LYCOPODIUM ALKALOIDS

VII.[1] LYCODOLINE (ALKALOID L.8)[2,3]

W. A. AYER AND G. G. IVERACH
Department of Chemistry, University of Alberta, Edmonton, Alberta

Received July 15, 1964

ABSTRACT

Lycodoline (alkaloid L.8) is shown to have the structure and stereochemistry depicted in II. The transformation of lycodoline into lycopodine is described. The use of infrared spectroscopy in assigning the configuration at C-12 and the nitrogen in these and related alkaloids is described. The effect of the configuration at C-12 on the optical rotatory dispersion spectra and on the mass spectra of lycopodine (I) and 12-epilycopodine (X) is discussesd.

Lycopodium alkaloid L.8, for which we have chosen the name lycodoline, was first isolated by Manske and Marion in 1943 from *L. annotinum* Linn. (1). This substance is of particular interest since it is one of the most widely distributed of the minor alkaloids of the Lycopodiaceae, having also been isolated from *L. annotinum* var. *acrifolium* (2) (the substance as isolated from this species was originally designated alkaloid L.30, but it was later shown (3) that L.30 is identical with L.8), *L. selago* (4), *L. fawcettii* (5), *L. lucidulum* (6), *L. clavatum* (7, 8), and *L. prostratum* (9). The lycodoline used in this investigation was isolated from *L. annotinum* and was identical with an authentic sample of alkaloid L.8 provided by R. H. Manske.

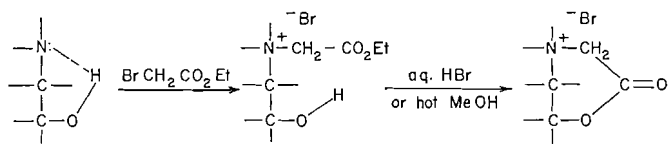
Earlier workers had established that lycodoline has the molecular formula $C_{16}H_{25}O_2N$ (1, 2, 4, 5, 10), that the oxygens are present as a ketonic carbonyl group and a hydroxyl group (10), and that the nitrogen is tertiary (5, 10). Our analytical and spectroscopic data confirmed these conclusions and, in addition, revealed the presence of a secondary C–methyl group (0.68 mole of volatile acid on Kuhn–Roth oxidation, doublet at 9.14 τ in the nuclear magnetic resonance (n.m.r.) spectrum). Lack of olefinic absorption in the n.m.r. spectrum, coupled with the fact that lycodoline is recovered unchanged on attempted catalytic hydrogenation, leads to the conclusion that there are no carbon–carbon double bonds and that the molecule is tetracyclic.

The environment of the carbonyl group in lycodoline was defined in the following manner. The infrared spectrum, measured in CCl_4, showed absorption at 1703 cm^{-1}, accompanied by a band at 1410 cm^{-1}, indicative of the grouping —CO—CH_2— (11). Neither of these absorption bands was present in dihydrolycodoline ($C_{16}H_{27}O_2N$), the product obtained by lithium aluminum hydride reduction of the carbonyl group. Dehydration of dihydrolycodoline with thionyl chloride in methylene chloride at room temperature yielded anhydrodihydrolycodoline ($C_{16}H_{25}ON$), which showed a single olefinic proton at 4.56 τ (mult.) in its n.m.r. spectrum. Since it will be shown that the hydroxyl group lost in the dehydration is that one produced in the reduction of the keto group, then, provided that no rearrangement has occurred during the dehydration, the grouping —CH—CO—CH_2— must be present in lycodoline.

Concerning the environment of the nitrogen and hydroxyl group, it was found that

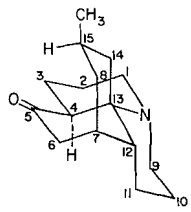
[1]*Part VI, W. A. Ayer, A. N. Hogg, and A. C. Soper. Can. J. Chem. 42, 949 (1964).*
[2]*A portion of this work was reported in a preliminary communication: W. A. Ayer and G. G. Iverach. Tetrahedron Letters, No. 3, 87 (1961).*
[3]*Taken in part from the Ph.D. thesis of G. G. Iverach, University of Alberta, 1963; presented at the XIXth International Congress of Pure and Applied Chemistry, London, July 10–17, 1963.*

