[Chem. Pharm. Bull. 26(10)3150—3153(1978)]

UDC 547.944.057 : 547.594.3.04

Synthetic Studies on the Lycopodium Alkaloids. IV.[1] Total Synthesis of *dl*-Anhydrolycodoline and *dl*-Lycopodine

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(Received June 19, 1978)

The total synthesis of *dl*-anhydrolycodoline is reported. The amino-ketone (**3**), obtained from the amine (**4**) in four steps, was treated with acrylyl chloride to give the amide (**1**). Unfortunately, the intramolecular Michael-type cyclization of **1** to the lactam (**9**) for lycodoline 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; lycodoline; intramolecular Michael reaction; dicyclohexyl-18-crown-6; dehydration

The Lycopodium alkaloids with unique frameworks[3] are attractive as synthetic targets and have stimulated much synthetic effort which has culminated in the total syntheses of annotinine,[4] lycopodine,[5] 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 lycodoline[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 anhydrolycodoline was converted into it.[10]

The initial goal of our synthesis was the acrylyl amide (**1**). Unfortunately, in our hand, the urethane (**2**) reported previously[1] 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 benzyl urethane (**5**) in 78% yield, which reproduced 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 established by the nuclear magnetic resonance (NMR) signal of its acetate (**7**) at 5.36 δ (m, half-

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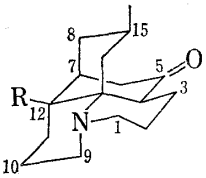
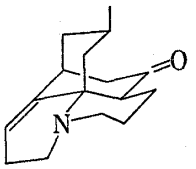
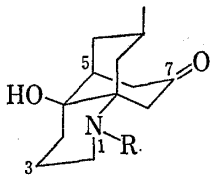


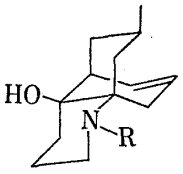
lycopodine (R=H)
lycodoline (R=OH)



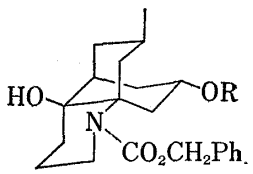
anhydrolycodoline



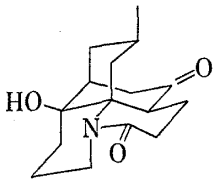
1 : R=COCH=CH$_2$
2 : R=CO$_2$Et
3 : R=H
8 : R=CO$_2$CH$_2$Ph



4 : R=H
5 : R=CO$_2$CH$_2$Ph



6 : R=H
7 : R=Ac



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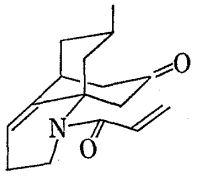

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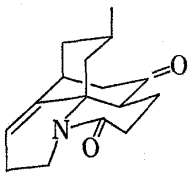

11

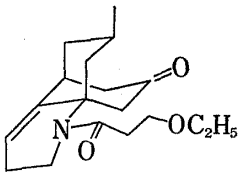

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Chart 1

band width ($W_{1/2}$)=28 Hz) due to the carbinyl hydrogen.[1] Oxidation of **6** with Jones reagent gave the ketol (**8**) which showed the infrared (IR) bands at 3300 and 1700 cm^{-1}. Reductive removal of the protective group of **8** with 10% Pd-C proceeded to give **3** in 90% yield. The desired acrylyl amide (**1**) was obtained, in 83% yield, by reaction of **3** with acrylyl 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, anhydrolycodoline 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[8] gave an intractable mixture, it proceeded smoothly with conc. sulfuric acd 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, *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 cm^{-1}, the NMR signal centered at 4.67 δ (1H, d-t, J=10 and 3 Hz) due to C$_9$-equatorial H deshielded by the lactam carbonyl, in addition to the disappearance of signals due to the acrylyl 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 cm^{-1}, and the NMR signals at 1.18 δ (3H, t, J=6 Hz) and 3.50 δ (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

11) H. Dugas, M.E. Hazenberg, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, **1967**, 4931.
12) T. Momose *et al.* discussed minutely on the cyclization of some simple octahydro-7(1H)-quinolones. See, T. Momose, S. Uchida, and T. Imanishi, *Chem. Pharm. Bull.* (Tokyo), **26**, 972 (1978).

dl-anhydrolycodoline in 63% yield, which solidified on standing, but turned dark on exposure to air with decomposition. Its IR spectrum in carbon tetrachloride was identical with that of the natural base.

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 $CHCl_3$ and NMR spectra were recorded for solution in $CDCl_3$ 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. $MgSO_4$ prior to evaporation. Column chromatography was performed on silica gel (Mallinckrodt) or alumina (Woelm W-200, neutral).

