9-Benzyl-N,N,3-trimethyladeninium Bromide (IVe)——A solution of IIIa (3.544 g, 20 mmol) and benzyl bromide (6.8 g, 40 mmol) in DMAc (40 ml) was kept at 40° for 48 hr. The resulting precipitate was filtered off, washed with ethanol (20 ml), and dried to give 5.91 g (85%) of a colorless solid. The combined filtrate and washing were evaporated to dryness *in vacuo* and the residue was dissolved in a little ethanol. An additional crop (0.57 g, 8%) was obtained by adding ether (100 ml) to this solution. Recrystallization from isopropanol gave colorless plates, mp 213—214° (dec.).

N,N-Diethyl-3,9-dimethyladeninium Iodide (IVg)——A mixture of IIId (1.44 g, 7.02 mmol), methyl iodide (0.87 ml, 14 mmol), and DMAc (10 ml) was kept at 40° for 24 hr. The resulting mixture was treated in a manner similar to that described for IVa, giving 2.19 g (90%) of IVg. Recrystallization from ethanol gave colorless pillars, mp 231—232° (dec.) [lit.[4] 231.5—232.5° (dec.)].

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A Convenient Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo-[2,3-*a*]quinolizine

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A convenient synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) is described. The condensation of tryptamine (**2**) with diethyl (2-formylethyl)malonate (**3a**), followed by treatment with alkali, gave the lactam ester (**5a**). Decarbethoxylation of **5a** with LiCl–H_2O–Me_2SO afforded the lactam (**8a**), which was reduced with $LiAlH_4$ to give the indoloquinolizine (**1**). The lactam (**8b**) which has an ethyl group at C_3 was prepared from tryptamine (**2**) and diethyl ethyl(2-formylethyl)malonate (**3b**) instead of **3a**.

Keywords——indole alkaloid; synthesis; octahydroindolo[2,3-*a*]quinolizine; Pictet-Spengler reaction; lactamization

Several syntheses of the indoloquinolizine (**1**), even before its isolation[2] from natural source, have been reported.[3] In the present paper, a convenient synthesis of **1** is described. This forms a part of our work on the synthesis of *Corynanthé* type alkaloids.

The indoloquinolizine (**1**) is considered to be composed of a tryptamine moiety and the residual C-5 unit. In our synthetic plan, the aldehyde (**3a**),[4] prepared from acrolein and diethyl malonate, was chosen as the C-5 unit equivalent, since an ester group can easily be removed in a later step.

The Pictet–Spengler reaction of tryptamine (**2**) with the aldehyde (**3a**) was carried out in 80% acetic acid (AcOH) at room temperature to afford in quantitative yield of a mixture

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of the tetrahydro-β-carboline (**4a**) and the lactam ester (**5a**) in a 7: 3 ratio. The structural assignment of **4a** was based on the spectral data for **4a** and for the acetate (**6**) which was derived from **4a** by treatment with acetic anhydride and pyridine. When the above Pictet–Spengler reaction was run under reflux, the product ratio of **4a** to **5a** changed to 1: 4, but prolonged heating did not cause an appreciable change of the ratio. In order to simplify the work-up procedure, lactamization of **4a** to **5a** was attempted under various conditions, and treatment of **4a** with ethanol and 25% potassium carbonate (1: 1, v/v) was found to afford **5a** in good yield. **5a** is probably a mixture of epimeric isomers, as it showed 2 spots on a thin layer chromatogram (TLC) ($CHCl_3$/MeOH; 9: 1), and two sets of quartets and triplets with slightly different chemical shifts were observed in the proton nuclear magnetic resonance (NMR) spectrum. However, separation of the isomers was not attempted, since the asymmetric center was to be lost.

The lactam ester (**5a**) was saponified with aq. NaOH in EtOH to give the acid (**7**), which was then pyrolyzed to give the lactam (**8a**)[5] in moderate yield. In order to improve the yield, one-step decarbethoxylation of **5a** was attempted using LiCl–H_2O–Me_2SO[6], and in this case **8a** was obtained in 89% yield. The lactam (**8a**) was reduced with $LiAlH_4$ to give the indoloquinolizine (**1**) in 83% yield, mp 152—153°; 64% overall yield from tryptamine (**2**).

