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ALKALOIDS OF *LYCOPODIUM PANICULATUM*: THE STRUCTURE OF PANICULINE

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

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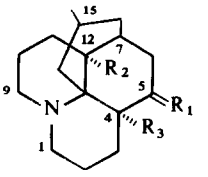
Key Word Index—*Lycopodium paniculatum*; Lycopodiaceae; lycopodium alkaloids; paniculine; deacetylpaniculine; anhydrodeacetylpaniculine; lycoclavine: flabellidine.

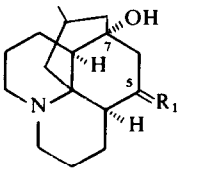
Abstract—Three new alkaloids isolated from *Lycopodium paniculatum* were identified as paniculine (7α-hydroxyacetyldihydrolycopodine), deacetylpaniculine and anhydrodeacetylpaniculine. Other known alkaloids isolated include flabellidine, lycoclavine, together with deacetyllycoclavine previously obtained as a degradation product of lycoclavine.

A previous paper reported the isolation of several bases present in *Lycopodium paniculatum* Desvaux [1]. They included the known alkaloids lycopodine, dihydrolycopodine, acetyldihydrolycopodine [2] together with paniculatine, a representative of a new type of lycopodium alkaloid with a novel ring system. The physical and spectroscopic properties of 3 other new alkaloids designated P_2, P_4 and P_5 were also reported. The present work described the structure elucidation of these bases together with the isolation and identification of other alkaloids present in this plant.

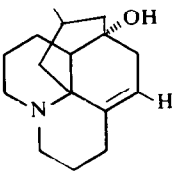
P_2, $C_{18}H_{29}NO_3$, named paniculine, contains a secondary acetoxyl and a tertiary OH group [1]. Its general structure is readily apparent from its MS which shows a base peak at $M^+ - 57$, characteristic of alkaloids with the lycopodine skeleton without substituents on ring D [2]. Treatment of P_2 with phosphorus pentachloride and hydrogenation of the reaction product replaced the OH group by H. The product was identical with acetyldihydrolycopodine (**1**) thereby establishing the attachment of the acetyl group at C-5 of paniculine. Basic hydrolysis of paniculine afforded a diol, deacetylpaniculine*, also present as a naturally occurring compound in *L. paniculatum*. Oxidation of deacetylpaniculine (Jones' reagent) gave a hydroxyketone which was different (TLC, IR) from either lycodoline (**2**) or flabelliformine (**3**). This finding eliminates C-12 or C-4 as the tertiary carbon bearing the OH group. Since C-15 is precluded on the basis of ^{1}H NMR and MS data, the hydroxyketone is **4** and, therefore, the structure of paniculine is as represented in **5**. The spectral properties of **4** (UV and ORD) are also in agreement with placement of the OH group at C-7 and confirm the stereochemistry at the N atom and C-12 [3]. Deacetylpaniculine (**6**) was easily dehydrated to yield a trisubstituted olefin whose properties (see Experimental) are in accord with structure **7**, identical in all respects with the natural compound designated P_5.



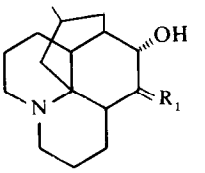
1 $R_2 = R_3 = H$; $R_1 = \beta$-OAc, α-H
2 $R_1 = O$; $R_2 = OH$; $R_3 = H$
3 $R_1 = O$; $R_2 = H$; $R_3 = OH$



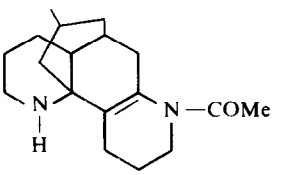
4 $R_1 = O$
5 $R_1 = \beta$-OAc, α-H
6 $R_1 = \beta$-OH, α-H



7



8 $R_1 = \beta$-OH, α-H
9 $R_1 = \beta$-OAc, α-H
10 $R_1 = O$



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P_4 is shown to be deacetyllycoclavine (**8**), a lycopodium alkaloid not previously isolated as a natural product, but obtained and described [5] by Ayer and co-workers after hydrolysis of lycoclavine (**9**) and also by $LiAlH_4$ reduction of L20 (**10**) by the same author [6]. Its identity was confirmed by comparison of the spectroscopic properties of several of its derivatives (see Experimental) with authentic samples or published data. Two other known lycopodium alkaloids, lycoclavine (**9**) and flabellidine (**11**) were isolated and identified.

* Inubushi, in his work in connection with serratidine [4], reports the structure of a derivative whose properties (mp, IR, MS) are closely similar to deacetylpaniculine. No direct comparison has been made.

EXPERIMENTAL

Melting points are uncorr. MS were determined by direct inlet, 70 eV, 100 mA, 80–180°, and ^{1}H NMR at 60 MHz, $CDCl_3$–TMS.

Extraction. The procedure followed for the isolation and characterization of **5**, **7** and **8** is described in [1].

Deacetylpaniculine (**6**). Fraction D [1] (2.2 g) was chromatographed on Al_2O_3 and eluted with mixtures of $CHCl_3$–MeOH of increasing polarity. **6** (1.2 g) was purified by conversion into its hydrobromide, mp 275° (EtOH–Et_2O). The free base purified by sublimation and crystallization (Me_2CO), mp 172–174°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 and 3580. ^{1}H NMR: δ 0.9 (3H, *d*, J = 6 Hz, C-16), 3–3.8 (2H, *m*), 3.9 (1H, *m*). MS: *m/e* 265 (M^+, 10%), 222 (4), 209 (24), 208 (100), 190 (7), 172 (7), 144 (5).

