the method of S. Yamada, *et al.*[7] Hydrochloride: Colorless minute needles (from MeOH). m.p. 228~229° (decomp.). [Lit. 7. m.p. 227.5° (decomp.)]. *Anal.* Calcd. for $C_{13}H_{17}O_2N_2Cl$: C, 58.10; H, 6.38; N, 10.42; Cl, 13.19. Found: C, 58.23; H, 6.42; N, 10.25; Cl, 13.38.

N-Benzyl-1-methyltryptophan Methyl Ester (XI)——The foregoing ester (IX) (49.2 g.) was condensed with benzaldehyde (23.0 g.) in the usual manner to produce a N(b)-benzylidene derivative (X) (68.3 g., 100%) as a yellow-orange viscous oil, which was dissolved in MeOH (200 ml.) and reduced with $NaBH_4$ (4.0 g.). After removal of the solvent, the residue was mixed with H_2O and extracted three times with AcOEt. The AcOEt extract was shaken vigorously with 10% HCl (120 ml.) to separate white crystals, which were collected and washed with H_2O, then with AcOEt to yield 74 g. (95.5%) of XI·HCl salt, m.p. 224~226° (decomp.). Recrystallized from MeOH to form colorless needles, m.p. 232° (decomp.). *Anal.* Calcd. for $C_{20}H_{23}O_2N_2Cl$: C, 66.94; H, 6.46; N, 7.81; Cl, 9.88. Found: C, 66.90; H, 6.40; N, 8.01; Cl, 10.18.

The free base of XI was obtained as a colorless viscous oil, $b.p_{1.0}$ 200~205° (without decomp.). Picrate: Yellow needles (from MeOH), m.p. 176~177°. *Anal.* Calcd. for $C_{26}H_{25}O_9N_5$: C, 56.62; H, 4.57; N, 12.70. Found: C, 56.32; H, 4.52; N, 13.09.

Methyl N-Benzyl-N-[1-methoxycarbonyl-2-(1-methyl-3-indolyl)ethyl] succinamate (XII)——A mixture of XI (61.0 g.), succinic anhydride (20.0 g.) and benzene (200 ml.) was refluxed for 2 hr. After cooling, the condensation product was extracted thoroughly with Na_2CO_3 solution [Na_2CO_3 (20 g.) in H_2O (300 ml.)], the extract was filtered, made congo-red acid with HCl and extracted with AcOEt. After evaporating the solvent ot dryness, the residue was esterified by the usual method to yield 58.0 g. (70.2%) of XII as a yellow- orange semi-solid. IR $\nu_{max}^{capil.}$ cm^{-1}: 1740 (ester), 1660 (amide).

Bischler-Napieralski Reaction of the Amide (XII)——A mixture of the above-obtained amide (XII) (5.8 g.) and $POCl_3$ (30 ml.) was gently refluxed for 10 hr. After removal of the excess $POCl_3$ *in vacuo*, the tarry residue was cautiously decomposed with ice-water and repeatedly extracted with warm H_2O (total volume about 600 ml.). The combined aqueous solutions were washed with benzene, filtered with charcoal and the orange-red filtrate was evaporated *in vacuo* to dryness. Anhydrous MeOH (120 ml.) was added to the residue and the whole was saturated with dry HCl gas with ice-cooling. After standing overnight, MeOH was evaporated to leave a tarry residue, which was dissolved in ice-water and mixed with NaI (3.0 g.) solution and extracted with $CHCl_3$. From the $CHCl_3$ extract, there was obtained a yellow-brown syrupy residue (about 3.2 g.), which was purified from MeOH-ether. A small amount (about 0.3 g.) of 1-(2-methoxycarbonylethyl)-2-benzyl-9-methyl-9*H*-pyrido[3,4-*b*]indolium iodide (XIV) separated out. After repeated recrystallization from MeOH-ether, it formed faint yellow prisms, m.p. 197~198° (decomp.).

*4 All melting points are uncorrected. The IR absorption spectra were measured with Nippon Bunko Model IR-S spectrophotometer.

14) K. Biemann: J. Am. Chem. Soc., 83, 4801 (1961); "Mass Spectrometry of Organic Ions," Ed. F. W. McLafferty. p. 569 (1963). Academic Press, New York.

15) E. Leete: J. Org. Chem., 23, 631 (1958).