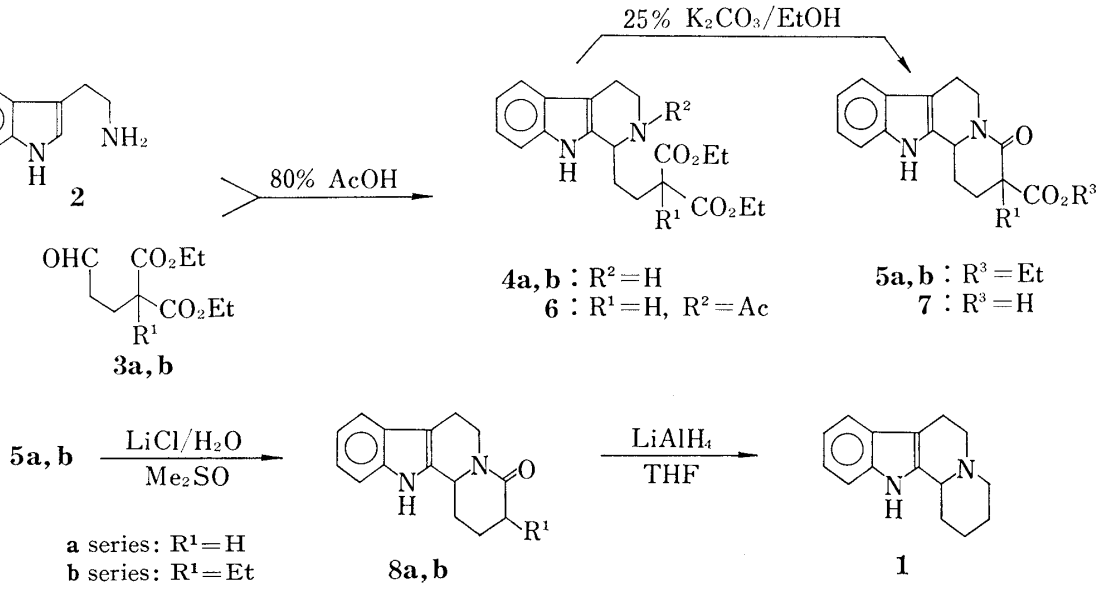

Chart 1

The present synthetic route may be developed to an efficient synthesis of *Corynanthé* type alkaloids (**10**), which have an ethyl group and a β-methoxy acrylic ester group at C_3 and C_2, respectivity. The unsaturated lactam (**9**) is considered to be an appropriate intermediate for the synthesis of **10**. The condensation of tryptamine (**2**) with the aldehyde (**3b**)[4] followed by treatment with alkali gave the lactam ester (**5b**) in 70% yield; this showed one spot on TLC using several solvent systems, and two clear triplets and a quartet due to ethyl and ethoxycarbonyl groups were observed in the NMR spectrum. Though the above observations suggested that the obtained compound (**5b**) is a single isomer, the possibility that **5b** is a mixture of epimeric isomers cannot be ruled out. However, further investigation was not carried out, since the asymmetric center is lost in the desired compound (**9**).

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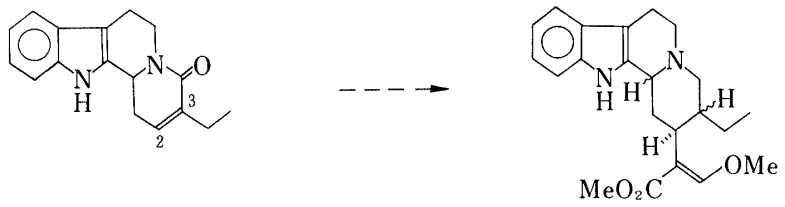
The decarbethoxylation of **5b** gave two lactams (**8b**), major (less polar) (51%) and minor (23%), whose configurations were not determined. Attempts to convert **8b** to **9** and an alternative synthesis of **9** are in progress.