lycodoline was resistant to both acetylation and mild oxidation (CrO_3–pyridine, CrO_3–acetic acid), suggesting that the hydroxyl as well as the nitrogen was tertiary. The position of the —OH stretching vibration in the infrared spectra of lycodoline and its derivations was especially informative. The infrared spectrum of lycodoline, measured in dilute carbon tetrachloride, showed a concentration-independent band at 3545 cm^{-1}. It is known (12) that intramolecular hydrogen bonding causes a concentration-independent shift of the —OH stretching vibration from the non-bonded 3615–3635 cm^{-1} region to lower frequency. In this case, we attribute the shift to intramolecular hydrogen bonding between the hydroxyl group and the tertiary nitrogen. The alternate possibility, that the association is between the hydroxyl group and the ketonic carbonyl group, was ruled out by the observation that dihydrodeoxylycodoline (in which the carbonyl group has been converted to a methylene group by Wolff–Kishner reduction) also shows H-bonded hydroxyl absorption (3545 cm^{-1}). Dihydrolycodoline showed —OH stretching vibrations at 3625 cm^{-1} (non-bonded) and 3550 cm^{-1} (H-bonded), while its dehydration product, anhydrodihydrolycodoline, displayed only the H-bonded absorption (3565 cm^{-1}), showing that it is the original hydroxyl group of lycodoline which is retained in the dehydration product. These studies indicate that the hydroxyl group and the nitrogen are in close proximity to one another. The fact that they are vicinal was shown in the following manner: reaction of lycodoline with ethyl bromoacetate gave a salt (A) which showed absorption in the infrared (Nujol) at 3240, 1753, and 1717 cm^{-1}, attributable to hydroxyl, ester carbonyl, and ketonic carbonyl stretching vibrations, respectively. Hydrolysis of the ester salt (A) with aqueous hydrobromic acid gave a lactone salt (B), which showed no hydroxyl absorption in the infrared, but showed carbonyl bands at 1756 (lactone) and 1705 (ketone) cm^{-1}. The lactone salt also formed to some extent when the ester was recrystallized from hot methanol. The ease of formation of the lactone, coupled with the fact that the lactonic carbonyl absorbs at essentially the same frequency as the ester carbonyl, strongly suggests that the lactone is six-membered. An analogous pair of salts was prepared from dihydrodeoxylycodoline. In this case the ester absorbed at 1747 cm^{-1} and the lactone at 1754 cm^{-1}, confirming the assignments made above.

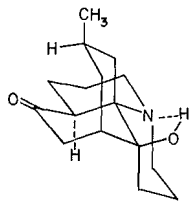


With these structural features established, it seemed possible that lycodoline might be very simply related to lycopodine (I), the most commonly occurring *Lycopodium* alkaloid. Replacement of the C-12 hydrogen in lycopodine by hydroxyl leads to a structure (II) which incorporates all of the features of lycodoline defined to this point. Structure III, the C-12 epimer of II, would also fit the evidence presented so far. The optical rotatory dispersion curve for lycodoline was positive and very similar to that of lycopodine (13). Since, however, the Octant Rule (14) states that substituents at C-4 of the carbonyl-containing ring have little or no effect on the dispersion curve, it was not possible to exclude structure III on this basis.

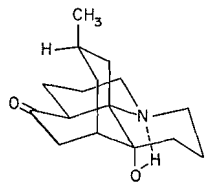
Evidence that lycodoline does indeed have the carbon–nitrogen skeleton shown in II and III was obtained in the following manner. Dihydrodeoxylycodoline, the product of



I.

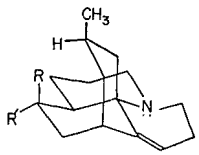


II.

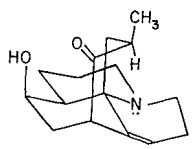


III.

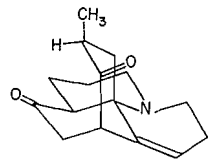
Wolff–Kishner reduction of lycodoline, was dehydrated with phosphorus pentoxide in refluxing toluene. The product, anhydrodihydrodeoxylycodoline (IV), could not be obtained in crystalline form, but was conveniently isolated and characterized in the form of its hydrochloride. The free base showed no hydroxyl absorption in the infrared and a single olefinic proton at 4.64 τ (poorly resolved triplet) in its n.m.r. spectrum. Oppenauer oxidation of acrifoline (V) (15) gave the diketone VI, which was assigned the stereochemistry shown, since the transformation of C-5 from tetrahedral to trigonal should remove the non-bonded interaction which forces ring D into a boat conformation (16) and since the equilibrating conditions of the reaction should then favor the equatorial conformation for the methyl group. Wolff–Kishner reduction of the diketone VI yielded anhydrodihydrodeoxylycodoline (IV), confirming the proposed skeleton. Since the Wolff–Kishner reduction does not necessarily lead to the most stable of two possible epimers (17), this result does not establish the configuration at C-15.