Anal. Calcd. for $C_{23}H_{23}O_2N_2I$: C, 56.45; H, 4.74; N, 5.72; I, 26.55; OMe, 6.34. Found : C, 56.81; H, 4.77; N, 5.66; I, 26.85; OMe, 6.47. UV λ_{max}^{EtOH} mμ (log ε) : 269 (4.50), 315 (4.28). 393 (3.69); λ_{min} (log ε) : 245 (4.15); 290 (3.85), 340 (2.92).

The crude syrupy iodide was reduced with $NaBH_4$ in the usual manner to yield an orange-yellow syrupy base, which was dissolved in MeOH and allowed to stand in a refrigerator. After several days, a small amount of colorless crystals separated out. The crystals were identical with the methyl 2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (XV) α-isomer prepared by the Pictet-Spengler reaction as described below.

Pictet-Spengler Reaction of the N-Benzyl Ester (XI): Methyl 2-Benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (XV)——A mixture of N-benzyl ester (XI) hydrochloride (26.5 g.), methyl 3-formylpropionate (11.0 g.), b.p_{17} 78～80° (prepared from 3-methoxycarbonylpropionyl chloride by the Rosenmund reduction[16,17]) and 50% MeOH (300 ml.) was gently refluxed for 40 hr. During which time colorless crystals separated out, which were collected and washed with a small volume of cold MeOH to give a tetrahydro-β-carboline (XV), 18.3 g. (59%), m.p. 137～140°

This product consisted mainly of the α-isomer accompanied by a small amount of the β-isomer. From the mother solution, there was obtained a small amount of white crystals (about 1.5 g.), which were relatively rich in the β-isomer as revealed by thin-layer chromatography.*5

In order to separate the α- and β-isomers, the Pictet-Spengler's product was dissolved in benzene and chromatographed on silica gel (50 times). The benzene effluent contained mainly the α-isomer and the subsequent elution with benzene-AcOEt (4:1) gave mainly the β-isomer. Chromatography on silica gel was repeated until the two isomers became free from each other. The α- and β-isomers thus separated were recrystallized from MeOH.

α-Isomer : Colorless prisms (from MeOH), m.p. 144～145°. IR ν_{max}^{Nujol} cm^{-1} : 1730 (ester). *Anal.* Calcd. for $C_{25}H_{28}O_4N_2$: C, 71.41; H, 6.72; N, 6.66; OMe, 14.76. Found : C, 71.09; H, 6.80; N, 6.66; OMe, 14.47.

Picrate : Yellow-orange needles (from MeOH), m.p. 149～150°. *Anal.* Calcd. for $C_{31}H_{31}O_{11}N_5$: C, 57.32; H, 4.81; N, 10.78. Found : C, 57.22; H, 4.74; N, 10.77.

β-Isomer : Colorless plates (from MeOH), m.p. 195～196° (decomp.). IR ν_{max}^{Nujol} cm^{-1} : 1730; 1715 (ester). *Anal.* Calcd. for $C_{25}H_{28}O_4N_2$: C, 71.41; H, 6.72; N, 6.66. Found : C, 71.12; H, 6.22; N, 7.06.

Picrate : Yellow needles (from MeOH), m.p. 178～179° (decomp.). *Anal.* Calcd. for $C_{31}H_{31}O_{11}N_5$: N, 10.77. Found : N, 11.01.

Hydrolysis of XV α-isomer with Sodium Hydroxide——2-Benzyl-3-carboxy-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*]indole-1-propionic acid(XVI). A mixture of XV α-isomer (2.10 g.), NaOH(0.82 g.), H_2O (5 ml.) and MeOH (50 ml.) was refluxed for 80 hr. After concentration, the residue was dissolved in H_2O, neutralized with AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed, dried and evaporated to leave a viscous syrup, which was purified from benzene to give a diacid (XVI), 1.50 g. (76.5%), as colorless prisms, m.p. 211～212° (decomp.). IR ν_{max}^{Nujol} cm^{-1} : 1705 (acid). *Anal.* Calcd. for $C_{23}H_{24}O_4N_2$: C, 70.39; H, 6.16; N, 7.14. Found : C, 70.79; H, 6.01; N, 7.00.

Esterification of the Diacid (XVI) with Diazomethane——A solution of the above diacid (XVI) (0.50 g.) in MeOH (20 ml.) was mixed with a solution of CH_2N_2 in ether and worked up as usual to yield colorless prisms, 0.51 g., m.p. 144～145°, identical with XV α-isomer (melting point test, IR spectrum and thin-layer chromatography).

