

THE REVISED STRUCTURE OF PENSTEMIDE

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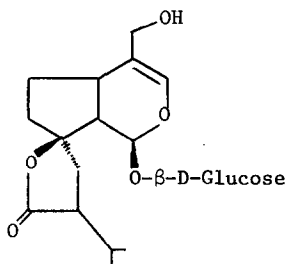
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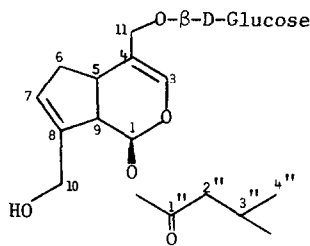
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**Abstract** The original structure of the antitumor agent, penstemide, has been revised to an isovaleroyl type iridoid glucoside based upon additional physical data.

The isolation and identification of the antitumor agent, penstemide (**Ia**) was reported in *Tetrahedron Letters*, No. 46, pp. 4119-4120 (1976). A reexamination of the physical data along with additional new information necessitates modifying the structure to **Ib**.



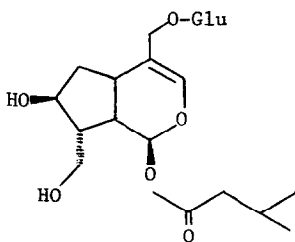
**Ia**



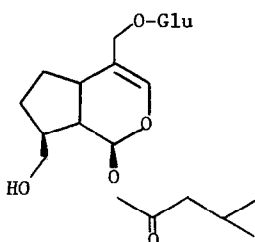
**Ib**

Absorptions at  $\delta$ 6.4 and 5.7 (PMR) together with presence of signals from an isovaleroyl group ( $\delta$ 0.8, 2.0 and 2.4) indicate a "valeriana-iridoid." This is confirmed by the  $^{13}\text{C-NMR}$  data (Table I).

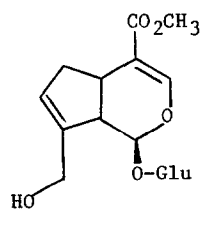
The glucose moiety is attached to C-11 since C-1' ( $\delta$ 102.0) absorbs downfield from the expected  $\delta$ 99.0-100.5 when attached at C-1.<sup>1,2</sup> This is consistent with the model compounds patri-noside (**II**) and dihydropenstamide (**III**). Furthermore, the high field signal for C-1 ( $\delta$ 93.5) is consistent with the isovaleroyl group in this position.<sup>4</sup>



**II**



**III**



**IV**

The PMR signal at  $\delta$ 5.8 together with  $^{13}\text{C}$ -NMR signals at 130.5 (d) and 141.8 (s) indicate a trisubstituted double bond in the five-membered ring. The remaining carbon atoms can be accounted for as follows: Four methinyl groups, one methylene group and one hydroxy methylene group.

Comparison of the  $^{13}\text{C}$ -NMR signals with geniposide (IV) demonstrates a good correlation for the five-membered ring. Likewise, the remaining carbon signals correlate well with II and III.

TABLE I:  $^{13}\text{C}$ -NMR (22.63 MHz) Spectral Data

Atom	Ib	II	III	IV	Ib Ac <sub>5</sub>	II Ac <sub>6</sub>	III Ac <sub>6</sub>	IV Ac <sub>6</sub>
C-1	93.1	93.5	93.2	98.1	91.9	91.3	91.0	96.1
C-3	140.4	140.0	140.2	153.4	140.5	140.1	140.1	151.0
C-4	115.7	116.1	115.0	112.4	113.1	112.7	111.7	112.1
C-5	36.7	33.0	35.8	35.1	36.1	33.1	35.8	33.9
C-6	37.2	39.6	30.1	38.9	37.2	37.5	29.7	38.6
C-7	130.5	72.6	27.7	129.8	131.5	74.0	27.1	131.1
C-8	141.8	47.8	42.6	142.3	137.8	43.2	38.8	137.3
C-9	46.4	41.8	43.6	46.6	46.0	42.1	43.5	46.5
C-10	60.4	61.3	65.9	60.0	62.0	62.5	67.0	61.9
C-11	70.0	69.0	69.8	170.8	69.3	68.7	68.7	167.3
C-1'	102.0	103.3	102.2	99.8	99.2	99.1	99.0	96.8
C-1''	175.3	175.9	176.0		171.6	171.8	171.5	
C-2''	43.7	43.8	43.8		43.2	43.2	43.0	
C-3''	26.1	26.2	26.2		25.5	25.6	25.3	
C-4''	22.4	22.4	22.3		22.3	22.3	22.0	

Solvents: D<sub>2</sub>O (DSS) for Ib, II, III and IV; CHCl<sub>3</sub> (TMS) for acetates.

Hydrogenolysis (H<sub>2</sub>/PtO<sub>2</sub> in MeOH) provides additional evidence for the C-11 glucosidic linkage since glucose was identified by TLC and paper chromatography after work-up. When the glucose moiety is attached to C-1, the glucosidic bond remains intact.<sup>5</sup>

Acetylation of penstemide, [ $\alpha$ ]<sub>D</sub><sup>20</sup> -24° (c, 0.9 in MeOH), provides a pentaacetate: [ $\alpha$ ]<sub>D</sub><sup>18</sup> -24° (c, 0.7 in CHCl<sub>3</sub>); PMR  $\delta$ 2.0 (16H, 5 x OAc and 3''-H); Calc. for C<sub>31</sub>H<sub>42</sub>O<sub>15</sub>: C, 56.87; H, 6.46. Found: C, 57.23; H, 6.64. This confirms the presence of 5 OH groups. Comparison of the respective  $^{13}\text{C}$ -NMR's is convincing. Therefore, the correct structure of penstemide is designated by Ib.

Geniposide (IV) was also isolated and identified by comparison with an authentic sample of geniposide (TLC and NMR). Recently, Kooiman has reported the presence of aucubin, catalpol and catalpol esters in 15 different species of *Penstemon*.<sup>6</sup>

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