IV. R = R′ = H
IX. R = R′ = O



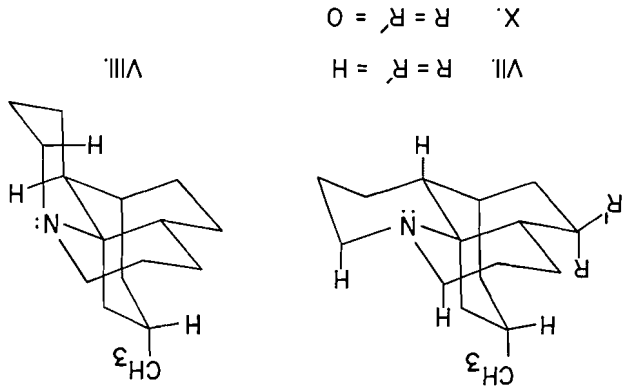
V.



VI.

Catalytic hydrogenation of the olefin IV gave a mixture of the saturated amines VII (major product) and VIII, which was separable by chromatography. Compound VIII, in the form of its methiodide, was identical with dihydrodeoxylycopodine (13), the product of Wolff–Kishner reduction of lycopodine, thus rigorously establishing the carbon–nitrogen skeleton as well as the configuration at C-15. Compound VII, the major product of the reduction formed by addition of hydrogen from the less hindered side of the olefin IV, was also prepared from dihydroacrifoline (15, 16) by Oppenauer oxidation, followed by Wolff–Kishner reduction of the previously reported (16, 18) diketone.

The amines VII and VIII showed significant differences in their infrared spectra in the C—H stretching region. Bohlmann has pointed out (19, 20) that a series of absorption bands between 2700 and 2850 cm^{-1} are prominent in the infrared spectra of quinolizidine derivatives, in which at least two hydrogens *alpha* to the nitrogen are oriented *trans* diaxial to the electron pair on the nitrogen. In agreement with this generalization, amine VII shows well-developed bands in this region (Fig. 1) while the amine VIII does not. This observation provides us with a method for distinguishing between compounds which are epimeric at C-12 (and hence at the nitrogen), and thus between structures II and III for lycodoline. As shown in Fig. 2, lycodoline does not display these prominent bands and



thus must possess structure II. Compounds with a double bond in the 11,12-position are free to take up either conformation about the nitrogen. Acrifoline (V) (Fig. 2), the olefin IV, and the diketone VI show prominent bands in the 2700–2850 cm^{-1} region, and hence must exist largely in the conformation shown. The formation of the epimers VII and VIII in the hydrogenation of anhydrodihydrodeoxylycodoline (IV) provides further evidence for the location of the double bond in IV, and thus the hydroxyl group in lycodoline.

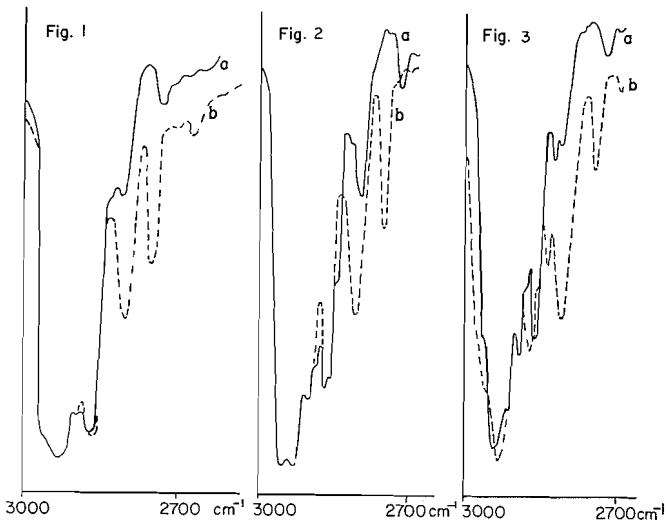


FIG. 1. Infrared spectrum of (*a*) the amine VIII, (*b*) the amine VII.
FIG. 2. Infrared spectrum of (*a*) lycodoline, (*b*) acrifoline.
FIG. 3. Infrared spectrum of (*a*) lycopodine, (*b*) 12-epilycopodine.

In order that we might more firmly establish the position of the carbonyl group in lycodoline, we now sought to transform lycodoline (II) directly into lycopodine (I). Dehydration of lycodoline with phenylphosphoric dichloride–pyridine gave anhydrolycodoline (IX) in 90% yield. Anhydrolycodoline was an unstable oil that was characterized by means of its mass spectrum (Fig. 4*a*). The n.m.r. spectrum showed a single olefinic proton at 4.44 τ (triplet, J = 3.5 c.p.s.) and the infrared spectrum (CCl_4) showed carbonyl absorption at 1698 cm^{-1} and C=C absorption at 1650 cm^{-1}. Catalytic hydrogenation of the perchlorate of IX, followed by liberation of the bases and chromatography over

alumina, gave a mixture of lycopodine (isolated in 10% yield) and 12-epilycopodine (isolated in 65% yield). 12-Epilycopodine (X) displayed well-developed bands in the 2700–2850 cm^{-1} region (see Fig. 3) as expected for the *trans*-quinolizidine system. The infrared spectrum of lycopodine is shown in Fig. 3 for comparison.

