Synthetic Studies on the Lycopodium Alkaloids. IV. \(^1\) Total Synthesis of
\(dl\)-Anhydrolycodoline and \(dl\)-Lycopodine

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The total synthesis of \(dl\)-anhydrolycodoline is reported. The amino-ketone (3),
obtained from the amine (4) in four steps, was treated with acryl chloride to give the
amide (1). Unfortunately, the intramolecular Michael-type cyclization of 1 to the lactam
(9) for lycopodine did not take place for a stereoelectronic reason. Dehydration of 1
with conc. sulfuric acid afforded the anhydro-amide (10), which was cyclized in the presence
of sodium ethoxide and dicyclohexyl-18-crown-6 to give the tetracyclic lactam (11) in a
moderate yield. Reduction of 11 with lithium aluminum hydride followed by oxidation
with Jones reagent afforded \(dl\)-anhydrolycodoline.

Keywords—the Lycopodium alkaloids; anhydrolycodoline; lycopodine; lycopodine;
intramolecular Michael reaction; dicyclohexyl-18-crown-6; dehydration

The Lycopodium alkaloids with unique frameworks\(^9\) are attractive as synthetic targets
and have stimulated much synthetic effort which has culminated in the total syntheses of
annotinine,\(^5\) lycopodine,\(^9\) and serratinine\(^6\) in recent years. In the course of our synthetic
studies on these alkaloids, our preceeding communications have dealt with an approach
directed toward lycopodine\(^7\) and the total synthesis of anhydrolycodoline,\(^8\) which was isolated
from Lycopodium alopecuroides L. in 1968.\(^9\) We wish to describe in this paper the details of
the work, which also constitutes a formal total synthesis of lycopodine, since anhydrolycodyline was converted into it.\(^10\)

The initial goal of our synthesis was the acryl amide (1). Unfortunately, in our hand,
the urethane (2) reported previously\(^11\) could not be used for further purpose, since it resisted
all attempts to remove the amino protective group to get the amine (3). Hence the protective
group was changed to benzyloxycarbonyl group with success as follows.

Treatment of the amino-alcohol (4)\(^1\) with chlorobenzyl carbonate in the presence of
anhydrous potassium carbonate yielded the benzylo urethane (5) in 78% yield, which repro-
duced the starting amine on reduction with 10% Pd-C in atmospheric pressure of hydrogen.
Hydroboration of 5 followed by oxidation with hydrogen peroxide afforded the diol
(6) regio- and stereoselectively in 70% yield. The structure of 6 was unambiguously estab-
lished by the nuclear magnetic resonance (NMR) signal of its acetate (7) at 5.36 δ (m, half-

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band width \((W_{1/2})=28\) Hz due to the carbonyl hydrogen.\(^{11}\) Oxidation of 6 with Jones reagent gave the ketol (8) which showed the infrared (IR) bands at 3300 and 1700 \(\text{cm}^{-1}\). Reductive removal of the protective group of 8 with 10\% Pd-C proceeded to give 3 in 90\% yield. The desired acryl amide (1) was obtained, in 83\% yield, by reaction of 3 with acryl chloride in the presence of triethyl amine.\(^{11}\)

All attempts directed toward lycodoline were unfruitful, since the intramolecular Michael-type cyclization of 1 to the lactam (9) did not take place for the stereoelectronic reason discussed previously\(^{7,12}\): the base-catalyzed reactions recovered the starting material, and the acid-catalyzed ones gave complex mixtures of products.

At this stage, anhydrolcodoline was chosen as the target, because inspection of Dreiding model showed that the intramolecular cyclization of the anhydro-amide (10), if obtained, would satisfy the stereoelectronic requirement. Although dehydration of 1 with phenylphosphonic dichloride in pyridine\(^9\) gave an intractable mixture, it proceeded smoothly with conc. sulfuric acid in methylene dichloride to give 10 in 85\% yield. The intramolecular cyclization of 10 was attempted without success under various conditions in the presence of catalysts, \(\text{i.e.}\) \(p\)-toluenesulfonic acid, potassium tert-butoxide etc. Treatment of 10 with a catalytic amount of sodium ethoxide in boiling ethanol gave a mixture of the desired lactam (11) and the ethanol adduct (12) in 45\% and 31\% yields, respectively. The former was obtained exclusively, in 56\% yield, on treatment of 10 with a catalytic amount of sodium ethoxide and dicyclohexyl-18-crown-6 in boiling dimethylformamide. The structures of 11 and 12 were established from their IR, NMR and mass (MS) spectra. The former exhibited the IR bands at 1700 and 1620 \(\text{cm}^{-1}\), the NMR signal centered at 4.67 \(\delta\) (1H, d-\(\tau, J=10\) and 3 Hz) due to \(\text{C}_\text{α}\)-equatorial H deshielded by the lactam carbonyl, in addition to the disappearance of signals due to the acryl moiety, and the molecular ion (M\(^+\)) at \(m/e\) 259 in MS. On the other hand, the latter exhibited the IR bands at 1700 and 1640 \(\text{cm}^{-1}\), and the NMR signals at 1.18 \(\delta\) (3H, t, \(J=6\) Hz) and 3.50 \(\delta\) (2H, q, \(J=6\) Hz) due to the ethoxyl group which was confirmed by double resonance experiments, and M\(^+\) at \(m/e\) 305 in MS. Reduction of 11 with lithium aluminum hydride followed by oxidation with Jones reagent afforded

