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ALKALOIDS OF *LYCOPODIUM ALOPECUROIDES* L.—V[a]

THE STRUCTURE OF ALOPECURIDINE

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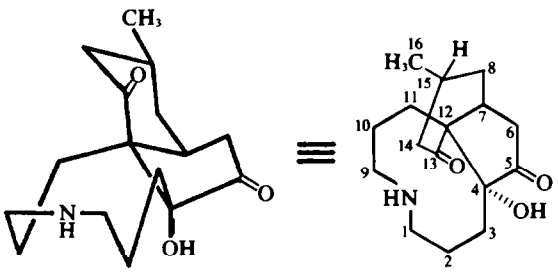
Abstract—Alopecuridine, an alkaloid from *Lycopodium alopecuroides* L., is shown to be 4α-hydroxyfawcettimine 1. Calcium-ammonia reduction of alopecuridine 1 followed by acetylation gives N-acetylfawcettimine (5). A single crystal X-ray crystallographic analysis defines the complete structure and stereochemistry of N-acetylalopecuridine.

In part 1 of this series[2] we described the isolation from *Lycopodium alopecuroides* L. of a compound $C_{16}H_{25}O_3N$, mp 171–172°, which we named alopecuridine. At that time it was suggested that the somewhat anomalous IR spectra displayed by alopecuridine and derivatives indicated the possibility that it was a hydroxylated fawcettimine. This is now shown to be the case. Aleopecuridine is 4α-hydroxyfawcettimine, which may exist in either the aminoketone form 1 or the carbinolamine form 2, explaining the IR behavior discussed previously.[2] Since both the hydrobromide and the hydroperchlorate of alopecuridine show a single carbonyl band (1750 cm^{-1}) in the IR they are of the carbinolamine form 2. Acetylation of alopecuridine furnishes[2] the N-acetyl derivative 3.

Proof of structure for alopecuridine was obtained in the following manner. Reduction of alopecuridine with calcium in ammonia[3] gave mixed crystals of fawcettimine 4† and a dihydrofawcettimine. The mixture of the two components showed a single spot on thin layer chromatography with R_f value identical with that of fawcettimine. When the mixture was treated with perchloric acid in acetone fawcettimine perchlorate

[a] Part 4. See reference 1.

†The configuration at C-4 in fawcettimine has not previously been determined. However, the tendency towards carbinolamine formation is similar to that of alopecuridine and thus fawcettimine is tentatively assigned the same configuration at C-4. N-Acetylfawcettimine and N-acetylalopecuridine show similar positive Cotton effects at 300 nm in their CD spectra.



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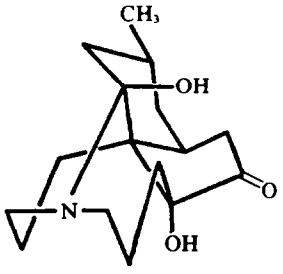

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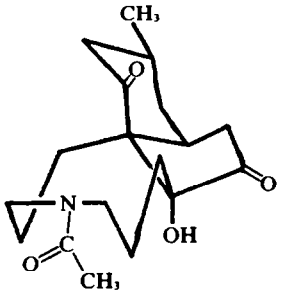

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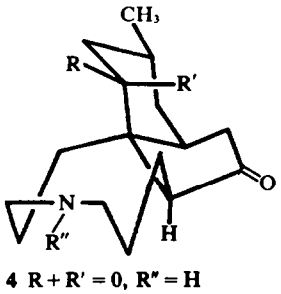
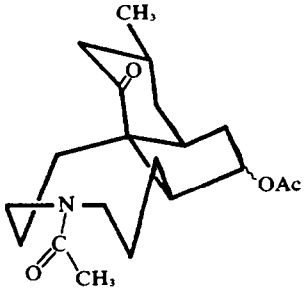


4 R + R′ = O, R″ = H
5 R + R′ = O, R″ = Ac
6 R = H, R′ = OAc, R″ = Ac



7

separated. Acetylation of the mixture gave N-acetylfawcettimine **5** and an N,O-diacetyldihydrofawcettimine, separable by chromatography over alumina. The N,O-diacetyldihydrofawcettimine proved to be different from the known N,O-diacetyldihydrofawcettimine (N,O-diacetylchanodihydro-8-deoxyserratinine **6**[4]). The IR spectrum (ν_{max} 1735, 1695, 1640 cm^{-1}) indicates the retention of the six-membered ketone and structure **7** is assigned to the new dihydrofawcettimine derivative.

Formation of fawcettimine by calcium-ammonia reduction of alopecuridine shows that the latter is a hydroxylated fawcettimine with the hydroxyl group located α to a carbonyl group. Since N-acetylalopecuridine was recovered unchanged from attempted Jones' oxidation and was resistant to further acetylation, the hydroxyl group appeared to be tertiary and thus, by exclusion, located at C-4. In order to verify this conclusion and at the same time establish the stereochemistry at C-4, the structure of N-acetylalopecuridine has been established by X-ray diffraction methods.