Unexpectedly, the optical rotatory dispersion curve for compound X showed a negative Cotton effect (extrema at 306 and 265 mμ, amplitude $-5100°$). Since the absolute configuration of lycopodine has been ascertained (6, 21), the cause of this anomoly is not readily apparent, but the fact that lycodoline shows a positive curve similar to that of lycopodine, whereas the C-12,N epimer X shows a negative Cotton curve, serves further to exclude structure III as a possibility for lycodoline.

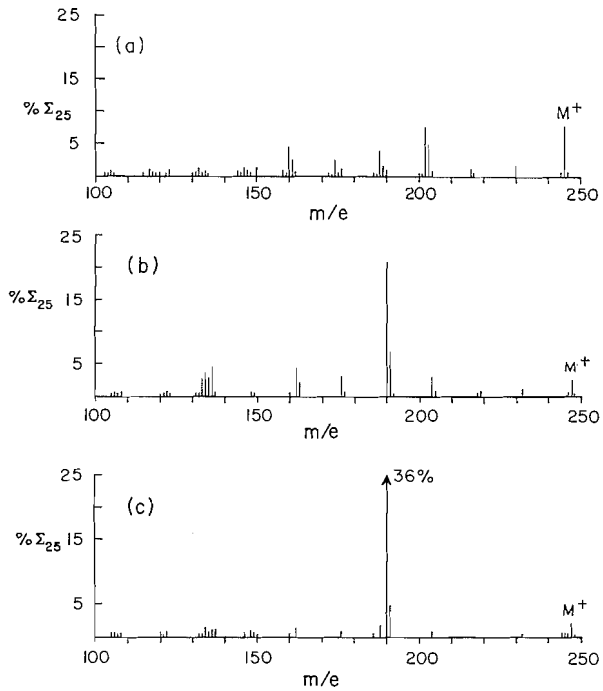
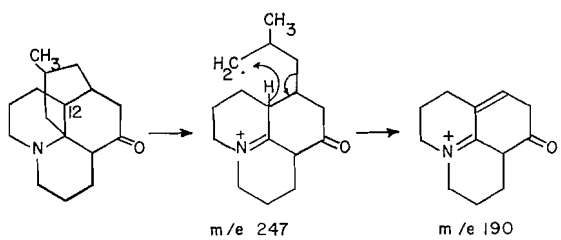


FIG. 4. Mass spectrum of (*a*) anhydrolycodoline, (*b*) 12-epilycopodine, (*c*) lycopodine.

The mass spectrum of 12-epilycopodine (X) (Fig. 4*b*) is worthy of comment. MacLean has suggested (22) that loss of ring D in lycopodine and related alkaloids, upon electron impact, may occur as shown in the following manner.



The base peak in the mass spectrum of 12-epilycopodine (Fig. 4*b*), like that of lycopodine (Fig. 4*c*), occurs at *m/e* 190. However, in the case of the epi compound X, the 190 peak

accounts for only 21% of $\sum_{25}$ (sum of the relative intensities of all peaks from mass 25 to the molecular weight (23)), whereas in lycopodine it accounts for 36%. This indicates that if a cyclic mechanism, such as that shown above, is operative, a *cis* arrangement of the C-12 hydrogen and the bridged ring facilitates, but is not necessary for, loss of the bridge. The mass spectrum of anhydrolycodoline (IX, Fig. 4*a*) again emphasizes the necessity of a hydrogen at C-12 for easy loss of the bridge (22), since in this case the parent peak is now the most intense peak in the spectrum, and the 188 peak (corresponding to loss of the bridge plus a hydrogen) is only 4% of $\sum_{25}$. In lycodoline (II), the mass spectrum of which has already been discussed (22), the parent peak is again the most intense peak in the spectrum.