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**Experimental**

All melting points were measured with a microscopic hot-stage apparatus and are uncorrected. Unless otherwise stated IR spectra were measured for solution in CHCl₃ and NMR spectra were recorded for solution in CDCl₃ at 60 Mc using TMS as internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The MS spectra were taken with a Shimadzu LKB-9000. The organic extracts were dried over anhyd. MgSO₄ prior to evaporation. Column chromatography was performed on silica gel (Mallinckrodt) or alumina (Woelm W-200, neutral).

**Benzyl 2,3,4,4a,5,β,6,8-Hexahydro-4aa-hydroxy-10a-methyl-1H,5,8aa-propanoquinoline-1-carboxylate (5)**

— A suspension of the amino-alcohol (4; 207 mg), chlorobenzyl carbonate (1 ml) and anhyd. K₂CO₃ (1 g) in dry C₅H₅ (25 ml) was refluxed for 6 hr. After cooling and removing inorganic substances, the organic layer was washed with brine, dried and evaporated to give a residue (403 mg), which was subjected to chromatography on alumina (5 g). Elution with C₅H₅ afforded 265 mg (78%) of 5 as a colorless solid, which was recrystallized from n-hexane as colorless leaflets, mp 85.5—86°C. IR νmax cm⁻¹: 3350 (OH), 1685 (urethane). NMR δ: 0.86 (3H, d, J=6 Hz, CH-CH₃), 1.03 (1H, s, OH, disappeared with D₂O), 5.00 (2H, s, CH₂CH₂H), 5.56 (2H, m, -CH₂-C=CH-), 7.24 (5H, s, C₅H₅). MS m/e: 341 (M⁺). Anal. Calcd. for C₂₂H₂₃NO: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.85; H, 7.89; N, 4.09.

**Benzyl 2,3,4a,5β,6,7,8-Octahydro-4aa-hydroxy-10a-methyl-1H,5,8aa-propanoquinoline-1-carboxylate (6)**

— To a stirred mixture flushed with N₂ of 5 (450 mg) and NaBH₄ (401 mg) in dry THF (39 ml), was added a solution of freshly distilled BF₃-etherate (1.64 ml) in dry THF (3 ml) at room temperature over a period of 1 hr followed by stirring for 1 hr. Before this was added carefully H₂O (4 ml) and then 3 N NaOH (4 ml) with ice-cooling, 50% H₂O₂ (4 ml) followed by stirring at 40°C for 2 hr. After adding brine (100 ml), the mixture was extracted with AcOEt thoroughly and the extract was washed with brine, dried and evaporated to give a residue (320 mg), which showed two main spots on thin-layer chromatography indicating the contamination by the regioisomer (the 6β-ol isomer). Recrystallization of the solid from n-hexane-acetone gave 300 mg (70%) of 6 as colorless needles, mp 186—187°C. IR νmax cm⁻¹: 3600, 3350 (OH), 1680 (urethane). NMR δ: 0.86 (3H, d, J=4 Hz, CH-CH₃), 2.14 (2H, s, OH, disappeared with D₂O), 4.96 (2H, s, CH₂CH₂H), 7.21 (5H, s, C₅H₅). MS m/e: 350 (M⁺). Anal. Calcd. for C₂₃H₂₄NO: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.81; H, 7.88; N, 3.77.

Its acetate (7) obtained in the usual manner showed the following data. NMR δ: 0.83 (3H, d, J= 5 Hz, CH-CH₃), 1.79 (1H, s, OH), 1.91 (2H, s, COCH₂), 4.98 (2H, s, CH₂CH₂H), 5.36 (1H, m, W₁/₂=28 Hz, CH-OCCH₃), 7.24 (5H, s, C₅H₅). MS m/e: 401 (M⁺). Found: C, 69.81; H, 7.88; N, 3.77.