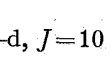
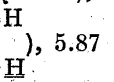
Benzyl 2,3,4,4a,5β,8-Hexahydro-4aα-hydroxy-10α-methyl-1H-5,8aα-propanoquinoline-1-carboxylate (5)——A suspension of the amino-alcohol (**4**; 207 mg), chlorobenzyl carbonate (1 ml) and anhyd. K_2CO_3 (1 g) in dry C_6H_6 (25 ml) was refluxed for 6 hr. After cooling and removing inorganic substances, the 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 C_6H_6 afforded 265 mg (78%) of **5** as a colorless solid, which was recrystallized from *n*-hexane as colorless leaflets, mp 85.5—86°. IR ν_{max} cm^{-1}: 3350 (OH), 1685 (urethane). NMR δ: 0.86 (3H, d, J=6 Hz, CH–C$\underline{H}_3$) 1.93 (1H, s, O$\underline{H}$, disappeared with D_2O), 5.00 (2H, s, C$\underline{H}_2C_6H_5$), 5.56 (2H, m, –C$\underline{H}$=C$\underline{H}$–), 7.24 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 341 (M^+). *Anal.* Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.65; H, 7.89; N, 4.09.

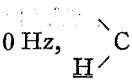
Benzyl 2,3,4,4a,5β,6,7,8-Octahydro-4aα,7β-dihydroxy-10α-methyl-1H-5,8aα-propanoquinoline-1-carboxylate (6)——To a stirred mixture flushed with N_2 of **5** (450 mg) and $NaBH_4$ (491 mg) in dry THF (39 ml), was added a solution of freshly distilled BF_3-etherate (1.64 ml) in dry THF (3 ml) at room temperature over a period of 1 hr followed by stirring for 1 hr. To this was added carefully H_2O (4 ml) and then 3 N NaOH (4 ml) with ice-cooling, 30% H_2O_2 (4 ml) followed by stirring at 40° 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 (520 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 330 mg (70%) of **6** as colorless needles, mp 186—187°. IR ν_{max} cm^{-1}: 3600, 3350 (OH), 1680 (urethane). NMR δ: 0.86 (3H, d, J=4 Hz, CH–C$\underline{H}_3$), 2.14 (2H, s, O$\underline{H}$, disappeared with D_2O), 4.96 (2H, s, C$\underline{H}_2C_6H_5$), 7.21 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 359 (M^+). *Anal.* Calcd. for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.81; H, 7.88; N, 3.77.

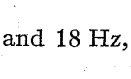
Its acetate (**7**) obtained in the usual manner showed the following data. NMR δ: 0.88 (3H, d, J=5 Hz, CH–C$\underline{H}_3$), 1.79 (1H, s, O$\underline{H}$), 1.91 (3H, s, COC$\underline{H}_3$), 4.98 (2H, s, C$\underline{H}_2C_6H_5$), 5.36 (1H, m, $W_1/_2$=28 Hz, C$\underline{H}$–OAc), 7.24 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 401 (M^+).

Benzyl 2,3,4,4a,5β,6,7,8-Octahydro-4aα-hydroxy-10α-methyl-7-oxo-1H-5,8aα-propanoquinoline-1-carboxylate (8)——To a stirred solution of **6** (260 mg) in purified acetone (5 ml) was added dropwise Jones reagent (0.25 ml) with ice-cooling and the stirring was continued for 15 min at room temperature. After decomposing the excess oxidant with MeOH, the mixture was extracted with $CHCl_3$. The dried solvent was evaporated to give a brown solid (240 mg), which was subjected to chromatography on silica gel. Elution with $CHCl_3$ afforded 220 mg (82%) of **8**, which was recrystallized from *n*-hexane–acetone as colorless leaflets, mp 146—149°. IR ν_{max}^{KBr} cm^{-1}: 3425 (OH), 1662 (urethane). NMR δ: 0.82 (3H, fused d, CH–C$\underline{H}_3$), 2.28 (1H, s, O$\underline{H}$) 5.00 (2H, s, C$\underline{H}_2C_6H_5$), 7.24 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 365 (M^+). Its 2,4-dinitrophenylhydrazone was prepared in the usual manner as orange-red crystals from AcOEt, mp 233—234°. *Anal.* Calcd. for $C_{27}H_{31}N_5O_7$: C, 60.32; H, 5.81; N, 13.03. Found: C, 60.35; H, 5.78; N, 13.23.

