

THE SYNTHESIS OF (1R,2S,8S)- AND (1S,2S,8S)-1-HYDROXYMETHYL-2-HYDROXYPYRROLIZIDINE:
PETASINECINE AND ITS C-1 EPIMER

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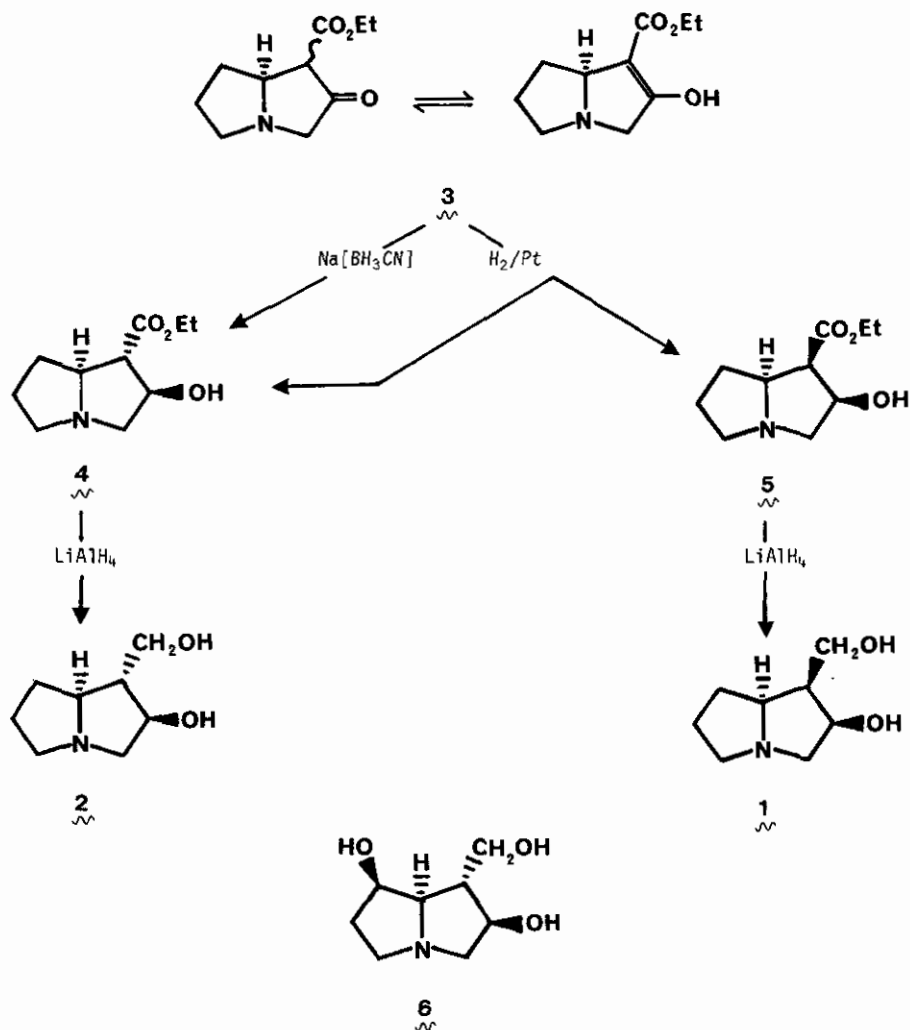
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Abstract - The hydrogenation of (8S)-1-ethoxycarbonylpyrrolizidin-2-one in aqueous acetic acid, over Adam's catalyst, afforded a separable mixture of (1R,2S,8S)- and (1S,2S,8S)-1-ethoxycarbonylpyrrolizidin-2-ol. Reduction of the individual epimers with lithium aluminium hydride gave the corresponding diols, the (1R,2S,8S)-compound being petasinecine.

A few years ago Yamada *et al.*¹ reported the isolation, from *Petasites japonicus* Maxim, of two new pyrrolizidine alkaloids. Both of these were shown to be derivatives of a 2-hydroxy-1-hydroxy-methylpyrrolizidine, which was deduced to be the (1R,2S,8S)-stereoisomer $\mathbf{1}$. This base, not previously encountered in a natural product, was named petasinecine.

We report here the synthesis of petasinecine, and its C-1 epimer $\mathbf{2}$ from (8S)-1-ethoxycarbonylpyrrolizidin-2-one ($\mathbf{3}$) an intermediate which we had previously prepared from (S)-proline, and used for the synthesis of (-)-isoretro-necanol, (-)-trachelanthamidine, and (-)-supinidine ($\mathbf{2}$).

