Phytochemistry, 1979, Vol. 18, pp. 1721–1723. © Pergamon Press Ltd. Printed in England. 0031-9422/79/1001-1721 $02.00/0

ALKALOIDS OF *LYCOPODIUM MAGELLANICUM*

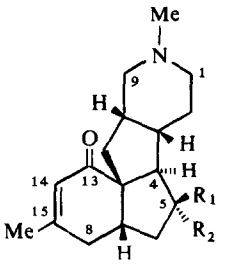
LUIS A. LOYOLA, GLAUCO MORALES and MARIANO CASTILLO
Departamento de Química, Facultad de Ciencias, Universidad de Chile, Santiago, Chile

(*Received* 8 *January* 1979)

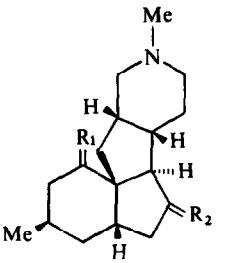
Key Word Index—*Lycopodium magellanicum*; Lycopodiaceae; lycopodium alkaloids; magellaninone.

Abstract—Six alkaloids have been isolated from *Lycopodium magellanicum*. These include the known alkaloids lycopodine, acetyldihydrolycopodine, lycodine, *N*-methyllycodine, acetylfawcettine and a new alkaloid, 5-dehydromagellanine. The chemical correlation of magellanine and paniculatine and the establishment of their absolute configuration are described.

In our preliminary communication [1], the isolation of the 'strong bases' and the structural elucidation of magellanine (**1a**), a new type of lycopodium alkaloid, were reported. The present paper describes further work on the fractions containing the 'weak bases', as well as the chemical correlation between magellanine (**1a**) and paniculatine (**2a**) and the determination of the absolute configuration of these alkaloids.



1a R_1 = OH; R_2 = H
1b R_1 = $-O_2CC_6H_5$; R_2 = H
1c R_1R_2 = O



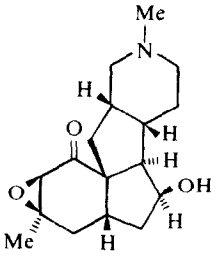
2a R_1 = α-OH, β-H; R_2 = O
2b R_1 = O; R_2 = H, H
2c R_1 = R_2 = O
2d R_1 = α-$O_2CC_6H_5$, βH; R_2 = O
2e R_1 = α-OH, β-H R_2 = H, H

Fractionation of the 'weak bases' extract enabled 5 known alkaloids to be isolated: lycopodine, *N*-methyllycodine, lycodine, acetylfawcettine and acetyldihydrolycopodine [2]. These alkaloids were all identified by comparison of their chromatographic and spectroscopic properties with those of authentic samples or by transformation into known products. A sixth alkaloid, magellaninone, is new but its spectral properties show that it is a close derivative of **1a**. Elemental analysis is in agreement with the formula $C_{17}H_{23}NO_2$, which differs from that of magellanine in the absence of two H atoms. The absence of a band attributable to an OH group in its IR spectrum, together with the appearance of a strong band at 1720 cm^{-1}, not present in magellanine, suggests that magellaninone is a dehydro derivative of the former. The remaining spectral properties (see Experimental) are in agreement with this view, in particular the MS, which shows a strong M^+ (*m/e* 273, 100%) and ions of high intensity (50–80%) in the low mass region corresponding to N-containing ions. This is a distinctive fragmentation pattern for alkaloids with the ring system found in magellanine and paniculatine and clearly differentiates alkaloids of this type from other ring systems found in the lycopodium family [1, 3]. That the new alkaloid is indeed 5-dehydromagellanine **1c**, was readily confirmed by mild oxidation of magellanine (Jones' reagent) affording a product identical in all respects with the natural compound.

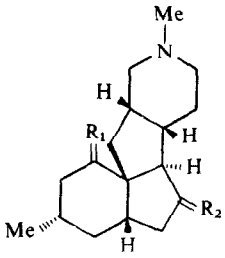
The absolute configuration of paniculatine and magellanine has now been determined and is as represented by the formulae used in this paper. The configuration at C-5 of magellanine and C-13 of paniculatine was determined by application of the method developed by Horeau [4]. Treatment of both alkaloids with (±)-α-phenylbutyric anhydride in pyridine led, in each case, to an excess of (−)-α-phenylbutyric acid, indicating that the carbinol atoms have the *S*-configuration. The same result was obtained by application of the benzoate rule for the determination of the configuration of secondary alcohols [5]. Finally, in agreement with these assignments, 13-dehydro-5-deoxopaniculatine (**2b**) shows a positive Cotton effect in its ORD curve. Thus, both alkaloids possess the same chirality.