Epimerization of XV β-Isomer with Sodium Hydroxide——A mixture of XV β-isomer (8 mg.), NaOH (20 mg.), H_2O (1 ml.) and MeOH (20 ml.) was refluxed for 20 hr. and worked up as for the α-isomer to give an acidic product which showed the same property on thin-layer chromatography as the diacid (XVI) derived from the α-isomer. The above acidic product was esterified with CH_2N_2 by the usual method to yield colorless prisms, 8 mg., m.p. 142～143°. This was proved to be identical with XV α-isomer by the mixed melting point test, IR spectrum and thin-layer chromatography.

Dieckmann Reaction of the Tetrahydro-β-carboline (XV): Methyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-carboxylate (XVII)——To a boiling mixture of XV (21.0 g., m.p. 137～140°*6), NaH (51.2% oil dispersion) (6.0 g.) (previously washed three times with hexane to remove the mineral oil) and dehydrous toluene (100 ml.) was added dropwise a mixture of MeOH (2 ml.) and toluene (8 ml.) over a period of 1 hr. and the whole was gently refluxed for additional 2 hr. After standing overnight, the reaction mixture was mixed cautiously with AcOH (about 10 ml.) in order to decompose excess NaH and then basified with saturated $NaHCO_3$ solution, followed by extraction with benzene. The benzene solution was washed, dried and evaporated to afford an orange-yellow caramel-

*5 Silica gel Benzene-AcOEt (4:1) H_2SO_4. α-isomer, Rf about 0.7; β-isomer, Rf about 0.1.

*6 The Pictet-Spengler's product, containing mainly the α-isomer and a small amount of the β-isomer, was directly used without separation of the isomers.

16) K. B. Wiberg, P. K. Barnes, J. Albin : J. Am. Chem. Soc., **79**, 4994 (1957).

17) W. S. Johnson, R. P. Linstead, R. R. Whetstone : J. Chem. Soc., **1950**, 2219.

like residue, which solidified on warming with MeOH (150 ml.). After cooling, XVII was collected to give 15.0 g., 77.5%, m.p. 148~150°. It was insoluble in NaOH solution but gave reddish violet color in the $FeCl_3$-test. A small portion of the product was recrystallized from MeOH–AcOEt to form colorless plates, m.p. 150.5~151.5°. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1625 (enol-form of β-ketoester). *Anal.* Calcd. for $C_{24}H_{24}O_3N_2$: C, 74.20; H, 6.23; N, 7.21. Found: C, 74.23; H, 6.15; N, 7.15.
Picrate: Faint yellow needles (from AcOH), m.p. 207° (decomp.). *Anal.* Calcd. for $C_{30}H_{27}O_{10}N_5$: C, 58.34; H, 4.41; N, 11.34. Found: C, 58.78; H, 4.20; N, 11.32.

Methyl 5-Methyl-8-methoxycarbonyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XVIII)——A mixture of XVII (15.6 g.), K_2CO_3 (15.6 g.), NaI (7.8 g), methyl bromoacetate (15.6 g.) and dehydrous MeCOEt (300 ml.) was refluxed for 72 hr. After removing the solvent *in vacuo*, the residue was mixed with ice-water and extracted with benzene. The benzene extract was washed, dried and evaporated to leave a yellow-orange syrup. Since this did not solidify, it was purified as picrate. By recrystallization from MeOH, XVIII picrate was obtained as yellow-orange prisms, m.p. 168~170° (decomp.), in a yield of 20.0 g. (71.7%). On further recrystallization, the melting point was raised to 171~172° (decomp.). *Anal.* Calcd. for $C_{33}H_{31}O_{12}N_5$: C, 57.47; H, 4.53; N, 10.16. Found: C, 57.56; H, 4.60; N, 10.16. The free base of XVIII was recovered as a faint yellow viscous syrup from the above picrate by treatment with LiOH solution.