EXPERIMENTAL

Ultraviolet spectra were measured in 95% ethanol and, unless otherwise specified, infrared spectra in carbon tetrachloride. For hydrogen-bonding studies, spectra were determined on 0.1, 0.05, and 0.01 *M* solutions in CCl_4 using a Perkin–Elmer Model 221 or 441 spectrophotometer. Nuclear magnetic resonance spectra were measured on ca. 5–10% w/v solutions in chloroform or deuterochloroform using a Varian Associates Model A-60 spectrometer. Internal tetramethylsilane was used as standard. Some of the optical rotatory dispersion curves were obtained by Dr. M. M. Marsh, Eli Lilly, Indianapolis; the others were determined by Mr. R. N. Swindlehurst of these laboratories using a Rudolph Automatic Recording Spectropolarimeter. The mass spectra were determined on an AEI MS2-H mass spectrometer. Samples were introduced through a heated inlet system maintained at 200°. Melting points were determined on a hot stage and are uncorrected. The alumina used for column chromatography, unless otherwise specified, was basic alumina of activity III–IV. Thin-layer chromatograms were carried out on 0.25 mm layers of Alumina G (Research Specialties Co., Richmond, California) and were developed with Dragendorff's reagent (24). Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62–70°. Microanalyses are by Pascher Mikroanalytisches Laboratorium, Bonn, West Germany, and C. Daessle, Montreal, Quebec.

Isolation of Lycodoline

Lycopodium annotinum L. was extracted as previously described (1) and most of the annotinine removed by crystallization (1). The resulting "annotinine-free" alkaloids were chromatographed over alumina. Lycodoline was eluted with ether and with ether – methylene chloride. Lycodoline has a characteristic sharp band at 960 cm^{-1} in the infrared which facilitates its detection. Suitable combination of fractions and crystallization from acetone gave lycodoline, m.p. 180–181°, identical with an authentic sample of alkaloid L.8 kindly furnished by R. H. Manske.

Infrared spectrum: ν_{max} 3545, 1703 cm^{-1}. Rotatory dispersion in methanol (*c*, 0.15): $[\alpha]_{308}$ +2660° (peak), $[\alpha]_{265}$ −6950° (trough).

Lithium Aluminum Hydride Reduction of Lycodoline

Lycodoline (148 mg) in ether (100 ml) was added to a slurry of $LiAlH_4$ (180 mg) in ether (75 ml) and the mixture refluxed for 18 h. Excess hydride was destroyed with wet ether and the solution extracted with dilute hydrochloric acid. The aqueous layer was made basic with aqueous ammonia and extracted with chloroform. Evaporation of the solvent and crystallization from acetone yielded dihydrolycodoline (0.10 g), m.p. 186–187°.

Calcd. for $C_{16}H_{27}O_2N$: C, 72.41; H, 10.26. Found: C, 72.16; H, 10.14.

Infrared spectrum: ν_{max} 3625, 3550 cm^{-1} (concentration independent).

Anhydrodihydrolycodoline

A solution of dihydrolycodoline (91 mg), methylene chloride (20 ml), and thionyl chloride (1.5 ml) was kept at room temperature for 2½ h. Then the solvents were removed at the pump. The oily residue was dissolved in dilute hydrochloric acid, washed with ether, and made basic with aqueous ammonia. Extraction with chloroform yielded a pale yellow oil (68 mg) which was chromatographed over alumina (2 g). Ether elution gave a colorless oil (62 mg) which was transformed to the hydrobromide in acetone solution. Recrystallization from acetone gave the analytical sample, m.p. 293–295°.

Calcd. for $C_{16}H_{25}ON \cdot HBr$: C, 58.55; H, 7.99. Found: C, 58.62; H, 8.11.

A sample of the free base was recovered from the hydrobromide and distilled at 130° at 0.5 mm. Infrared spectrum: ν_{max} 3565 (concentration independent), 1650 cm^{-1} (very weak). Nuclear magnetic resonance spectrum: 4.56 τ (1H, mult.), 9.08 τ (3H, poorly defined doublet).

Attempts to hydrogenate this olefin were not successful.

Dihydrodeoxylycodoline

Anhydrous hydrazine was added to a solution of sodium (0.5 g) in diethylene glycol (25 ml) until the solution refluxed at 190°. The solution was then cooled to 50° and lycodoline (200 mg) added, then the resulting

solution refluxed for 17½ h. The cooled reaction mixture was diluted with water, acidified with hydrochloric acid, continuously extracted with ether for 18 h (to remove diethylene glycol), made basic with aqueous ammonia, and extracted six times with chloroform. Evaporation of the chloroform left a solid which was recrystallized from acetone to give dihydrodeoxylycodoline (175 mg), m.p. 122.5–123.5°.

Calcd. for $C_{16}H_{27}ON$: C, 77.05; H, 10.91; O, 6.42; N, 5.62. Found: C, 76.51, 76.84; H, 10.65, 10.74; O, 6.82; N, 5.57.

Infrared spectrum: ν_{max} 3545 (concentration independent).