In earlier work on these alkaloids, chemical correlation between paniculatine and magellanine was sought through their conversion into the common diketone derivative **2c**, readily obtained by combination of hydrogenation and oxidation steps. The products so obtained, **4b** and **2c**, were not identical, however. That

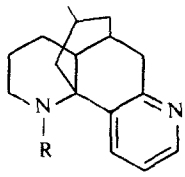
these products differed in the configuration at C-15—the new asymmetric centre created during the hydrogenation of magellanine—was established by comparison of the chiroptical properties of the products obtained by hydrogenation and epoxidation of magellanine. The ORD curve of 14,15-dihydromagellanine (**4a**) showed a negative Cotton effect, which was interpreted according to the octant rule [6] as the C-15 Me group having an α-orientation, implying hydrogenation from the β-side of the molecule. On the other hand, epoxidation of magellanine gave a crystalline product, epoxymagellanine (**3**), whose ORD curve showed a positive Cotton effect [7], a result to be expected if the epoxidation of the double bond also proceeded by attack of the reagent from the β-side of the molecule. Since the C-15 Me group in paniculatine, and, therefore, in paniculatinone, has been shown to be β, it follows that both diketones are epimeric at C-15.



3



4a R_1 = O; R_2 = β-OH, α-H
4b R_1 = R_2 = O



5 R = Me
6 R = H

EXPERIMENTAL

All mps are uncorr. ^{1}H NMR spectra were obtained at 60 MHz in $CDCl_3$ and are reported in δ units (ppm) downfield from the internal TMS. MS were obtained at 70 eV.

Isolation of bases. The mixture (11 g) of the 'weak-bases' [1] was subjected to a 60 tube countercurrent distribution between $CHCl_3$ (stationary phase) and McIlvane's buffer (pH 5). The distributed material was divided into 4 fractions. Fraction A (4.8 g) yielded *N*-methyllycodine (**5**) (0.5 g), a number of unidentified bases and neutral material.

N-Methyllycodine (**5**). Mp 87–88° (Et_2O) (lit. 91–92°) [8]. MS: *m/e* 256 (M^+, 48%), 241 (8), 213 (39), 200 (46), 199 (M − 57, 100%), 185 (39) and 175 (45). ^{1}H NMR: δ 0.8 (3H, *br s*, C-15 Me), 2.6 (3H, *s*, N-Me), 7.1 (1H, *dd*, *J* = 6 and 4 Hz), 8.1 (1H, *dd*, *J* = 2 and 6 Hz), 8.4 (1H, *dd*, *J* = 2 and 4 Hz). *N*-Methyllycodine was transformed into lycodine (**6**) in 31% yield by essentially the same procedure described [8] for the conversion of the obscurines into lycodine.

Column chromatography of fractions B (1.4 g) and C (3.2 g) allowed the separation of acetyldihydrolycopodine (0.95 g), acetylfawcettine (0.35 g), lycodine (0.12 g) and lycopodine (0.9 g), identified by comparison with authentic samples.

Fraction D (0.6 g) yielded magellaninone as an oil, characterized as its perchlorate, mp 244–45° (Me_2CO). (Found: C, 54.81; H, 6.59; N, 3.68. Calc. for $C_{17}H_{25}NO_2 HClO_4$: C, 54.11; H, 6.95; N, 3.71%). Spectral data (free base): UV λ_{max}^{EtOH} nm: 239 (log ε 3.9); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950–2800, 1720 and 1650. ^{1}H NMR: δ 2 (3H, *s*, C-15 Me), 2.3 (3H, *s*, N-Me), 5.95 (1H, *br s* $W_{1/2}$ = 5 Hz, C-14 H); MS: *m/e* 273 (M^+, 100%), 272 (72), 258 (48), 245 (16, M − 28), 202 (13), 190 (22), 111 (30), 110 (61), 96 (57), 84 (47), 71 (50), 70 (65), 58 (76), 57 (46). Hydrogenation of **1c** afforded a product identical with 5-dehydro-14,15-dihydromagellanine (*vide infra*).