Ketone Fission of the Ketoester (XVIII): Methyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XIX)——A solution of XVIII, recovered from its picrate (8.4 g.), and KOH (2.2 g.) in aqueous MeOH [MeOH (60 ml., H_2O (90 ml.)] was refluxed for 45 hr. MeOH was then removed *in vacuo* and the resulting aqueous solution was washed once with a mixture of benzene and ether and filtered with carbon. The filtrate was neutralized with AcOH (about 3 ml.) and extracted with $CHCl_3$. After removing the solvent, there was obtained a faint yellow foam (about 5.5 g.), which was heated at 120~130° in an oil-bath under 4 mm. Hg pressure for 1 hr. to complete decarboxylation. An orange glassy product thus obtained was dissolved in anhydrous MeOH (130 ml.) and esterified by the usual method to give XIX, 2.58 g. (52.7%), m.p. 147~150°. On recrystallization from MeOH, this formed colorless prisms, m.p. 155~157°. IR ν_{max}^{Nujol} cm^{-1}: 1725, 1715 (ester). *Anal.* Calcd. for $C_{25}H_{26}O_3N_2$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.20; H, 6.12; N, 6.90.
Hydrochloride: Colorless prisms (from MeOH–ether), m.p. 204~205° (decomp.). *Anal.* Calcd. for $C_{25}H_{27}O_3N_2Cl$: C, 68.41; H, 6.20; N, 6.38; Cl, 8.08. Found: C, 68.59; H, 6.16; N, 6.41; Cl, 8.20.

Ethyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XX)——γ-Ketoethylester (XX) was similarly prepared by ketone fission of XVIII followed by esterification with EtOH–HCl as a yellowish orange syrup in a yield of 60%. It could not be solidified and was characterized as the hydrochloride, which forms colorless plates (from EtOH–ether), m.p. 210~211° (decomp.). *Anal.* Calcd. for $C_{26}H_{29}O_3N_2Cl$: C, 68.94; H, 6.45; N, 6.18; Cl, 7.83. Found: C, 68.82; H, 6.55; N, 6.14; Cl, 7.62.

Methyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate Cyclic Ethylene Thioacetal (XXI)——A mixture of XIX (2.00 g.), ethane dithiol (10 ml.), BF_3–ether (10 ml.) and AcOH (4 ml.) was allowed to stand for 3 days at room temperature. The reaction mixture was poured onto ice-water, basified with $NaHCO_3$ and extracted with benzene. The benzene extract was washed with ice-cold 5% KOH and then with saturated NaCl solution, dried and evaporated to leave a colorless syrup, which was triturated with ether to form colorless plates of XXI, 1.53 g. (64.3%), m.p. 172~174°. On further recrystallization from ether, the melting point was raised to 175~176°. *Anal.* Calcd. for $C_{27}H_{30}O_2N_2S_2$: C, 67.72; H, 6.32; N, 5.85; S, 13.40. Found: C, 68.49; H, 6.03; N, 5.94; S, 13.66.

Desulfurization of this thioketal (XXI) with Raney Ni in EtOH gave a colorless syrup devoid of S, but the product was shown to be a mixture of three or four components by thin-layer chromatography and their separation was not successful.

Ethyl 5-methyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XXII)——A solution of the above-obtained γ-ketoethylester (XX) (6.0 g.) and concentrated HCl (3 ml.) in EtOH (120 ml.) was hydrogenated over 10% Pd-C catalyst (1.0 g.) at room temperature. After absorption of H_2 ceased, the catalyst was filtered off and washed with EtOH. The filtrates were combined and evaporated *in vacuo* to leave a syrupy residue, which was then dissolved in H_2O, washed with benzene and filtered with charcoal. The filtrate was basified with $NaHCO_3$ and extracted with benzene. The benzene solution was washed, dried and evaporated to leave a yellow caramel-like residue, which crystallized on warming with EtOH to form faint yellow prisms of XXII, 3.1 g., m.p. 138~141°. On further recrystallization from EtOH, the melting point was raised to 141.5~143°. *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.78; H, 6.44; N, 8.86.