9 **10**

Chart 2

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrometer and ultraviolet (UV) spectra with a Hitachi 340 spectrophotometer in 95% EtOH. NMR spectra were recorded on Hitachi R-24B and JEOL JNM4H-100 spectrometers in $CDCl_3$ (unless otherwise stated) with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a Hitachi RMU-6E mass spectrometer. TLC was performed on Merck precoated silica gel 60F-254. Column chromatography utilized Merck silica gel, 70—230 mesh. Organic solutions were dried with anhydrous Na_2SO_4. Abbreviations used are: singlet (s), triplet (t), quartet (q), multiplet (m), aromatic (arom), shoulder (sh).

Condensation of Tryptamine (2) with Diethyl (2-formylethyl)malonate (3a): 1-[3,3-Bis(ethoxycarbonyl)-propyl]-1,2,3,4-tetrahydro-β-carboline (4a) and Ethyl 4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (5a)——1) **3a**[4] (12.30 g, 1.2 eq.) was added to a solution of **2** (7.60 g) in 80% AcOH (60 ml) and the whole was stirred overnight at room temperature. The mixture was concentrated under reduced pressure, diluted with water and basified with 2 N Na_2CO_3. The pale yellow precipitate was filtered off and washed with EtOH to give **4a** (12.0 g, 70%). The filtrate was extracted with $CHCl_3$, then the extract was dried and concentrated. The residue was crystallized from ether–hexane to give **5a** (4.4 g, 29%). Analytical samples of **4a** and **5a** were recrystallized from EtOH–ether and EtOH–EtOAc, respectively. **4a**: mp 157—158°. IR ν_{max}^{KBr} cm^{-1}: 1730. MS *m/e*: 358 (M^+, 11%), 171 (100%). UV λ_{max}^{EtOH} (log ε): 225 (4.52), 277 (sh, 3.86), 281 (3.87), 290 (3.79). NMR δ: 1.22 (6H, t, $J=7$ Hz), 4.15 (4H, q, $J=7$ Hz), 4.70 (1H, m), 6.95—7.60 (4H, m, arom H), 9.39 (1H, s, indole NH, disappeared on addition of D_2O), 3.35 (secondary NH, intensity decreased on addition of D_2O). **5a**: mp 208—210°. IR ν_{max}^{KBr} cm^{-1}: 1730, 1600. MS *m/e*: 312 (M^+, 100%), 239 (54%), 184 (49%), 169 (31%). UV λ_{max}^{EtOH} nm (log ε): 223 (4.62), 274 (sh, 3.91), 280 (3.92), 290 (3.81). NMR δ (Me_2SO-d_6): 1.15 (6H, a set of t, $J=7$ Hz), 4.08 (4H, a set of q, $J=7$ Hz), 4.72—5.00 (2H, m), 6.90—7.50 (4H, m, arom H), 10.90 (1H, s, NH). *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.25; H, 6.49; N, 8.99.

2) A solution of **2** (15.2 g) and **3a** (24.6 g, 1.2 eq.) in 80% AcOH (125 ml) was stirred overnight at room temperature and then refluxed for 1 hr. The mixture was concentrated to one-half of its original volume and diluted with water (150 ml). The precipitate was filtrated off and washed with water and EtOH to give **5a** (17.6 g, 59%). The filtrate was basified with 2 N Na_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel (100 g). Eluates with 10% MeOH–$CHCl_3$ gave **4a** (4.30 g, 13%).

3) A solution of **2** (4.0 g) and **3a** (6.52 g, 1.2 eq.) in 80% AcOH (45 ml) was stirred for 6 hr at room temperature. The mixture was concentrated *in vacuo* below 40° to give an oil, which was dissolved in EtOH (100 ml). 25% aq. K_2CO_3 (100 ml) was added to the above solution and stirring was continued overnight at room temperature. Colorless crystals that precipitated were filtered off and washed with EtOH to provide **5a** (6.61 g, 85%, mp 200—204°). The mother liquor was concentrated and extracted with $CHCl_3$, then the extract was dried. Removal of the solvent followed by crystallization from EtOH gave **5a** (0.16 g, 2%, mp 208—210°).

