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Thomasidioic Acid and 6-Hydroxy-5,7-dimethoxy-2-naphthoic Acid: Are They Really Natural Products?

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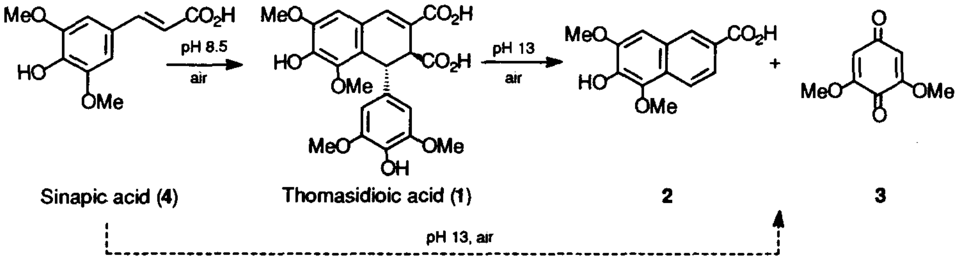
Abstract: It has been shown that air oxidation of alkaline aqueous solutions of sinapic acid produces both thomasidioic acid (**1**), and 6-hydroxy-5,7-dimethoxy-2-naphthoic acid (**2**) in high yield, with the relative amounts dependent on the basicity of the solution. It has also been shown that naphthoic acid **2** is a secondary oxidation product of thomasidioic acid, a reaction that also produces 2,6-dimethoxy-*p*-benzoquinone (**3**). The question of whether compounds **1**, **2** and **3** are really natural products, as previously reported, is discussed. © 1997 Elsevier Science Ltd.

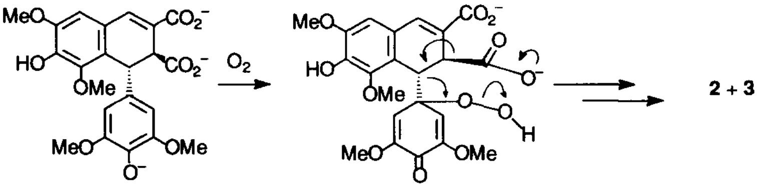
In 1969, two papers were published in which (±)-thomasidioic acid (**1**), 6-hydroxy-5,7-dimethoxy-2-naphthoic acid (**2**), and 2,6-dimethoxy-*p*-benzoquinone (**3**) were reported as isolates from aqueous extracts of the heartwood of *Ulmus thomasii Sarg.*[1,2] It was assumed that these compounds were natural products (products of biosynthesis).



As part of a study on the constituents of canola meal, we recently discovered that thomasidioic acid (**1**) was readily formed when sinapic acid (**4**) was air oxidized in dilute alkaline (pH 8.5) solutions.[3,4] While investigating the effect of pH on this reaction an interesting discovery was made. If sinapic acid was air oxidized in aqueous solution at pH 13 the major product was 6-hydroxy-5,7-dimethoxy-2-naphthoic acid (**2**) (72% after chromatography, 5:75:20 acetic acid:ethyl acetate:hexanes). A re-inspection of the NMR spectrum of the reaction run at pH 8.5 indicated that traces of the naphthoic acid **2** were also formed at the lower pH as well, and that its yield steadily increased with time. This observation led to the hypothesis that naphthoic acid **2** was being formed in a secondary oxidation of thomasidioic acid.

To test this hypothesis, thomasidioic acid was air oxidized in aqueous solution at pH 13. As suspected this reaction also yielded naphthoic acid **2** as the sole acidic product (80% after chromatography). Examination of the neutral fraction indicated the presence of 2,6-dimethoxy-*p*-benzoquinone **3**. It was identified by its ^{1}H and ^{13}C NMR spectra as well as by comparison of its retention time on HPLC to that of an authentic sample.

Although the exact mechanism is unknown, the reaction presumably begins from the phenolate anion of **1** (**1a**). This would explain the pH dependence of the reaction. After addition of oxygen by either an ionic or free radical mechanism, decarboxylative elimination would give the products **2** and **3**. When thomasidioic acid was simply stirred at pH 13 under nitrogen, no degradation took place proving the requirement for oxygen in this reaction.



1a

The fact that compounds **1**, **2** and **3** were all isolated together from basic aqueous extracts of *Ulmus thomasii Sarg.*, and the fact that all three are produced from air oxidation of sinapic acid in aqueous basic solutions suggests that there is at least the possibility that all three 'natural products' were formed from sinapic acid during the extraction procedure. Supporting this notion is the fact that the 'natural' thomasidioic acid was optically inactive.[1] Interestingly, sinapic acid was not reported as one of the constituents of the extract from *Ulmus thomasii Sarg*. This would be consistent with our suggestion, since sinapic acid would be completely oxidized to thomasidioic acid after a few hours in alkaline aqueous medium. Sinapic acid is a common constituent of many plants and it is not unlikely that it is also present in *Ulmus thomasii Sarg.*[5]

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