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Short Communication

A Convenient Semisynthetic Route to Hypericin

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Summary. A semisynthetic route to produce hypericin was established using *Cortex frangulae* as the starting point. The emodin isolated from it easily and in good yield was reduced to emodin anthrone by means of $SnCl_2$. The latter was reacted via a known oxidative dimerization and photocyclization reaction into hypericin.

Keywords. Emodin; Emodin anthrone; Hypericin; *Cortex frangulae.*

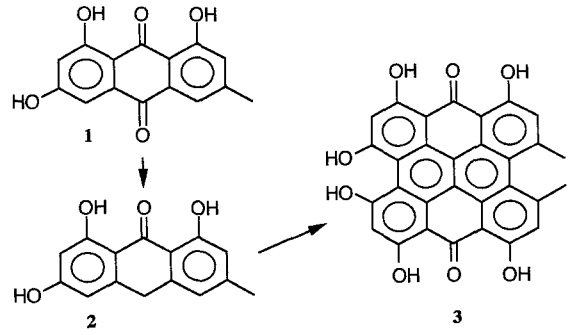
Ein bequemer semisynthetischer Zugang zu Hypericin

Zusammenfassung. Eine semisynthetische Route zur Darstellung von Hypericin unter Verwendung von *Cortex frangulae* als Ausgangsmaterial wurde erarbeitet. Das daraus einfach und in guten Ausbeuten isolierte Emodin wurde mit Hilfe von $SnCl_2$ zu Emodinanthron reduziert. Letzteres wurde dann über eine bekannte oxidative Dimerisierung und Photocyclisierung zu Hypericin umgesetzt.

A vivid interest in hypericin (**3**), initiated by its antiviral and antiretroviral properties [1], triggered a search for efficient methods to improve its accessibility. According to literature, **3** may be either isolated from natural sources like *Hypericum perforatum* [2], or it can be obtained by dimerization procedures starting from emodin derivatives [3–5]. However, accessibility using these methods suffers on the one hand from rather long synthetic routes [3, 4–6] or the tedious isolation from natural sources [3, 7]. Moreover, we experienced in the latter case that the content of **1** in the plant material varies dramatically from site to site and from season to season. On the other hand, the route from emodin (**1**) *via* emodin anthrone (**2**) to **3** would be a rather convenient one, if **1** was available in reasonable quantities and at a reasonable price. However, commercial **1** is rather expensive, and its isolation from rhubarb root [8] is hampered by low yields. Recently we developed a high yield synthesis of **2** [9], but one had still five demanding steps to go from a readily available starting material. We therefore developed a high yield semisynthetic procedure to prepare **1** and eventually **3**.

1 is known to be contained in form of its glycoside as a main constituent in the medicinally used *Cortex frangulae* [10, 11]. This bark is commercially available in large quantities at a reasonable price.

1000 g of dry *Cortex frangulae* were triturated with 3 l methanol during 2 h at room temperature. After maceration by means of an "Ultraturrax" device the solvent was filtered off and the residue extracted two times with 1 l portions of methanol in the same way. The resulting extract was evaporated on a rotatory evaporator, and the residue (150–175 g) was hydrolyzed by boiling it under reflux with 1 l $HCl_{conc.}/H_2O = 1:1$ per 100 g extract. One should provide sufficient head space in this procedure due to foaming. The resulting residue was filtered off, washed with water to neutral *pH* and dried in vacuum at room temperature (125–150 g). This material was then extracted by means of dichloromethane in a Soxhlet extractor until the eluate was slightly yellow coloured. Evaporation of the solvent and chromatography on silica ($CHCl_3/CH_3OH = 20/1$; the second yellow–orange band was collected) resulted in 10 g of pure **1**; m.p. 256 °C.



Reduction of **1** to form **2** was achieved in two ways. The reduction by means of HI in acetic acid resulted in yields of 90% [9, 12]. We found it cheaper and more convenient to adapt the procedure of Ref. [10] using $SnCl_2$. Thus, 1 g **1** was dissolved in 70 ml acetic acid and 2.8 g $SnCl_2 \cdot 2H_2O$ dissolved in 8 ml $HCl_{conc.}$ were added. After refluxing for 5 h and cooling to room temperature **2** is filtered off and dried in vacuum (yield 0.65 g; 88%). Its purity as judged from the spectroscopic data [9] is already sufficient for the next step.

To produce **3**, we used the procedure described in Ref. [13]. Although the yields reported in this patent (63%) could not be reproduced, this procedure proved nevertheless to be comparable to the one we described recently (56% [14]). For the purification of **3** it was found to be most effective to use chromatography of its salt on Sephadex LH-20 as described in Ref. [2b].

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