2-Acetyl-1-[3,3-bis(ethoxycarbonyl)propyl]-1,2,3,4-tetrahydro-β-carboline (6)——A mixture of **4a** (127 mg) and acetic anhydride (1 ml) in pyridine (2 ml) was allowed to stand overnight. The mixture was then poured into ice-water, neutralized with saturated $NaHCO_3$ and extracted with benzene. The extract was washed with 1 N HCl and water, dried and concentrated. The residue was crystallized from benzene–hexane

7) The signals at δ 2.20 and δ 4.15 suggest that the acetate (**6**) exists as a mixture of two possible rotamers in solution. Another methyl signal of the N-acetyl group could not be assigned.

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to provide the acetate (**6**, 116 mg, 82%). mp 158—159°. IR ν_{max}^{KBr} cm^{-1}: 1725, 1630. MS *m/e*: 400 (M$^+$, 17%), 214 (85%), 213 (100%), 171 (36%). UV λ_{max}^{EtOH} nm (log ε): 225 (4.62), 274 (sh, 3.89), 279 (3.90), 290 (3.80). NMR δ: 1.22 (6H, t, J=7 Hz), 2.20 (2.5 H,[7] s, >NCOCH$_3$), 4.15 (4H, a set of q,[7] J=7 Hz), 5.75 (1H, m), 6.90—7.50 (4H, m, arom H), 8.60 (1H, s, NH). *Anal.* Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 66.09; H, 7.04; N, 6.89.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-4-one (8a)——1) **5a** (9.92 g) was added to a solution of NaOH (2.72 g) in water (30 ml) and EtOH (160 ml), and the solution was refluxed for 2 hr under argon. The mixture was concentrated, diluted with water and washed with CH_2Cl_2. The aqueous layer was acidified with conc.HCl to pH 3 and extracted with 10% MeOH–$CHCl_3$. The extract was washed with brine and dried. Removal of the solvent followed by crystallization from benzene gave 4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylic acid (**7**, 6.84 g, 76%). mp 139—142°. IR ν_{max}^{KBr} cm^{-1}: 1730, 1605. UV λ_{max}^{EtOH} nm (log ε): 224 (4.59), 274 (sh, 3.88), 281 (3.89), 290 (3.79). MS *m/e*: no M$^+$, 240 (100%), 239 (47%), 170 (36%), 169 (48%). *Anal.* Calcd for $C_{16}H_{16}N_2O_3 \cdot 1/2H_2O$: C, 65.51; H, 5.84; N, 9.55. Found: C, 65.31; H, 6.04; N, 9.16.

The acid (**7**, 6.80 g) was subjected to pyrolysis at 180—200° under reduced pressure (20—25 mmHg) for 4 hr. The crude product was dissolved in 3% MeOH–$CHCl_3$, and the solution was washed with 2 N Na_2CO_3 then dried over K_2CO_3. After removing the solvent by evaporation, the residue was crystallized from EtOH to provide **8a** (5.01 g, 87%). mp 237—240°. Recrystallization from EtOH raised the melting point to 246—248° (lit.[5] 245—247.5°). IR ν_{max}^{KBr} cm^{-1}: 1600. MS *m/e*: 240 (M$^+$, 100%), 239 (51%), 170 (32%), 169 (47%). UV λ_{max}^{EtOH} nm (log ε): 223 (4.62), 274 (sh, 3.89), 281 (3.90), 290 (3.78).

2) A solution of **5a** (2.00 g), LiCl (0.54 g, 2 eq.) and water (0.13 ml, 1.1 eq.) in Me_2SO (10 ml) was refluxed for 4 hr under argon. The solvent was removed under reduced pressure, and the residue was shaken with $CHCl_3$ and water. The organic layer was washed with water, dried and concentrated. Crystallization of the residue from EtOH gave **8a** (1.37 g, 89%, mp 243—247°).