Single crystals of **3**, m.p. 225–227° (from methanol), are monoclinic prisms of space group $P2_1$ with cell dimensions $a = 2{\cdot}790 \pm 0{\cdot}001$, $b = 7{\cdot}611 \pm 0{\cdot}002$, $c = 11{\cdot}903 \pm 0{\cdot}001$ Å, $\beta = 104{\cdot}98°$ and $Z = 2$. 1384 intensity measurements were collected by the W-2θ scan method using a Picker manual four-circle diffractometer with graphite-monochromated CuKα radiation. The structure was solved by the symbolic addition procedure.[5] A total of six reflections (three two-dimensional and three three-dimensional) were chosen for the original specification and unknown symbols. A single highly reliable intersymbolic relationship reduces to only ten sets when the numerical values for these unknown symbols are evaluated. Tangent formulae were applied for 257 reflections ($|E| \geq 1{\cdot}30$). Only one set out of ten gave the lowest R_t value and this revealed all the heavy atoms without spurious peaks in the E-map synthesis. Refinement was carried out by full-matrix least squares calculations, the anisotropic temperature factors being used in the last several cycles for all the heavy atoms. The hydrogen atoms were located from a difference Fourier map and included in further refinement with isotropic temperature factors. The final R-factor for all observed reflections was 8·0%. A perspective view of **3** along the *b* axis is shown in Fig. 1. This shows that alopecuridine is indeed 4α-hydroxyfawcettimine.

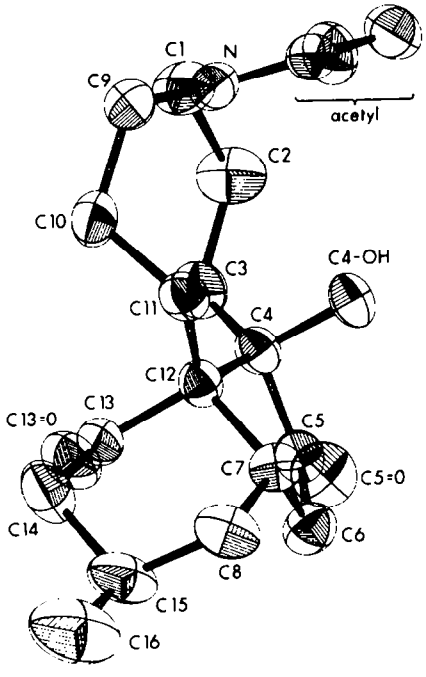


Fig. 1. The molecular structure of N-acetylalopecuridine viewed along the *b* axis.

Since the absolute stereochemistry of fawcettimine is known by correlation with serratinine,[6] structure **1** represents the absolute stereochemistry of alopecuridine.

EXPERIMENTAL†

N-Acetylalopecuridine **3**. N-Acetylalopecuridine, prepared as previously described[2] was recrystallized from methanol to give elongated prisms, mp 225–227°. IR identical with published[2] spectrum. NMR ($CDCl_3$) δ: 1·08 (d, J = 6 Hz, $CHCH_3$), 2·09 (s, $COCH_3$), Mass spectrum *m/e*: 321 (M^+, 26), 293(100), 250(31), 192(39), 164(64), 150(57), 123(48). Circular dichroism (*c* 0·003 M, methanol): $\Delta\epsilon_{300} + 0{\cdot}34$.

Calcium-ammonia reduction of N-acetylalopecuridine **3**. Calcium metal was added in small pieces to a solution of alopecuridine (78 mg) in liquid ammonia (25 ml) until the solution remained blue. After a further 5 min ammonium chloride (0·5 g) was added and the ammonia allowed to evaporate. Water was added and the solution extracted with chloroform. Crystallization of the residue from acetone provided crystals (30 mg), mp 160–162°. Treatment of the mother liquors with perchloric acid gave fawcettimine hydroperchlorate, mp 224–226° (from methanol-acetone, reported 225–226°[7]), identical (IR, mixed mp) with an authentic sample.

The crystalline material, the m.p. of which did not change on repeated recrystallization, was acetylated overnight with pyridine-acetic anhydride. The resulting solid (25 mg) showed two spots on TLC and was separated by chromatography over alumina. Elution with ether gave compound **7**, mp 192–194°; IR (Nujol); 1735, 1695, 1640 cm^{-1}; molecular weight, 349·2256 (high resolution mass spectrometry, $C_{20}H_{31}NO_4$ requires 349·2253). Elution with chloroform: ether (1:1) gave N-acetyfawcettimine, mp 143–145°, identical (mixed mp, IR, TLC) with an authentic sample.

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†The general experimental details are the same as those given in previous Parts of this series.[1,2]