**Benzyl 2,3,4,4a,5β,6,7,8-Octahydro-4aa-hydroxy-10a-methyl-7-oxo-1H,5,8aa-propanoquinoline-1-carboxylate (8)**

— To a stirred solution of 6 (260 mg) in purified acetic anhydride (5 ml) was added dropwise Jones reagent (0.25 ml) with ice-cooling, and the mixture was continued for 15 min at room temperature. After decomposing the excess oxidant with MeOH, the mixture was extracted with CHCl₃. The dried solvent was evaporated to give a brown solid (240 mg), which was subjected to chromatography on silica gel. Elution with CHCl₃ afforded 220 mg (82%) of 8, which was recrystallized from n-hexane-acetone as colorless leaflets, mp 146—149°C. IR νmax cm⁻¹: 3425 (OH), 1662 (urethane). NMR δ: 0.82 (3H, fused d, CH-CH₃), 2.28 (1H, s, OH), 5.00 (2H, s, CH₂CH₂H), 7.24 (5H, s, C₅H₅). MS m/e: 365 (M⁺). Its 2,4-dinitrophenylhydrazone was prepared in the usual manner as orange-red crystals from AcOEt, mp 233—234°C.

**Benzyl 2,3,4,4a,5β,6,7,8-Octahydro-4aa-hydroxy-10a-methyl-7-oxo-1H,5,8aa-propanoquinoline (3)**

— A solution of 8 (733 mg) in EtOH (40 ml) was hydrogenated in the presence of 10% Pd-C (80 mg) at atmospheric pressure of hydrogen until absorption of gas ceased. Removing the catalyst and evaporation of the solvent gave a solid mass (427 mg), which was recrystallized from n-hexane-acetone to give colorless needles, mp 168—169°C. IR νmax cm⁻¹: 3450 (broad, OH and NH), 1700 (CO). Anal. Calcd. for C₂₄H₂₃NO: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.07; H, 9.51; N, 6.17.

**1-Acryl-2,3,4,4a,5β,6,7,8-octahydro-4aa-hydroxy-10a-methyl-7-oxo-1H,5,8aa-propanoquinoline (1)**

— To a stirred solution of 3 (170 mg) and triethylamine (0.2 ml) in CHCl₃ (10 ml) was added dropwise a solution of acryl chloride (110 mg) in CHCl₃ (3 ml) with ice-cooling. The mixture was stirred at room temperature overnight, washed with brine, dil. HCl and buffer, and dried. Evaporation of the solvent gave a solid mass, which was recrystallized from n-hexane-C₅H₅ to afford 104 mg (83%) of 1 as colorless needles, mp 201—202°C. IR νmax cm⁻¹: 3300 (OH), 1700 (CO), 1640 (amide), 1610 (C=O). NMR δH: 5.50 (1H, d-d, J=10 and 3 Hz, \( \text{H} \)), 5.87 (1H, d-d, J=18 and 3 Hz, \( \text{H} \)), 6.60 (1H, d-d, \( \text{H} \)), 7.07 (5H, s, C₅H₅), 7.24 (5H, s, C₅H₅), 7.24 (5H, s, C₅H₅). MS m/e: 341 (M⁺). Anal. Calcd. for C₂₄H₂₄NO: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.85; H, 7.89; N, 4.09.
$J=18$ and 10 Hz.  $\text{C}=\text{C}\text{H}$.  MS m/e: 277 (M$^+$).  Anal. Calcd. for C$_{14}$H$_{23}$NO$_3$: C, 69.28; H, 8.36; N, 7.34.
5.05.  Found: C, 69.55; H, 8.46; N, 5.18.

1-Acryl-2,3,5,6,7,8-hexahydro-10a-methyl-7-oxo-1H-5,8aa-propanoquinoline (10) —— A solution of 1 (200 mg) in CH$_2$Cl$_2$ (30 ml) was added dropwise with conc. H$_2$SO$_4$ (0.3 ml) with ice-cooling and the mixture was stirred at the same temperature for 3 hr and then at room temperature for 2 hr. The mixture was washed with brine, sat. NaHCO$_3$ and brine, and dried. Evaporation of the solvent gave a brown residue (194 mg), which was subjected to chromatography on silica gel. Elution with CHCl$_3$ afforded 160 mg (85%) of 10, which was recrystallized from n-hexane as colorless plates, mp 110—111°C. IR $\nu_{\text{max}}$ cm$^{-1}$: 1700 (CO), 1640 (amide), 1610 (C=C). NMR $\delta$: 0.90 (3H, d, $J=5.5$ Hz, CH-CH$_3$), 5.68 (1H, d-d, $J=3$ and 10 Hz, $\text{C}=\text{C}\text{H}$), 5.92 (1H, t, $J=5$ Hz, C=CH-CH$_3$), 6.18 (1H, d-d, $J=3$ and 18 Hz, $\text{C}=\text{C}\text{H}$), 6.67 (1H, H$^\prime$). MS m/e: 259 (M$^+$). Anal. Calcd. for C$_{15}$H$_{24}$NO$_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.09; H, 8.05; N, 5.20.

