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(5αH)-6-Epidihydrocornin, the First Known Iridoid Glycoside With a Trans-fused Ring System

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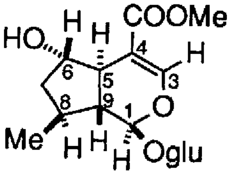
Abstract: An iridoid glycoside isolated from *Penstemon secundiflorus* contains a trans-fused cyclopentanopyran ring system, unlike all other known iridoid glycosides, which contain a cis-fused cyclopentanopyran.

Iridoid glycosides are common constituents of a select group of higher plant families and they currently encompass over 500 individual structures.[1-4] All of these contain a cis-fused bicyclic cyclopentanopyran ring system. We have now isolated, from fresh leaves of *Penstemon secundiflorus* Benth., the first trans-fused iridoid glycoside. It was assigned structure **1**, (5αH)-6-epidihydrocornin, from NMR analysis and a single crystal X-ray study of a tri-*p*-bromobenzoate derivative. *P. secundiflorus* from southern Colorado yielded an array of iridoid glycosides, including penstemoside, cornin, hastatoside, 8-epihastatoside, ß-dihydrohastatoside, and adoxoside. The major iridoid isolate (0.3% of the fresh leaf weight) was **1**.



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The ^1H and ^{13}C NMR spectra (including DEPT and HETCOR) for **1** were typical for iridoid glycosides related to **1** except for three pieces of data which were outside the range of those reported for all other iridoid glycosides: 1) the resonance of C-1 was at 103 ppm ("normal" 96 to 100 ppm), 2) the resonance for H-9 was at 1.5 ppm ("normal" 2.0 to 2.7 ppm), and 3) the allylic coupling of the H-3/H-5 resonances was 2.1 Hz ("normal" 0.5-0.9 Hz). Strong nOe enhancements for noncontiguous protons were seen between H-6 and H-9, H-8 and H-5, and H-8 and H-1, which showed that H-9 and H-6 were on the same side of the ring system, while H-8, H-5 and H-1 were together on the opposite side, as shown in **1**. Dreiding models indicated that the trans ring fusion caused significant conformational changes in the pyran ring which could account for the anomalies in the NMR spectra. The Oglucose substituent at C-1 takes up a pseudo-equatorial position, while it is pseudo-axial in cis-fused iridoids; the C-3/C-4 π-bond and the H-9 proton are tilted toward each other, which places the H-9 proton in a shielding region; and the H-5 C-H bond is parallell (rather than perpendicular) to the p-orbitals of the C-3/C-4 π-bond, which results in a maximum (rather than minimum) coupling constant.[5]

Because of the novelty of this suggested structure, the isolate was treated with *p*-bromobenzoyl chloride and the derivative mixture was purified by preparative TLC to yield crystals (mp 182° dec. from hexane/EtOAc) of the 2', 3', 6'- tri-*p*-bromobenzoate derivative. This was shown by a single crystal X-ray study[6] to have the structure given in Figure 1, which confirmed in all respects the assigned stereochemistry for **1**. A trans-fused structure was once postulated for an isomer of deoxyloganic acid from *Nepata cataria*, but was subsequently reassigned[7] a cis-fused structure, with absolute stereochemistry at C-5 and C-9 opposite to that of other iridoid glycosides.

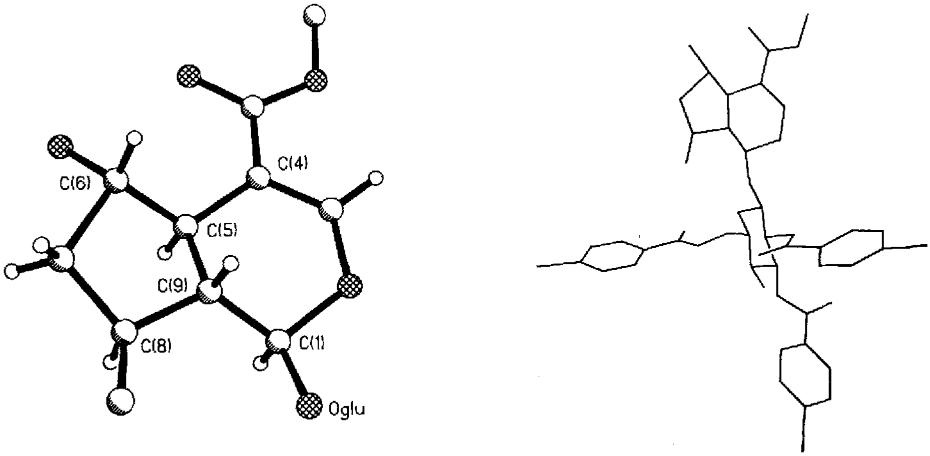

Fig. 1. Iridoid portion (left) and complete molecule (right, line-bond structure) of the 2',3',6'-tri-*p*-bromobenzoate derivative of **1**, computer drawn from the single crystal X-ray data.

There are no known instances of epimerization at C-5 among the hundreds of iridoid isolations and it seems likely that the trans ring fusion for **1** is set at the time of cyclization from an acyclic monoterpene precursor.[8]

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