The catalytic hydrogenation of $\mathbf{3}$, as its hydrochloride salt², was carried out at 0°C in aqueous acetic acid (1:1 v/v) over platinum black, at 40-50 psi. Hydrogen uptake was complete after 3 h. After removing the catalyst and solvents, the residue was basified (K_2CO_3 aq.) and extracted with chloroform at 0°C. Analysis of these extracts by GC-MS revealed the presence of ethyl isoretro-necanolate, ethyl trachelanthamidinate, and two hydroxy-esters. This mixture was separated by flash-chromatography over silica gel 60 (0.04-0.063 mm; CHCl_3 -MeOH- NH_4OH 85:14:1 to 70:25:5) to yield a mixture of the (1R,8S)- and (1S,8S)-1-ethoxycarbonylpyrrolizidines (8%), and two 1-ethoxycarbonyl-2-hydroxypyrrolizidines: $\mathbf{4}$ (50%), m.p. 72-73°C, $[\alpha]_D^{25} +24^\circ$ (c, 1.5 EtOH), hydrochloride salt m.p. 126-127°C; and $\mathbf{5}$ (36%), m.p. 64.5-65.5°C, hydrochloride salt, m.p. 172-173°C $[\alpha]_D^{25} -35.6^\circ$ (c, 1.0 EtOH)³. Although the hydrochloride of $\mathbf{5}$ was stable, the free base underwent slow isomerisation to $\mathbf{4}$ when its solutions were kept at room temperature. Since this behaviour was consistent with a C-1 *endo+exo* epimerisation of the ethoxycarbonyl function⁴ and given also that hydrogenation was expected to occur from the less-hindered α -face, we therefore made the stereochemical assignments shown in $\mathbf{4}$ and $\mathbf{5}$.



Sodium cyanoborohydride reduction of 3 at pH ca. 4 in aqueous solution proceeded slowly, but finally gave a high yield of a single hydroxy-ester which proved to be 4. Here too we reasoned that the reduction would have been stereospecific, yielding an endo 28-ol, as preceded by the sodium borohydride reduction of (\pm)-8 α -1-ethoxycarbonylpyrrolizidine-2,3-dione⁵, i.e. the formation of 4 in this reduction is evidence for the (2S)-configuration in it, and in 5. Confirmation of these conclusions was provided by the lithium aluminium hydride reduction of the individual epimeric hydroxy-esters. Thus 4 gave a crystalline diol, m.p. 114-115°C, $[\alpha]_D^{26} +40.3^\circ$ (c, 1.0 EtOH), an analysis of whose 200 MHz ¹H-NMR spectrum revealed coupling constants for the

H-1, -2, and -3, protons in excellent accord with those reported^{6,7} for croalbinecine (=helifolinecine) (**6**)⁸, i.e. this diol is (1S,2S,8S)-2-hydroxy-1-hydroxymethylpyrrolizidine (**2**), the C-1 epimer of petasinecine, and a compound, at least as yet, unknown in nature. Aasen and Culvenor⁵ had previously prepared (\pm)-**2**, m.p. 99-101°C, by a different route.

Finally, a similar reduction of **5** yielded another crystalline diol, the expected (1R,2S,8S)-compound, m.p. 134-134.5°C, $[\alpha]_D^{26}$ -32° (c, 1.25 EtOH); lit.¹, m.p. 132-134°C, $[\alpha]_D^{25}$ -20°; (c, 0.25 EtOH) whose IR spectrum (KBr disc) was indeed superimposable upon that of an authentic specimen of petasinecine (**1**). A mixed melting point of the two diol samples was also undepressed.

We have thus completed the first chiral synthesis of petasinecine and its C-1 epimer.

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8. For **2** in D₂O, at 200 MHz; J_{1,2} = 8 Hz, J_{2,3} = 6 and 8.4 Hz; for **5** in D₂O, at 270 MHz⁶; J_{1,2} = 7.5 Hz, J_{2,3α} = 4 Hz, J_{2,3β} = 8.5 Hz; in D₂O, at 100 MHz⁷; J_{1,2} = 8 Hz, J_{2,3α} = 5.8 Hz, and J_{2,3β} = 8 Hz. In contrast for **1**, in D₂O, at 200 MHz, we find J_{1,2} = 4.5 Hz, J_{1,8} = 8 Hz, J_{2,3α} = 4 Hz, J_{2,3β} = 1.5 Hz; in D₂O, at 60 MHz⁹; J_{1,2} = 5 Hz, J_{1,8} = 8.2 Hz, J_{2,3α} = 4.2 Hz, J_{2,3β} = 1.5 Hz.
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