The Intramolecular Cyclization of 10 with Sodium Ethoxide (11) and (12) —— A solution of 10 (100 mg) in EtOH (50 ml) was heated under reflux in the presence of a catalytic amount of freshly prepared NaOEt for 12 hr. After concentrating the solvent, the residue was extracted with CHCl$_3$ and the extract was washed with brine and dried. Evaporation of the solvent gave a brown residue (100 mg), which was subjected to chromatography on alumina (2 g). Elution with CH$_2$Cl$_2$ gave 36 mg (31%) of the ethanol adduct (12) in the earlier elute and 45 mg (45%) of the lactam (11) in the later eluate. The lactam (11) was recrystallized from isopropyl ether to afford colorless plates, mp 182—184°C. MS m/e: 259 (M$^+$). IR $\nu_{\text{max}}$ cm$^{-1}$: 1700 (CO), 1620 (lactam). NMR $\delta$: 0.83 (SH, fused d, CH-CH$_3$), 5.79 (1H, t, $J=5$ Hz, C=CH), 4.67 (1H, d-d, $J=10$ and 10 Hz, C$_6$-equatorial H). Anal. Calcd. for C$_{15}$H$_{24}$NO$_3$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.09; H, 7.90; N, 5.15. The ethanol adduct (12); MS m/e: 305 (M$^+$). IR $\nu_{\text{max}}$ cm$^{-1}$: 1700 (CO), 1640 (amide), 1200 (C-O-C). NMR $\delta$: 0.90 (3H, d, $J=5.5$ Hz, CH-CH$_3$), 1.18 (3H, t, $J=6$ Hz, OCH$_2$CH$_3$), 3.50 (2H, q, $J=6$ Hz, OCH$_2$CH$_3$), 5.82 (1H, t, $J=4.5$ Hz, C=CH$_3$).

**dl-1-Oxohydrocodoline (11)** —— A mixture of 10 (77 mg) and a catalytic amount of freshly prepared NaOEt and dicyclohexyl-18-crown-6 in dry DMF (30 ml) was heated under N$_2$ at 160°C for 24 hr. After evaporating DMF in vacuo, the residue was extracted with CHCl$_3$, and the extract was washed with brine, and dried. Evaporation of the solvent gave a brown oil, which was subjected to chromatography on silica gel (2 g). Elution with CHCl$_3$ gave 43 mg (56%) of 11, which was identical with that mentioned above.

**dl-Anhydrohydrocodoline** —— A suspension of 11 (101 mg) and lithium aluminum hydride (35 mg) in dry dioxane (40 ml) was heated with stirring under N$_2$ at 100—105°C for 10 hr. After decomposing the excess reducing agent with an aqueous solution of potassium sodium tartrate, the inorganic substances were filtered off and the mother liquor was concentrated. The residue was extracted with CHCl$_3$ and the extract was washed with brine, and dried. Evaporation of the solvent gave an oily residue (71 mg), which showed no carbonyl absorption in the IR spectrum and turned dark on exposure to air. The crude alcohol was oxidized with Jones reagent (0.15 ml) at ice-cooling temperature and the mixture was stirred at room temperature for 5 min. After adding H$_2$O (5 ml) and making alkaline with K$_2$CO$_3$, the mixture was extracted with CHCl$_3$, and the extract was washed with brine, and dried. Evaporation of the solvent gave 60 mg (64%) of a brown residue, which showed almost no impurity on TLC. It was subjected to chromatography on alumina (1.5 g). Elution with C$_2$H$_5$OH afforded 31 mg of dl-anhydrohydrocodoline, which solidified on standing and melted at 86—91°C, but turned dark on exposure to air with decomposition. IR $\nu_{\text{max}}$ cm$^{-1}$: 2700—2850 (Bohmann bands), 1703 (CO). NMR $\delta$: 0.79 (3H, d, $J=5$ Hz, CH-CH$_3$), 5.59 (1H, t, $J=4$ Hz, C-CH$_3$). MS m/e: 245 (M$^+$). Its hydrochloride was recrystallized from isopropyl ether—MeOH as colorless plates, mp 204—205.5°C (dec.). Anal. Calcd. for C$_{19}$H$_{24}$ClNO: C, 68.19; H, 8.59; N, 4.97. Found: C, 67.87; H, 8.16; N, 4.74.

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