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

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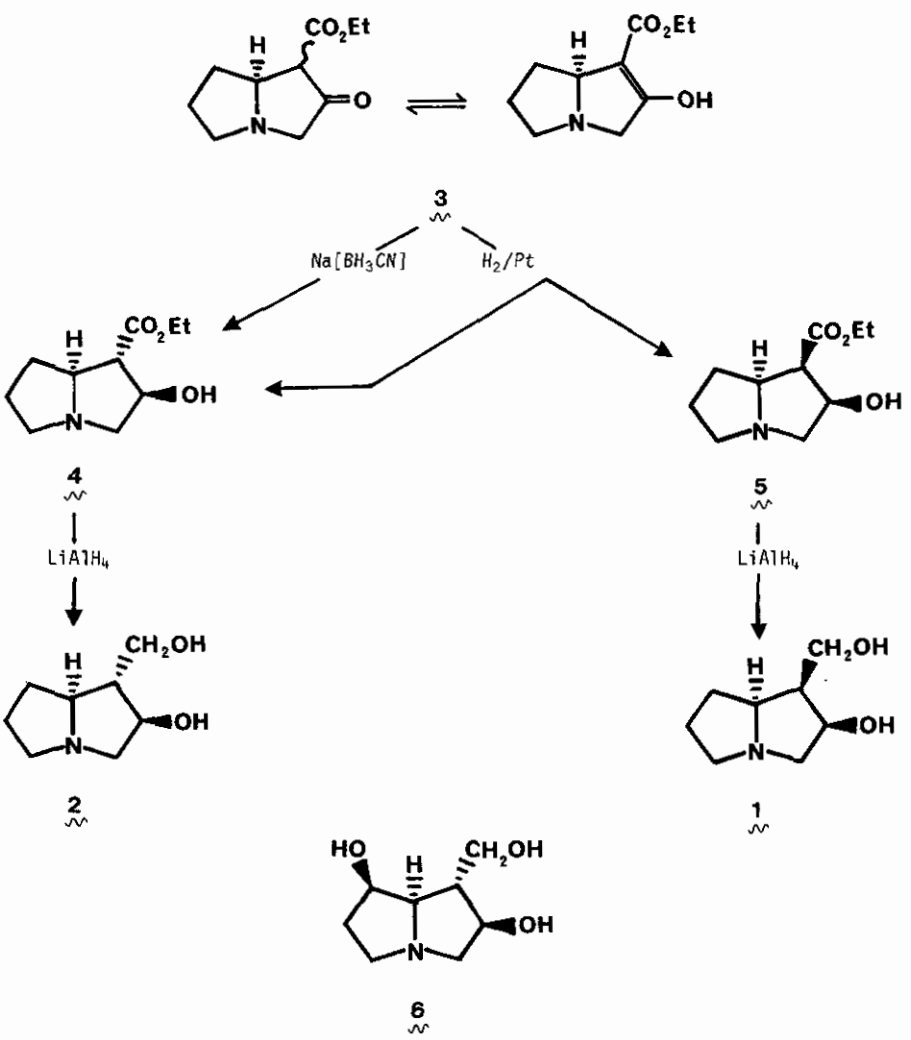
Abstract - The hydrogenation of (8S)-1-ethoxycarbonylpyrrolizidin-2-one in aqueous acetic acid, over Adam's catalyst, afforded a separable mixture of (1R,2S,8S)- and (1S,2S,8S)-1-ethoxycarbonylpyrrolizidin-2-ol. Reduction of the individual epimers with lithium aluminium hydride gave the corresponding 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-hydroxymethylpyrrolizidine, which was deduced to be the (1R,2S,8S)-stereoisomer (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 (2) from (8S)-1-ethoxycarbonyl pyrrolizidin-2-one (3) an intermediate which we had previously prepared from (S)-proline, and used for the synthesis of (-)-isoretronecanol, (-)-trachelanthamidine, and (-)-supinidine (2).

The catalytic hydrogenation of 3, as its hydrochloride salt[2], 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 isoretronecanolate, 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: 4 (50%), m.p. 72-73°C, $[\alpha]_D^{25}$+24° (c, 1.5 EtOH), hydrochloride salt m.p. 126-127°C; and 5 (36%), m.p. 64.5-65.5°C, hydrochloride salt, m.p. 172-173°C $[\alpha]_D^{25}$-35.6° (c, 1.0 EtOH)[3]. Although the hydrochloride of 5 was stable, the free base underwent slow isomerisation to 4 when its solutions were kept at room temperature. Since this behaviour was consistent with a C-1 *endo*⇌*exo* epimerisation of the ethoxycarbonyl function[4] and given also that hydrogenation was expected to occur from the less-hindered α-face, we therefore made the stereochemical assignments shown in 4 and 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 2β-ol, as precedented by the sodium borohydride reduction of (±)-8α-1-ethoxycarbonylpyrrolizidine-2,3-dione[5], 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° (c, 1.0 EtOH), an analysis of whose 200 MHz ^{1}H-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 Culvenor[5] had previously prepared (±)-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. 132-134C°, $[\alpha]_D^{25}$-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 D_2O, at 200 MHz; $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 6 and 8.4 Hz; for 6 in D_2O, at 270 MHz[6]; $J_{1,2}$ = 7.5 Hz, $J_{2,3\alpha}$ = 4 Hz, $J_{2,3\beta}$ = 8.5 Hz; in D_2O, at 100 MHz[7]; $J_{1,2}$ = 8 Hz, $J_{2,3\alpha}$ = 5.8 Hz, and $J_{2,3\beta}$ = 8 Hz. In contrast for 1, in D_2O, at 200 MHz, we find $J_{1,2}$ = 4.5 Hz, $J_{1,8}$ = 8 Hz, $J_{2,3\alpha}$ = 4 Hz, $J_{2,3\beta}$ = 1.5 Hz; in D_2O, at 60 MHz[9]; $J_{1,2}$ = 5 Hz, $J_{1,8}$ = 8.2 Hz, $J_{2,3\alpha}$ = 4.2 Hz, $J_{2,3\beta}$ = 1.5 Hz.
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