The perchlorate, recrystallized from acetone–ethyl acetate, melted at 273–275°.

Calcd. for $C_{16}H_{27}ON \cdot HClO_4$: C, 54.95; H, 8.07; N, 4.01. Found: C, 54.95; H, 8.07; N, 4.14.

Ester Salt (A) from Lycodoline

A solution of lycodoline (45 mg), ethyl bromoacetate (1.5 ml), and benzene (4 ml) was refluxed for 2 h. Filtration of the cooled reaction mixture gave the quaternary bromide (40 mg), m.p. above 340°, which was recrystallized from methanol–ether.

Calcd. for $C_{20}H_{32}O_4NBr$: C, 55.81; H, 7.50. Found: C, 55.51; H, 7.46.

Infrared spectrum: ν_{max}^{Nujol} 3240 (hydroxyl), 1753 (ester), 1717 cm^{-1} (ketone).

Ester Salt (A) from Dihydrodeoxylycodoline

The salt, prepared as above, melted at 212–213°.

Calcd. for $C_{20}H_{34}O_3NBr$: C, 57.69; H, 8.23; Br, 19.78. Found: C, 58.74; H, 8.53; Br, 19.78.

Infrared spectrum: ν_{max}^{Nujol} 3248 (hydroxyl), 1748 cm^{-1} (ester).

Lactone Salt (B) from Lycodoline

The ester salt from lycodoline (140 mg) was refluxed with 4 *N* HBr (10 ml) for 24 h. Then the solvent was evaporated and the residue recrystallized from methanol to give the lactone salt, m.p. above 340°.

Calcd. for $C_{18}H_{26}O_3NBr$: C, 56.26; H, 6.82; Br, 20.80. Found: C, 55.85; H, 6.64; Br, 21.50.

Infrared spectrum: ν_{max}^{Nujol} 1757 (lactone), 1710 cm^{-1} (ketone).

Lactone Salt (B) from Dihydrodeoxylycodoline

The lactone salt was prepared as described above for lycodoline and, after recrystallization from methanol–ether, melted at 325–326°.

Calcd. for $C_{18}H_{28}O_2NBr$: C, 58.38; H, 7.62. Found: C, 57.85; H, 7.35.

Infrared spectrum: ν_{max}^{Nujol} 1754 cm^{-1} (lactone).

Anhydrodihydrodeoxylycodoline (IV)

(A) From Dihydrodeoxylycodoline

A mixture of dihydrodeoxylycodoline (143 mg), phosphorus pentoxide (1 g), and toluene (100 ml) was heated under reflux for 3 h. Then the excess phosphorus pentoxide was decomposed with ice. The resulting two phase system was separated and the organic layer washed thoroughly with dilute hydrochloric acid. The combined acid solutions were washed with ether, made basic with aqueous ammonia, and extracted with chloroform. Evaporation of the chloroform left an oily residue (139 mg) which showed no hydroxyl absorption in its infrared spectrum. This product was dissolved in dilute hydrochloric acid and the hydrochloride extracted into chloroform. The hydrochloride hemihydrate obtained was recrystallized from acetone–ether, m.p. 232–233.5°.

Calcd. for $C_{16}H_{25}N \cdot HCl \cdot \frac{1}{2}H_2O$: C, 69.40; H, 9.83; Cl, 12.80. Found: C, 69.21, 69.60; H, 9.52, 9.65; Cl, 12.93.

The n.m.r. spectrum of the free base liberated from the purified hydrochloride showed signals at 4.64 τ (1H, poorly resolved triplet, J = 3 c.p.s.), and at 9.16 τ (3H, doublet, J = 5.5 c.p.s.).

(B) From Dehydroacrifoline (VI)

Dehydroacrifoline hydrobromide (210 mg, see below) was added to a solution of sodium, diethylene glycol, and hydrazine, made up as described for the preparation of dihydrodeoxylycodoline. The solution was refluxed for 14 h at 190°, then allowed to distil until the reflux temperature reached 215–220°. The solution was kept at this temperature for 11 h. Then the cooled solution was diluted with dilute hydrochloride acid and continuously extracted with ether for 1 day. The aqueous solution was made basic and extracted with chloroform to give a yellow oil, which was dissolved in dilute hydrochloric acid and the hydrochloride extracted into chloroform. Evaporation of the chloroform left a crystalline residue, which was recrystallized from acetone–ether to give anhydrodihydrodeoxylycodoline (IV) hydrochloride hemihydrate identical in melting point, mixed melting point, infrared spectrum ($CHCl_3$), and optical rotation ($[\alpha]_D^{23°}$ −28° (*c*, 1.9, ethanol)) with that prepared from lycodoline.

