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Structure of Oxolucidine A, a Lycopodium Alkaloid

Motoo Tori,*[a] Tatsue Shimoji,[a] Shigeru Takaoka,[a] Katsuyuki Nakashima,[a] Masakazu Sono,[a] and William A. Ayer[b]

[a] *Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan*
[b] *Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada*

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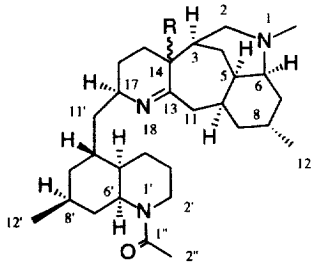
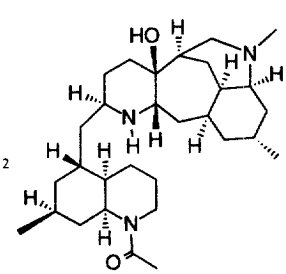
Abstract: A *Lycopodium* alkaloid, oxolucidine A, was treated with $NaBH_4$ followed by *p*-bromobenzoyl chloride to afford a tribenzoate derivative, which was analyzed by X-ray crystallography to establish the stereostructure. The structure of lucidine A was also determined from these results except for the configuration at C-14.

Keywords: Alkaloids; Natural products; NMR; X-Ray crystal structures

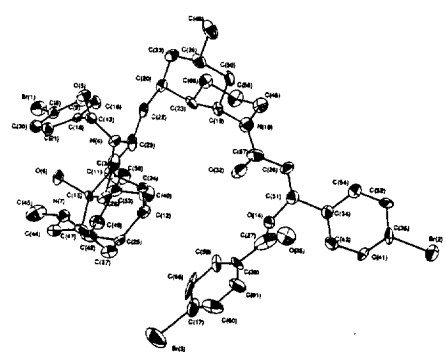
Lycopodium plants have long been studied and many alkaloids have been reported thus far [1-7]. Most of the compounds reported have a common formula of $C_{10}N$ or $C_{16}N$ [7], however, among them we have previously reported $C_{30}N_3$ alkaloids [5] named lucidine A (**1**), lucidine B, oxolucidine A (**2**), and oxolucidine B. Structures of these alkaloids were highly complicated to solve by simple NMR techniques or simple degradation procedures. Thus, studies in this area are neglected for some time. Recently, huperzine has been isolated from *Huperzia serrata* (=*L. serratum*) as a potent inhibitor against the acetylcholine esterase [8]. This prompted us to reinvestigate the chemical constituents of the *L. lucidulum* extracts. Weak bases were separated using ten-funnel countercurrent distribution as we reported before [6]. Separation of lucidines A (**1**), B, oxolucidines A (**2**), and B was carried out by aluminum column chromatography with different activities, followed by reversed-phase HPLC using CH_3CN-H_2O (7:3) as solvent system. Oxolucidines A (**2**) and B were also obtained from lucidines A (**1**) and B on exposure to the air [5, 9]. Because there is an



R=H lucidine A (**1**)
R=β–OH oxolucidine A (**2**)



dihydrooxolucidine A (**3**)



The ORTEP drawing of compound **4**

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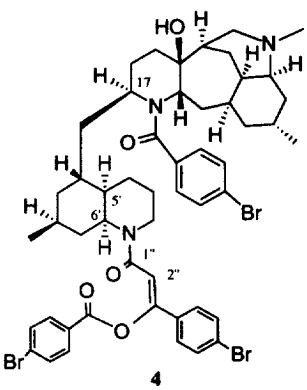
acetamide moiety, its NMR is not so easy to analyze at the room temperature [10, 11]. We now report the full structure of oxolucidine A (**2**) established by X-ray crystallographic analysis.

Oxolucidine A (**2**) was converted into dihydrooxolucidine A (**3**) [12], $C_{30}H_{51}N_3O_2$, by treatment with $NaBH_4$ in MeOH. This in turn was treated with *p*-bromobenzoyl chloride and triethylamine in CH_2Cl_2 to afford crystals (m.p. 228-232 °C) [13] from MeOH. The ^1H NMR spectrum of this compound **4** showed the presence of more than two *p*-bromobenzoyl moiety and no acetamide group. The FABMS spectrum showed the multiplet molecular ion peak at *m/z* 1038, 1036, 1034, and 1032 indicating the presence of the three *p*-bromobenzoyl groups. Because it is not easy to analyze its NMR spectra, X-ray analysis was performed to yield a very unusual structure having two *p*-bromobenzoyl unit at N-acetamide position [14]. This type of structure can be found in the literature [15], although it is unusual to obtain such a compound from simple *p*-bromobenzoylation. Because the η value was +1.081, the absolute configuration of **4** was determined as depicted in the formula. The three chiral centers of **2** at C-17, 5', and 6' positions are the same as those of spirolucidine [6], while different from those of oxolucidine B [5, 6].

The presence of lucidine A and oxolucidine A has been known for a long time, but their structures have been unknown, and this problem has now successfully been solved using X-ray crystallographic analysis. Although the choline esterase inhibitory activity of lucidine A and oxolucidine A has been tested, they showed no activity at all.



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[12] **3**; $[\alpha]_D^{21}$ +3.9 (c 0.79, $CHCl_3$); HRMS found *m/z* 485.3903. Calcd for $C_{30}H_{51}N_3O_2$ 485.3903; MS *m/z* 485 (M^+), 467 (base), 452, 424, 410, 291, 273, 259, 248, 235; IR (FTIR) 3400, 2925, 2860, 2775, 1635, 1620, 750 cm^{-1}. ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 168.8, 72.5, 58.6, 58.5, 52.8, 46.9, 43.2, 41.9, 39.9, 38.5, 38.4, 38.3, 36.5, 34.5, 33.8, 33.6, 32.4, 27.1, 26.9, 26.5, 25.8, 25.7, 25.6, 22.9, 22.6, 22.5, 22.3, 21.6, 21.5.
[13] **4**; mp. 228-232℃ (from MeOH); $[\alpha]_D^{21}$ +7.3 (c 1.1, $CHCl_3$); HRMS (FAB) found *m/z* 1032.2150 $[M+H]^+$. Calcd for $C_{51}H_{61}O_5N_3Br_3$ 1032.2155; MS (FAB) *m/z*: 1038, 1036, 1034, 1032 $[M+H]^+$, 1017, 850, 624, 459, 329, 307, 183 (base), 154, 136; FTIR 3450, 2925, 2860, 2775, 1740, 1625 cm^{-1}; ^1H NMR (600 MHz) ($CDCl_3$) δ 0.75 (3 H, d, *J* = 6.32 Hz), 1.24 (3 H, d, *J* = 7.14 Hz), 1.25 (3 H, s).
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