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On the Synthesis of Hypericin by Oxidative Trimethylemodin Anthrone and Emodin Anthrone Dimerization: Isohypericin

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Summary. The base catalyzed oxidative dimerization of emodin anthrone exclusively yields hypericin. However, on oxidative dimerization of trimethylemodinanthrone a mixture of hexamethylhypericin and hexamethylisohypericin was obtained. Chromatographic separation of the hexabenzoyl derivatives was achieved, and by saponification about equal amounts of hypericin and isohypericrin were produced. Isohypericin could be characterized for the first time by its spectroscopic data and its protonation and deprotonation pK_a and pK_a* values.

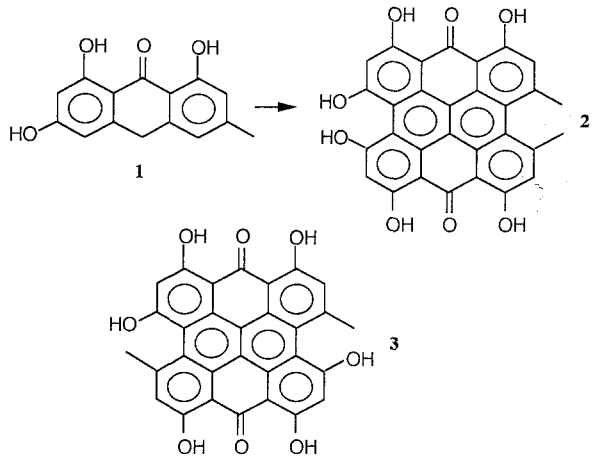
Keywords. Trimethylemodin anthrone; Emodin anthrone; Hypericin; Isohypericin; Spectroscopic properties; pK_a-values; Synthesis.

Zur Synthese von Hypericin durch oxidative Dimerisierung von Trimethylemodinanthron und Emodinanthron: Isohypericin

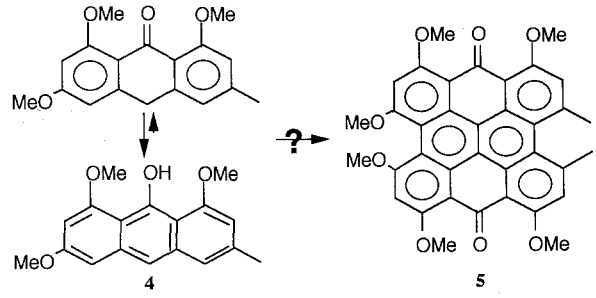
Zusammenfassung. Die basenkatalysierte oxidative Dimerisierung von Emodinanthron liefert ausschließlich Hypericin. Oxidative Dimerisierung von Trimethylemodinanthron ergibt jedoch ein Gemisch von Hexamethylhypericin und Hexamethylisohypericin. Die Hexabenzoylderivate wurden chromatographisch getrennt, und Hypericin und Isohypericin konnten aus diesen Derivaten durch Verseifung freigesetzt werden. Isohypercin konnte erstmals durch seine spektroskopischen Daten und seine Protonierungs- und Deprotonierungs-pK_a- und pK_a*-Werte charakterisiert werden.

Introduction

Emodin anthrone (**1**) serves as the immediate precursor in the "symmetrical dimerization" synthesis of hypericin (**2**) [1 – 3]. According to literature [1 – 3] this base catalyzed oxidative dimerization specifically and exclusively yields the C_{2v}-symmetrically substituted **2** and not the C_{2h}-symmetrically substituted isomer isohypericin (**3**). This was proven by the comparison of the absorption spectra, NMR spectra, and the chromatographic behavior of the compound produced [1 – 3] with those of authentic material from natural sources, or samples of **2** prepared by the "unsymmetrical dimerization" route [4, 5]. Although **3** has been mentioned and discussed occasionally [1 – 3], it could never be isolated and characterized.