Reductive Methylation of XXII: Ethyl 9-oxo-5,12-dimethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XXIII) and Ethyl 9-Hydroxy-5,12-dimethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XXIV)——A solution of XXII (1.50 g.) and 37% formalin (0.60 g.) in EtOH (150 ml.) was hydrogenated over 10% Pd-C catalyst (1.5 g.) at room temperature, 150 ml. of H_2 being absorbed in about 8 hr. The catalyst was removed by filtration and washed with EtOH. The

combined filtrates were evaporated to leave a faint yellow syrup (1.5 g.), which was dissolved in benzene–hexane (1:1) and chromatographed on an alumina column (1.5×12 cm.). From the benzene–hexane (1:1) effluent(300 ml.), the objective N(b)-methyl compound (XXIII) was obtained as a colorless syrup, 1.12 g. (72.0%), which could not be solidified. IR $\nu_{max}^{capil.}$ cm^{-1}: 1725 broad (ester, ketone). The subsequent benzene AcOEt (1:1) effluent (200 ml.) contained mainly the alcohol compound (XXIV), which was recrystallized from benzene–hexane to form colorless needles, 0.18 g. (11.5%), m.p. 144~145.5°. IR ν_{max}^{Nujol} cm^{-1}: 3180 (OH), 1730 (ester). *Anal.* Calcd. for $C_{20}H_{26}O_3N_2$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.53; H, 7.33; N, 8.29.

Ethyl 9-oxo-5,12-dimethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate Cyclic Ethylene Thioacetal (XXV)——A mixture of XXIII (1.05 g.), AcOH (1 ml.), ethane dithiol (3 ml.) and BF_3–ether (3 ml.) was allowed to stand at room temperature for 2 days and worked up as above for XXI to yield XXV, 0.99 g. (76.7%), as colorless plates (from benzene–hexane), m.p. 151~154°, which was raised to 154.5~156.5° on further recrystallization. IR ν_{max}^{Nujol} cm^{-1}: 1730 (ester). *Anal.* Calcd. for $C_{22}H_{28}O_2N_2S_2$: C, 63.43; H, 6.77; N, 6.72; S, 15.39. Found: C, 63.47; H, 6.27; N, 6.83; S, 15.26.

Ethyl 5,12-Dimethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-acetate (XXVI)——A solution of XXV (0.79 g.) in EtOH (80 ml.) was refluxed with Raney Ni catalyst (W-5, 8 ml.) for 6 hr. with vigorous stirring. The catalyst was removed by filtration and thoroughly washed with hot EtOH. The combined EtOH solutions were evaporated *in vacuo* to leave a syrupy residue, which was dissolved in benzene and passed through an alumina column. The desulfurized ester (XXVI) was obtained as a faint yellow viscous syrup, 0.48 g. (77.0%), which did not crystallize and was used directly for the next reaction. IR $\nu_{max}^{capil.}$ cm^{-1}: 1730 (ester).

5,12-Dimethyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloöct[*b*]indole-8-ethanol (XXVII)——To a suspension of $LiAlH_4$ (0.16 g.) in anhydrous ether (35 ml.) was added dropwise a solution of the above-obtained (XXVI) (0.45 g.) in the same solvent (35 ml.) with stirring and ice-cooling, then stirring was continued for 2 hr. at room temperature and further 2 hr. under refluxing. On working up as usual, 0.37 g. (95%) of XXVII was obtained as a faint yellow foam, which could not be solidified, and was characterized as its methiodide, which formed yellow-orange plates from MeOH–ether, m.p. 230~231° (decomp.). *Anal.* Calcd. for $C_{19}H_{27}ON_2I \cdot H_2O$: C, 51.01; H, 6.53; N, 6.26; I, 29.04. Found: C, 50.54; H, 6.24; N, 6.41; I, 28.98.

5,12-Dimethyl-1,2,3,4,6,7,12,12*b*-octahydro-2,6-metanoindolo[2,3-*a*]quinolizinium (XXVIII) Iodide——A mixture of the above-obtained alcohol (XXVII) (0.33 g.), tosylchloride (0.33 g.) and dry pyridine (1.0 ml.) was allowed to stand in a refrigerator for 3 days. After removal of pyridine *in vacuo*, the residue was washed with ether and dissolved in H_2O. The aqueous solution was washed once with benzene, filtered with charcoal and the filtrate was mixed with NaI solution and extracted thoroughly with $CHCl_3$. The $CHCl_3$ extract was washed with NaI solution, dried over Na_2SO_4 and evaporated to give a caramel-like residue, which was purified from MeOH–ether to form XXVIII iodide, 0.16 g. (35%), as faint yellow-orange minute needles, m.p. 250~252° (decomp.). *Anal.* Calcd. for $C_{18}H_{23}N_2I$: C, 54.42; H, 5.84; N, 7.05; I, 32.70. Found: C, 54.92; H, 5.81; N, 7.22; I, 32.54.

