Willow bark and its glucosides

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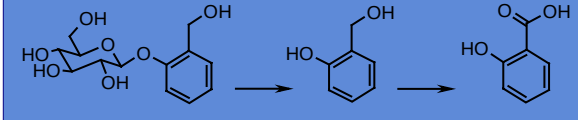
Introduction

The use of salicylates dates back to the time of Hippocrates (400 BC). He was the first who noted the analgesic and antipyretic properties of extracts of willow bark. The first scientific studies of salicylates began in 1763 when E. Stone showed the antipyretic properties of willow bark extract on feverish patients [1]. Anti-inflammatory effects were demonstrated in 1876 by T. J. Maclagan whose patients obtained relief from acute rheumatic fever when treated with salicin **1**, an important willow bark glucoside [2].

1. Metabolism of Salicin

The modern use of willow bark focuses on **1**, the precursor of salicylic acid **3** and its analgesic, anti-inflammatory and antipyretic activity. To date, the effect of **1** has not been understood fully.
3 is known to be the active metabolite of **1**, but the enzymatic and oxidative conversions in humans are only based on assumptions.
It is assumed that **1** is cleaved by bacterial enzymes to salicyl alcohol **2** and glucose; **2** is absorbed and oxidised to **3** [3].

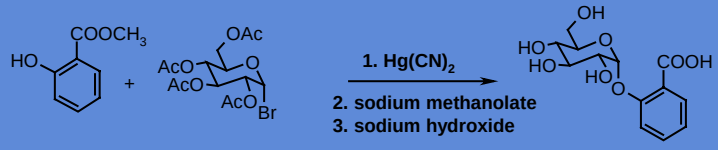


1 **2** **3**

2. α-Glucosides

We assume that β-glucosidases are essential for the enzymatic conversion of **1**. In humans, there are much fewer β- than α-glucosidases. We investigate the possibility that α-glucosides lead to a faster increase of **3** in blood than the naturally occuring β-glucosides. For this reason we synthesised different α-glucosides of **3** [4,5] and **1** [6].
To compare the increase of **3** from α- and β-glucosides, the β-glucoside of **4** was also synthesised [5]

Synthesis of 2-Carboxyphenyl-α-glucopyranoside



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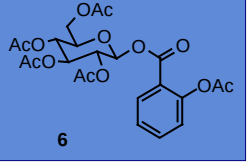
Synthesis of α-Isosalicin

α-Isosalicin **5** was synthesised from starch and **2** by using transglycosylation acticvity of amyloglucosidase. The synthesis was regio- and stereoselective, but the yield was less than 1%.

3. β-Glucosides

We further investigate the possibility that glucosides of **3** and acetylsalicylic acid cause less gastric injury than the unprotected acid-group. Therefor we try to synthesise salicylic acid 2-O-β-glucoside. So far, we have accomplished the synthesis of acetylsalicylic acid 2-O-β-tetra-acetylglucoside **6**.



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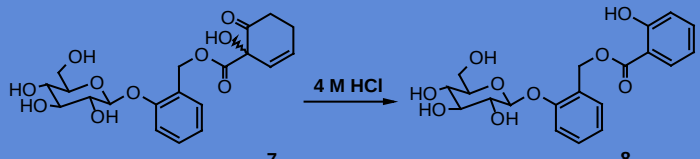
4. Salicortin and Salicoylsalicin

Another important glucoside of willow bark is salicortin **7**, one of the main precursors of salicin in the plant. **7** contains a cyclohexenecarboxylic acid moiety [7, 8]. We tried to convert this moiety into a salicylic acid residue. **7** was treated with artificial gastric fluid and 2 M-/4 M hydrochloric acid. In all cases salicylic acid was not detectable. By treating **7** with 4 M hydrochloric acid it was converted to salicoylsalicin **8**.



7 **8**

5. Outlook

α-Salicin and some glycosides with different sugar moieties are presently in development.
The increase of **3** in blood is going to be tested with these different glycosides.
We are further interested in the preparation of a salix extract with high content of **7**and/or **8** and the absorption and metabolism of the latter glucosides.

6. References

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