Lycoclavine (**9**) and *flabellidine* (**11**) were isolated by chromatography on Al_2O_3 of fraction E [1] and identified by comparison of their physical and spectroscopic properties with published data [5, 7].

Alkaline hydrolysis of paniculine. Treatment of **5** (30 mg) with 5% KOH–MeOH (10 ml) under reflux (5 hr) gave **6** (23 mg), mp 172–174° (Me_2CO–Et_2O), identical (co-TLC, IR, ^{1}H NMR and MS) with deacetylpaniculine described above.

Oxidation of **6**. **6** (15 mg) dissolved in Py (10 ml) containing CrO_3 (150 mg) was left at room temp. for 24 hr. Usual work-up afforded **4**, purified by sublimation, mp 57–59°. UV λ_{max}^{EtOH} nm: 220 (ε 900), 270 (ε 1500). IR ν_{max}^{KBr} cm^{-1}: 3400–3100, 1690, 1420. ^{1}H NMR: δ 0.9 (3H, *d*, J = 4 Hz, C-16), 3–4 (2H, *m*). MS: *m/e* 263 (M^+, 9%), 220 (2), 208 (6), 207 (16), 206 (100), 178 (11), 160 (5). ORD λ^{EtOH} nm (ϕ): 260 (−657), 270 (−3.944), 280 (−3.287), 290 (−657), 300 (+876), 310 (+2.727), 312 (+2.498), 320 (+2.235), 334 (=657), 366 (+184). **5** was recovered unchanged when oxidized under the same conditions.

Acetylation of **5**. Treatment of **5** (30 mg) with Ac_2O–Py at room temp. for 72 hr afforded a mixture of **5** (11 mg) and acetylpaniculine (16 mg), mp 190° dec (Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 2950–2850, 1730, 1250. ^{1}H NMR: δ 0.9 (3H, *d*, J = 7 Hz, C-16), 2 (6H, *s*, MeCO), 5.1 (1H, *t*, J = 6 Hz, C-5). MS: *m/e* 349 (M^+, 2%), 292 (3), 289 (5), 232 (38), 202 (24), 186 (11), 174 (12), 172 (100), 144 (45), 136 (6). Acetylation of **6** also gave acetylpaniculine and a monoacetylated product which was not fully characterized.

Dehydration of **6**. **6** (15 mg) in CH_2Cl_2 (2 ml) was treated with $SOCl_2$ (2 ml) at room temp. for 21 hr. Usual work-up afforded a crystalline product, **7** (14 mg), purified by sublimation and crystallization: mp 175–185° (Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 3250–3190, 1070. ^{1}H NMR: δ 0.9 (3H, *d*, J = 6 Hz, C-16), 3.3 (1H, *m*), 5.5 (1H, *m*). MS: *m/e* 247 (M^+, 20%), 218 (3), 204 (8), 190 (100), 172 (43). Compound **7** was recovered unchanged after attempted oxidation, hydrogenation or acetylation under usual conditions.

Reduction of paniculine. To a stirred soln of **5** (51 mg) in CH_2Cl_2 (20 ml), under N_2, PCl_5 (200 mg) was added in small portions. After 4 hr at room temp., the reaction mixture was worked up as usual affording a brown oily residue (55 mg). The residue was dissolved in EtOH (15 ml) containing PtO_2 and and hydrogenated overnight. The product (40 mg) was purified by sublimation yielding a crystalline compound (19 mg) identical (co-TLC, IR, MS) with **1**.

Acetylated derivatives of **8**. A soln of **8** (41 mg) in 3 ml of Ac_2O–Py (1:1) was kept at 92° for 20 hr. Usual work-up afforded a solid purified by sublimation; mp 115–118° (lit. 144–145° [5]). IR ν_{max}^{KBr} cm^{-1}: 2290–2850, 1740, 1725 and 1240. ^{1}H NMR: δ 0.96 (3H, *d*, J = 6 Hz, C-16), 2 (6H, *s*, MeCO), 4.6 (1H, *s*, C-6), 5 (1H, *d*, J = 6 Hz, C-5). MS: *m/e* 349 (M^+, 11%), 306 (4), 292 (40), 290 (13), 289 (15), 232 (100), 190 (82), 174 (15), 173 (19), 172 (15), 162 (18), 148 (12). A monoacetylated derivative of **8**, isomeric with **9**, was obtained as follows: **8** (100 mg) was kept at 0° for 19 hr in Ac_2O (2.5 ml)–Py (4 ml). TLC (Al_2O_3, Et_2O) of the reaction mixture showed 3 components (R_fs 0.1, 0.4 and 0.8). The product R_f 0.4 (25 mg) was isolated as an oil after chromatography (Al_2O_3) and PLC (Al_2O_3–Et_2O): mp of hydrobromide, 248–251°. IR ν_{max}^{film} cm^{-1}: 3500–3200, 1730 and 1250. ^{1}H NMR: δ 0.96 (3H, *d*, J = 6 Hz, C-16), 2.01 (3H, *s*, MeCO), 3.9 (1H, *d*, J = 4 Hz, C-5), 4.7 (1H, *s*, C-6).

Oxidation products of **8**. Treatment of **8** with Jones' reagent at room temp. afforded the known diosphenol derived from the 5,6-diketone, identical with an authentic sample obtained by SeO_2 oxidation of lycopodine [4]. Oxidation of **8** (Sarett) at 0° for 2 hr yielded a crystalline product, mp 245–246° (lit. 258–259° [6]), identical with an authentic sample of L20 (**10**). This product, also obtained by hydrolysis of 6α-bromolycopodine [5], was reduced back to **8** with $LiAlH_4$.

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