XXVIII Perchlorate, faint yellow needles (EtOH–ether), m.p. 217~218° (decomp.), was prepared by adding $NaClO_4$ to the above-mentioned aqueous filtrate. *Anal.* Calcd. for $C_{18}H_{23}O_4N_2Cl$: C, 58.93; H, 6.32; N, 7.64; Cl, 9.67. Found: C, 59.12; H, 6.25; N, 7.69; Cl, 9.68.

XXVIII Chloride: Colorless prisms (from MeOH–ether), m.p. 278~280° (decomp.). This was prepared from XXVIII iodide by treatment with excess AgCl in MeOH. *Anal.* Calcd. for $C_{18}H_{23}N_2Cl$: N, 9.25; Cl, 11.71. Found: N, 9.27; Cl, 11.30.

12-Methyl-1,2,3,4,6,7,12,12*b*-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine (I)——The above-obtained (XXVIII) chloride (30 mg.) was heated in a test tube (1×10 cm.) at 10^{-3} mm. Hg pressure, over a free flame for about 5 min. A faint yellow hard syrup thus obtained was dissolved in benzene, passed through an alumina column and the solvent was removed from the effluent to give a crystalline residue which was recrystallized from hexane to form colorless plates of I, 20 mg. (80%), m.p. 142~143°. *Anal.* Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10; mol. wt. 252.36. Found: C, 80.61; H, 7.57; N, 11.26; mol. wt. 252 (Mass); 256 (mean of 3 determinations by micro Rast method).

From a mixture of I (3.5 mg.) and MeI in ether, XXVIII iodide was recovered in a quantitative yield.

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Summary

12-Methyl-1,2,3,4,6,7,12,12*b*-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine (I), which represents the fundamental skeleton of sarpagine type indole alkaloids, was synthesized.

Thus methyl ester (XI) hydrochloride of N-benzyl-l-methyltryptophan was treated with methyl 3-formylpropionate to form tetrahydro-β-carboline derivative (XV), from which 6,10-imino-5*H*-cycloöct[*b*]indole derivative (XVII) was prepared by Dieckmann cyclization with sodium hydride under a certain working condition. This was condensed with methyl bromoacetate followed by ketone fission to yield ketoester (XX), from which N-benzyl group was reductively removed and then converted to N-methyl derivative (XXIII). The ethylene thioketal (XXV) of the latter was desulfurized as usual and the product was reduced by lithium aluminum hydride to furnish the corresponding alcohol (XXVII), which was tosylated with tosyl chloride in pyridine in the cold. Spontaneous quaternization of the tosylate took place forming the cyclized quaternary base (XXVIII), the chloride salt of which was submitted to pyrolysis reaction to produced the desired base (I).

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159. Junzo Shoji,*1 Shoji Shibata, Ushio Sankawa, Heihachiro Taguchi,*2 and Yoshiko Shibanuma*3 : Metabolic Products of Fungi. XXIV.*4 The Structure of Erythroskyrine, a Nitrogen-containing Coloring Matter of *Penicillium islandicum* Sopp.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**2 *and National Institute of Radiological Sciences**3)

More than dozen pigments have been isolated from several strains of *Penicillium islandicum* Sopp grown on the Czapek-Dox medium.[1] Erythroskyrine which was first isolated and studied by Howard and Raistrick[2] is unique among them as it contains nitrogen in its molecule. The present study has been carried out using laboratory cultivation of *P. islandicum* Sopp S-strain which was isolated from molded rice grains. The S-strain produces no anthraquinone pigments as similar as LSHTM BB 233 strain.[2] A minor pigment accompanied by erythroskyrine was removed by $CaHPO_4$-column chromatography, using hexane-acetone (10:1) as the solvent, and the pure erythroskyrine, orange red crystals, m.p. 130~133°, $[\alpha]_D$ +46.9°, thus obtained gave a molecular formula, $C_{26}H_{33}O_6N$, which was revised from the formula, $C_{24}H_{31}O_6N$, proposed by the earlier workers.[2]

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*1 Present address : School of Pharmaceutical Sciences, Showa University, Shinagawa-ku, Tokyo (庄司順三).
*2 Hongo, Tokyo (柴田承二, 三川 潮, 田口平八郎).
*3 Inage, Chiba (柴沼淑子).
*4 Part XXIII : This Bulletin, **11**, 1576 (1963).

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