2,3,4,4a,5β,6,7,8-Octahydro-4aα-hydroxy-10α-methyl-7-oxo-1H-5,8aα-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°. IR ν_{max} cm^{-1}: 3450 (broad, OH and NH), 1700 (CO). *Anal.* Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.07; H, 9.51; N, 6.17.

1-Acrylyl-2,3,4,4a,5β,6,7,8-octahydro-4aα-hydroxy-10α-methyl-7-oxo-1H-5,8aα-propanoquinoline (1)——To a stirred solution of **3** (170 mg) and triethylamine (0.2 ml) in $CHCl_3$ (10 ml) was added dropwise a solution of acrylyl chloride (110 mg) in $CHCl_3$ (3 ml) with ice-cooling. The mixture was stirred at room temperature overnight, washed with brine, dil. HCl and brine, and dried. Evaporation of the solvent gave a solid mass, which was recrystallized from *n*-hexane–C_6H_6 to afford 104 mg (83%) of **1** as colorless needles, mp 201—202°. IR ν_{max} cm^{-1}: 3300 (OH), 1700 (CO), 1640 (amide), 1610 (C=C). NMR δ^{DMSO-d_6}: 0.82 (3H, fused d, CH–C$\underline{H}_3$), 5.50 (1H, d–d, J=10 and 3 Hz, ), 5.87 (1H, d–d, J=18 and 3 Hz, ), 6.60 (1H, d–d,

J=18 and 10 Hz, ). MS *m/e*: 277 (M^+). *Anal.* Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.55; H, 8.46; N, 5.18.

1-Acrylyl-2,3,5β,6,7,8-hexahydro-10α-methyl-7-oxo-1H-5,8aα-propanoquinoline (10)——To a stirred solution of **1** (200 mg) in CH_2Cl_2 (30 ml) was added dropwise conc. H_2SO_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°. IR ν_{max} cm^{-1}: 1700 (CO), 1640 (amide), 1610 (C=C). NMR δ: 0.90 (3H, d, J=5.5 Hz, CH–C<u>H</u>$_3$), 5.68 (1H, d–d, J=3 and 10 Hz,), 5.92 (1H, t, J=5 Hz, C=C<u>H</u>–CH_2–), 6.18 (1H, d–d, J=3 and 18 Hz, ), 6.67 (1H, d–d, J=10 and 18 Hz, ). MS *m/e*: 259 (M^+). *Anal.* Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.05; 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 C_6H_6 gave 36 mg (31%) of the ethanol adduct (**12**) in the earlier eluate 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°. MS *m/e*: 259 (M^+). IR ν_{max} cm^{-1}: 1700 (CO), 1620 (lactam). NMR δ: 0.83 (3H, fused d, CH–C<u>H</u>$_3$), 5.79 (1H, t, J=5 Hz, C=C<u>H</u>), 4.67 (1H, d–t, J=10 and 3 Hz, C_9-equatorial H). *Anal.* Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.09; H, 7.99; N, 5.15. The ethanol adduct (**12**): MS *m/e*: 305 (M^+). IR ν_{max} cm^{-1}: 1700 (CO), 1640 (amide), 1200 (C–O–C). NMR δ: 0.90 (3H, d, J=5.5 Hz, CH–C<u>H</u>$_3$), 1.18 (3H, t, J=6 Hz, OCH_2C<u>H</u>$_3$), 3.50 (2H, q, J=6 Hz, O<u>C</u>H_2CH_3), 5.82 (1H, t, J=4.5 Hz, C=C<u>H</u>).

***dl*-1-Oxo-anhydrolycodoline (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° 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*-Anhydrolycodoline**——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° 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_2O (5 ml) and making alkaline with K_2CO_3, the mixture was extracted with CH_2Cl_2 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_6H_6 afforded 31 mg of *dl*-anhydrolycodoline, which solidified on standing and melted at 86—91°, but turned dark on exposure to air with decomposition. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2700—2850 (Bohlmann bands), 1703 (CO). NMR δ: 0.79 (3H, d, J=5 Hz, CH–C<u>H</u>$_3$), 5.59 (1H, t, J=4 Hz, C–C<u>H</u>). MS *m/e*: 245 (M^+). Its hydrochloride was recrystallized from isopropyl ether–MeOH as colorless plates, mp 204—205.5° (dec.). *Anal.* Calcd. for $C_{16}H_{24}ClNO$: C, 68.19; H, 8.59; N, 4.97. Found: C, 67.87; H, 8.16; N, 4.74.

Acknowledgement The authors are indebted to Professor W.A. Ayer, University of Alberta, for the IR spectrum of natural anhydrolycodoline. This work was supported in part by a Grant-in Aid for Scientific Research from The Ministry of Education, Science and Culture.