O-Benzoylmagellanine (**1b**). Treatment of **1a** (80 mg) with benzoylchloride (2 ml) in Py (5 ml) at room temp. for 24 hr and usual work-up gave an oily product purified by sublimation. M_D^{25} = +7.5° (M_D^{25} (magellanine) = −64.8 ($CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2900–2600, 1710, 1650, 1595. ^{1}H NMR: δ 1.95 (3H, *s*, C-15 Me), 2.15 (3H, *s*, N-Me), 5.5 (1H, *m*, $W_{1/2}$ = 14 Hz, C-5 H), 5.8 (*s*, $W_{1/2}$ = 4 Hz, C-14 H), 7.4–7.9 (5H, *m*, aromatics). MS: *m/e* 379 (M^+, 28%), 259 (32), 258 (100), 236 (16), 190 (12), 174 (28), 110 (24), 105 (52), 94 (24), 93 (30), 77 (48), 70 (80), 71 (36), 58 (52), 57 (44).

Epoxymagellanine (**3**). **1a** (80 mg) dissolved in 10 ml 5% H_2O_2–MeOH and 1 ml 0.1 N NaOH was left at room temp. overnight. Usual work-up gave a colourless oil (55 mg) purified by distillation. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250, 3000–2700, 1690. ^{1}H NMR: δ 1.4 (3H, *s*, C-15 Me) 2.2 (3H, *s*, N-Me), 3.3 (1H, *s*, C-14 H), 4.2 (1H, *m*, $W_{1/2}$ = 24 Hz, C-5 H). MS: *m/e* 291 (M^+ 14%), 290 (10), 276 (61), 220 (28), 190 (11), 110 (39), 109 (36), 108 (28), 97 (16), 96 (100), 71 (39), 70 (75), 58 (88), 57 (64). ORD (EtOH) λ nm (φ): 270 (−3.777), 280 (−4.755 min), 296 (+770), 312 (+4.097), 315 (+4.618 max), 334 (+462), 366 (+140), 404 (0), 435 (−10), 546 (−25), 579 (−31). *a* = +93.7.

14,15-Dihydromagellanine (**4a**). Catalytic hydrogenation of **1a** (220 mg) in EtOH (10 ml) over 5% Pd–C (100 mg) was carried out at room temp. for 12 hr. The product was purified by crystallization (EtOAc), mp 142–143°. IR ν_{max}^{KBr} cm^{-1}: 3150, 3000–2600, 1690. ^{1}H NMR; δ 0.9 (3H, *d*, *J* = 6 Hz, C-15 Me), 2.2 (3H, *s*, N-Me), 4.2 (1H, *m*, $W_{1/2}$ = 14 Hz, C-5 H). MS: *m/e* 277 (M^+, 100%), 276 (61), 262 (42), 260 (33), 249 (37), 248 (52), 206 (31), 111 (25), 110 (52), 97 (44), 96 (44), 94 (41), 70 (48), 71 (37), 58 (44), 57 (37). ORD (EtOH) λ nm (φ): 253 (−1.438), 280 (−840), 296 (−643 max), 312 (−791), 330 (−1.089 min), 365 (−392), 407 (−220), 435 (−160), 546 (−81). *a* = −4.5. The hydrogenation was repeated in the presence of $HClO_4$ with the same results.

5-Dehydro-14,15-dihydromagellanine (**4b**). Oxidation of **4a** (75 mg) with CrO_3 in Me_2CO and work-up as usual yielded the title compound (46 mg), mp 125–126° (Et_2O). IR ν_{max}^{KBr} cm^{-1}: 2900, 2700, 1730, 1690. ^{1}H NMR: δ 1 (3H, *d*, *J* = 6 Hz, C-15 Me), 2.2 (3H, *s*, N-Me). MS: *m/e* 275 (M^+, 100%), 274 (41), 260 (22), 219 (38), 204 (52), 191 (20), 110 (23), 96 (21), 94 (20).

13-Dehydropaniculatine (**2c**). Oxidation of **2a** (40 mg) with

CrO_3–Py during 4 hr at room temp. and usual work-up gave a mixture which after purification by PLC (Al_2O_3, Et_2O) and molecular distillation afforded 16 mg of an oil which could not be recrystallized or made to form any crystalline derivative. IR ν_{max}^{Nujol} cm^{-1}: 2970–2850, 2780, 1730, 1700. ^1H NMR: δ 1.1 (3H, *br s*, C-15 Me), 2.3 (3H, *s*, N-Me). MS: *m/e* 275 (M^+, 100%), 260 (11), 247 (31), 219 (38), 204 (32), 110 (75), 109 (33), 96 (43), 84 (33), 70 (63), 58 (70).