Hydrogenation of Anhydrodihydrodeoxylycodoline (IV)

The hydrochloride of IV (0.60 g) was shaken in methanol (100 ml) in the presence of platinum (from 300 mg of Adams' catalyst) and hydrogen (3 atm) for 3 h. Evaporation of the filtered reaction mixture left a crystalline residue (0.59 g) which was chromatographed on alumina (10 g). Elution with benzene (250 ml) removed the major component (0.50 g) (as evidenced by thin-layer chromatography of the fractions), and

elution with ether (200 ml) yielded the minor component (80 mg). The major component was dissolved in acetone and neutralized with 70% aqueous perchloric acid. Dilution of this solution with ethyl acetate yielded the crystalline perchlorate of the amine VII, which melted, after several recrystallizations from acetone – ethyl acetate, at 240–241°.

Calcd. for $C_{16}H_{27}N \cdot HClO_4$: C, 57.55; H, 8.45; N, 4.20. Found: C, 57.18; H, 8.51; N, 4.41.

The infrared spectrum of the free base showed prominent bands in the 2700–2850 cm^{-1} region (Fig. 1).

The minor component was shown to be dihydrodeoxylycopodine (VIII) in the following way. A portion (32 mg) of the material eluted with ether was dissolved in acetone (5 ml) and methyl iodide (1 ml) added. After 12 h at room temperature, the solvents were removed and the residue was recrystallized several times from acetone to give dihydrodeoxylycopodine methiodide, m.p. 290–291°, identical (mixed melting point, infrared spectrum) with an authentic sample (13).

Dehydroacrifoline (VI)

Acrifoline (V, 0.73 g) was dissolved in a solution of aluminum isopropoxide (0.8 g) in toluene (40 ml) and cyclohexanone (6 ml) added. The solution was refluxed for 3 h, diluted with benzene, and extracted with 1 *N* hydrochloric acid. The extract was washed with ether, made basic with aqueous ammonia, and extracted with chloroform to give a pale yellow oil (0.68 g) which was chromatographed over alumina (12 g). Elution with benzene (500 ml) gave an oily material (0.37 g) which was transformed to the hydrobromide in ethanol. Further elution with ether and chloroform gave unreacted acrifoline.

The ethanol solution of the hydrobromide was diluted with ethyl acetate. The resultant crystalline material was filtered off and recrystallized from ethanol – ethyl acetate to give dehydroacrifoline hydrobromide, m.p. 309–310° (sealed tube).

Calcd. for $C_{16}H_{21}O_2N \cdot HBr$: C, 56.56; H, 6.52; N, 4.12. Found: C, 56.21; H, 6.67; N, 3.76.

The infrared spectrum of the hydrobromide showed carbonyl absorption at 1728 and 1714 cm^{-1}, while the free base absorbed at 1712 and 1708 cm^{-1}.

Anhydrolycodoline (IX)

Lycodoline (II, 215 mg) was dissolved in a solution of phenylphosphonic dichloride (10 ml) and pyridine (10 ml) and the reaction mixture kept at 60–70° for 13 h. The excess phenylphosphonic dichloride was carefully decomposed with water. The resulting aqueous solution was made basic with 5% sodium hydroxide and extracted with chloroform to give, after evaporation of the chloroform, a deep red oil (0.20 g) which was chromatographed over alumina (6 g). Elution with benzene afforded a colorless oil (0.18 g) which showed a single spot on thin-layer chromatography but which rapidly colorized on standing. A portion was distilled (120° at 0.5 mm) and its mass spectrum recorded (see Fig. 4*a*). The infrared spectrum showed prominent bands in the 2700–2850 cm^{-1} region, no hydroxyl absorption, carbonyl absorption at 1698 cm^{-1}, and a weak band at 1655 cm^{-1} (C=C). Nuclear magnetic resonance spectrum: 4.44 τ (1H, triplet, J = 3.5 c.p.s.), 9.17 τ (3H, doublet, J = 5.5 c.p.s.). Rotatory dispersion in methanol (*c*, 0.08): $[\alpha]_{308}$ +1140° (peak), $[\alpha]_{264}$ −3900° (trough).

Hydrogenation of Anhydrolycodoline (IX)

A solution of anhydrolycodoline (170 mg) in methanol was acidified with perchloric acid and shaken with platinum (from 200 mg of Adams' catalyst) under hydrogen (3 atm). The catalyst was removed by filtration and the filtrate evaporated to a crystalline residue, which was dissolved in water, made basic with aqueous ammonia, and extracted with chloroform. The colorless oil (0.17 g), obtained when the chloroform was evaporated, showed two spots on thin-layer chromatography and was chromatographed over alumina (6 g), using pentane–ether, (400:1 to 9:1) as the eluant. Forty fractions (each 20 ml) were collected and each fraction was examined by thin-layer chromatography. Fractions 30–32 (17 mg) were homogeneous and showed an R_f identical with that of lycopodine. Crystallization from pentane–ether gave lycopodine, identical in melting point, mixed melting point, infrared spectrum, and optical rotation with an authentic sample.