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (1)——$LiAlH_4$ (1.33 g) was added portionwise to a stirred suspension of **8a** (2.10 g) in dry THF (160 ml) over a period of 30 min in an ice bath. The mixture was refluxed for 2.5 hr under argon. After cooling, anhydrous Na_2SO_4 (0.8 g) was added, the mixture was stirred for 20 min and then water was added to decompose excess $LiAlH_4$. The mixture was filtered and the filtrate was concentrated. Crystallization of the resulting oil from benzene–hexane gave **1** (1.64 g, 83%). mp 152—153°. MS *m/e*: 226 (M$^+$, 78%), 225 (100%), 197 (23%), 170 (18%), 169 (25%). The fragmentation pattern in the MS spectrum of compound (**1**) was identical with the published data.[8]

Ethyl 3-Ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3,-*a*]quinolizine-3-carboxylate (5b)——Diethyl ethyl(2-formylethyl)malonate (**3b**,[4] 3.83 g) was added to a solution of **2** (2.08 g) in 80% AcOH (20 ml), and the solution was stirred overnight at room temperature under argon. After removing the solvent by evaporation, the residue was treated with EtOH (30 ml) and 25% K_2CO_3 (30 ml) for a day at room temperature. Colorless crystals that precipitated were filtered off and washed with aq.EtOH to give **5b** (1.81 g). The organic layer of the filtrate was concentrated and the residue was extracted with $CHCl_3$. The extract was dried and concentrated. Crystallization of the residue from ether–hexane gave **5b** (1.28 g); 70% total yield. An analytical sample was recrystallized from acetone: mp 173—183°. IR ν_{max}^{KBr} cm^{-1}: 1725, 1625. MS *m/e*: 340 (M$^+$, 60%), 265 (83%), 184 (100%). UV λ_{max}^{EtOH} nm (log ε): 224 (4.52), 274 (sh, 3.82), 280 (3.83), 290 (3.73). NMR δ: 0.90 (3H, t, J=7 Hz), 1.27 (3H, t, J=7 Hz), 4.20 (2H, q, J=7 Hz), 7.00—7.60 (4H, m, arom H), 8.48 (1H, s, NH). *Anal.* Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.30; H, 7.02; N, 7.99.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-4-one (8b)——Decarbethoxylation of **5b** (6.75 g) was carried out by the procedure used in the conversion of **5a** to **8a** with LiCl (1.64 g), water (0.43 ml) and Me_2SO (30 ml). The crude product was chromatographed on silica gel (50 g). Eluates with benzene/EtOAc (4: 1) gave the major lactam (**8b**, 2.73 g, 51%). mp 197—198° (ether–hexane). Eluates with benzene/EtOAc (3: 2) gave the minor lactam of **8b** (1.23 g, 23%). mp 198—200° (ether–hexane). Analytical samples were recrystallized from acetone. Major lactam (**8b**, less polar): mp 198—199°. IR ν_{max}^{KBr} cm^{-1}: 1605. MS *m/e*: 268 (M$^+$, 100%), 169 (46%). UV λ_{max}^{EtOH} nm (log ε): 224 (4.56), 274 (sh, 3.86), 281 (3.87), 290 (3.78). NMR δ: 0.96 (3H, t, J=7 Hz), 4.76 (1H, m), 5.16 (1H, m), 7.00—7.60 (4H, m, arom H), 8.36 (1H, s, NH). *Anal.* Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.14; H, 7.49; N, 10.35. Minor lactam (**8b**): mp 206—207°. IR ν_{max}^{KBr} cm^{-1}: 1600. MS *m/e*: 268 (M$^+$, 100%), 169 (41%). UV λ_{max}^{EtOH} nm (log ε): 224 (4.56), 274 (sh, 3.87), 280 (3.87), 290 (3.78). NMR δ: 0.96 (3H, t, J=7 Hz), 4.76 (1H, m), 5.14 (1H, m), 7.00—7.60 (4H, m, arom H), 8.50 (1H, s, NH). *Anal.* Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.00; H, 7.47; N, 10.35.

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