5-Deoxopaniculatine (**2e**). A soln of **2a** (55 mg), Na (0.2 g) and dry hydrazine (20 ml) in diethylene glycol (10 ml) was heated at 180° for 16 hr, then at 210° for 23 hr. The product was purified by sublimation, affording a solid, mp 117–121°. IR ν_{max}^{KBr} cm^{-1}: 3440–3000, 2950–2850, 2800. ^1H NMR: δ 0.92 (3H, *d*, J = 7 Hz, C-15 Me), 2.2 (3H, *s*, N-Me), 3.6 (1H, *s*, $W_{1/2}$ = 7 Hz, C-13 H). MS: *m/e* 263 (M^+, 65%), 248 (50), 235 (13), 192 (28), 110 (25), 96 (39), 71 (53), 70 (44), 58 (100), 57 (63).

13-Dehydro-5-deoxopaniculatine (**2b**). Oxidation of **2e** (34 mg) with CrO_3 in Me_2CO and usual work-up gave 30 mg of the title compound which was purified by molecular distillation. IR ν_{max} cm^{-1}: 2950–2850, 2780, 1690. ^1H NMR: δ 1.02 (3H, *d*, J = 4 Hz, C-15 Me), 2.2 (3H, *s*, N-Me). MS: *m/e* 261 (M^+, 71%), 246 (26), 233 (43), 232 (48), 190 (30), 149 (100), 110 (58), 96 (55), 84 (35), 71 (60), 70 (100), 58 (77), 57 (84). ORD (EtOH) λ nm (ϕ): 260 (−783), 270 (−2610), 280 (−2870 min), 290 (+1305), 300 (+3654), 310 (+7047 max), 330 (+5742), 340 (4959), 350 (+1827), 366 (+417), 435 (+52), 579 (0). a = +99.2.

O-Benzoylpaniculatine (**2d**). **2a** (70 mg, $[\alpha]_D^{25}$ 57.72 (EtOH: *c* 1.66)), benzoylchloride (1.5 ml) and Py (3 ml) were refluxed for 2 hr. Usual work-up afforded a crystalline product (22 mg) purified by sublimation, mp 78–80°, $[\alpha]_D^{25}$ 88.5 (EtOH: *c* 1.33). IR ν_{max}^{KBr} cm^{-1}: 2950–2850, 1720, 1710, 1600, 1280. ^1H NMR: δ 1 (3H, *d*, J = 6 Hz, C-15 Me), 2.3 (3H, *s*, N-Me), 5.25 (1H, *m*, $W_{1/2}$ = 8 Hz, C-5 H), 7.5–7.9 (5H, aromatics). MS: *m/e* 381 (M^+, 17%), 277 (22), 276 (100), 105 (56), 77 (36), 71 (20), 70 (23), 58 (44), 57 (42). $M_D^{benzoate} - M_D^{paniculatine} = 337.2 - 159.8 = 177.4$.

Reaction of magellanine with α-phenylbutyric anhydride. **1a** (35 mg) was added to a soln of (±)-α-phenylbutyric anhydride (59 mg) in Py (1 ml) and the mixture allowed to stand at room temp. for 2 hr. Titration of the reaction mixture after addition of H_2O (2 ml) and C_6H_6 (3 ml) revealed that esterification was 42% complete. The α-phenylbutyric acid isolated showed a rotation of −0.15° (1 dm cell, C_6H_6) corresponding to an optical yield of 30%. Paniculatine, when subjected to the above procedure, also gave an excess of (−)-α-phenylbutyric acid with an optical yield of 25%.

Acknowledgement—Financial support by the Servicio de Desarrollo Cientifico de la Universidad de Chile is gratefully acknowledged.

REFERENCES

1. Castillo, M., Loyola, L. A., Morales, G., Singh, I., Calvo, C., Holland, H. L. and MacLean, D. B. (1976) *Can. J. Chem.* **54**, 2893.
2. MacLean, D. B. (1973) in *The Alkaloids* (Manske, R. H. E., ed.) Vol. 14. p. 347. Academic Press, New York.
3. Castillo, M., Morales, G., Loyola, L. A., Singh, I., Calvo, C., Holland, H. L. and MacLean, D. B. (1976) *Can. J. Chem.* **54**, 2900.
4. Horeau, A. and Kagan, H. B. (1974) *Tetrahedron* **20**, 2431.
5. Brewster, J. H. (1961) *Tetrahedron* **13**, 106.
6. Moffit, W., Woodward, R. B., Moscowitz, A., Klyne, W. and Djerassi, C. (1961) *J. Am. Chem. Soc.* **83**, 4013.
7. Legrand, M., Vincent, R. and Conmartin, J. (1961) *C.R.* **253**, 2378.
8. Ayer, W. A. and Iverache, G. E. (1960) *Can. J. Chem.* **38**, 1823.