Fractions 33–39 (0.15 g) were combined and rechromatographed over alumina (5 g). Elution with pentane (200 ml) removed only traces of material, while elution with benzene (50 ml) gave a crystalline fraction (0.11 g), which was recrystallized from pentane to give 12-epilycopodine (X), m.p. 89–90°.

Calcd. for $C_{16}H_{25}ON$: C, 77.67, H, 10.19; N, 5.66; molecular weight, 247. Found: C, 77.78; H, 9.99; N, 5.41; molecular weight, 247 (by mass spectrometry, see Fig. 4*b*).

Infrared spectrum: ν_{max} 2700–2850 cm^{-1} (see Fig. 3), 1698 cm^{-1}. Rotatory dispersion in methanol (*c*, 0.09): $[\alpha]_{306}$ −930° (trough), $[\alpha]_{265}$ +1130° (peak).

ACKNOWLEDGMENTS

We thank Dr. R. H. Manske for a sample of alkaloid L.8, Dr. P. Kebarle and Mr. A. N. Hogg for determining the mass spectra and for helpful discussion, Mr. R. N. Swindlehurst and Mrs. Gail Conway for determining the infrared and n.m.r. spectra, and Dr. M. M. Marsh for determining some of the optical rotatory dispersion curves. This research was

supported by grants from the National Research Council of Canada, to whom we express our thanks.

REFERENCES

1. R. H. MANSKE and L. MARION. Can. J. Res. B, **21**, 92 (1943).
2. R. H. MANSKE and L. MARION. J. Am. Chem. Soc. **69**, 212 (1947).
3. B. DOUGLAS, D. G. LEWIS, and L. MARION. Can. J. Chem. **31**, 272 (1953).
4. O. ACHMATOWICZ and W. RODEWALD. Roczniki Chem. **30**, 233 (1956).
5. R. H. BURNELL. J. Chem. Soc. 3091 (1959).
6. W. A. AYER, J. A. BEREZOWSKY, and D. A. LAW. Can. J. Chem. **41**, 649 (1963).
7. J. A. BEREZOWSKY. M.Sc. Thesis, University of Alberta, Edmonton, Alberta. 1962.
8. Y. INUBUSKI, Y. ISUDA, and T. SANO. Yakugaku Zasshi, **82**, 1083 (1962).
9. W. A. AYER and S. VALVERDE-LOPEZ. Unpublished.
10. G. S. PERRY and D. B. MACLEAN. Can. J. Chem. **34**, 1189 (1956).
11. R. N. JONES and C. SANDORFY. Technique of organic chemistry. Vol. IX. Interscience, New York. 1956. p. 498.
12. A. R. H. COLE. Technique of organic chemistry. Vol. XI. Part I. Interscience, New York. 1963. p. 148.
13. W. A. AYER and D. A. LAW. Can. J. Chem. **40**, 2088 (1962).
14. W. MOFFITT, R. B. WOODWARD, A. MOSCOWITZ, W. KLYNE, and C. DJERASSI. J. Am. Chem. Soc. **83**, 4013 (1961).
15. W. N. FRENCH and D. B. MACLEAN. Can. J. Chem. **39**, 2100 (1961).
16. F. A. L. ANET. Tetrahedron Letters, No. 20, 13 (1960).
17. C. DJERASSI, T. T. GROSSNICKLE, and L. B. HIGH. J. Am. Chem. Soc. **78**, 3166 (1956).
18. W. N. FRENCH and D. B. MACLEAN. Chem. Ind. London, 658 (1960).
19. F. BOHLMANN. Chem. Ber. **91**, 2157 (1958).
20. F. BOHLMANN and C. ARNDT. Chem. Ber. **91**, 2167 (1958).
21. K. WIESNER, J. E. FRANCIS, J. A. FINDLAY, and Z. VALENTA. Tetrahedron Letters, No. 5, 187 (1961).
22. D. B. MACLEAN. Can. J. Chem. **41**, 2654 (1963).
23. K. BIEMANN. Mass spectrometry: organic chemical applications. McGraw-Hill, New York. 1962. p. 44.
24. B. T. CROMWELL. *In* Modern methods of plant analysis. Vol. 4. *Edited by* K. Paech and M. W. Tracey. Springer-Verlag, Berlin. 1955. p. 373.