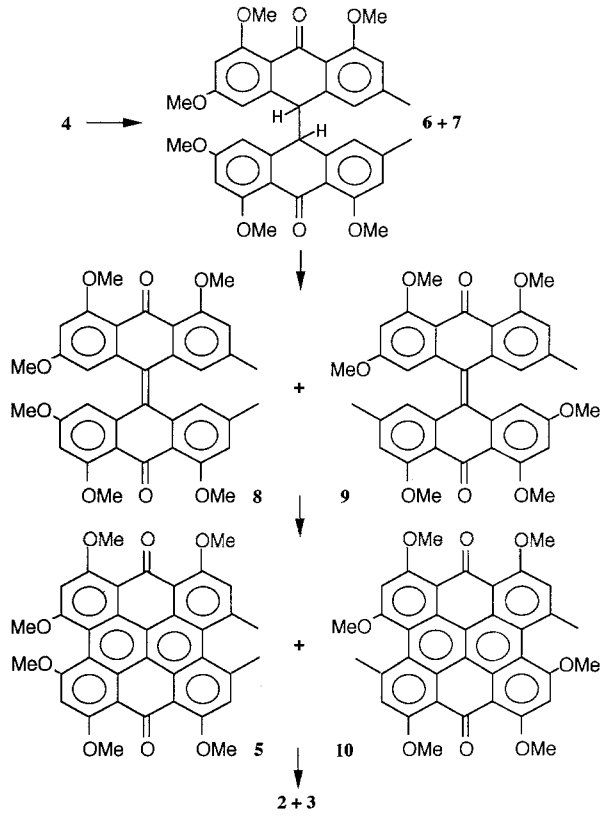
We recently reported an efficient synthesis of **1** [6] to provide easy access to **2**, which recently has become of interest due to its anti-retroviral properties [7]. As trimethylemodin anthrone (**4**) is the precursor of **1** it seemed to be of interest to proceed immediately from **4** by means of an oxidative dimerization to produce hexamethyl hypericin (**5**) from which, in principle, **2** could be derived by demethylation [2].



Moreover, a reaction of this kind could be favored because the dimerization reaction of **1** may be thought to start from the anthranol tautomer, and **4** was recently shown to be exclusively present in solution as its anthranol tautomer [6]. We will now report on the results of this investigation.

Results and Discussion

Dimerization of **4** with $FeCl_3$ to the *meso* and *racemic* bianthraquinoyl derivatives **6** and **7** was followed by oxidation with peroxodisulfate in analogy to the procedures contained in literature [8, 9] to yield the (*Z*) and (*E*) bianthrone diastereomers **8** and **9**. Photocyclization of this mixture resulted in a material which showed a chromatographic behavior and an absorption spectrum which was indistinguishable from that of **5**, which was prepared by methylation of authentic hypericin (**2**) [4]. However, in addition to the signals of hexamethylhypericin **5** the ^{1}H-NMR spectrum clearly revealed an analogous set of signals of about the same intensity, which was slightly shifted with respect to the signal set of **5**.

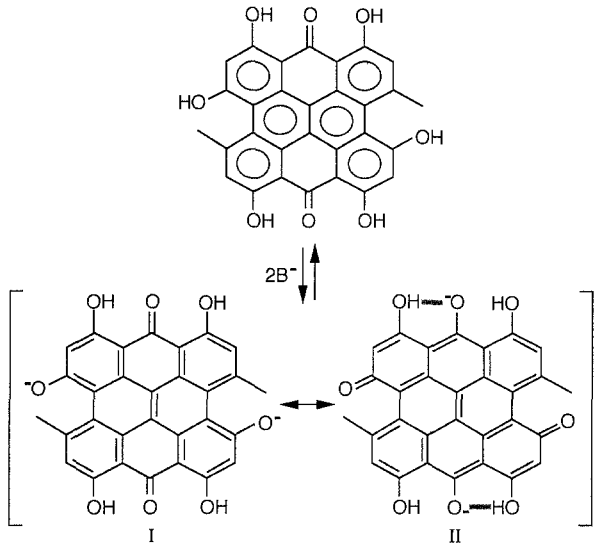


As the mixture of the two isomers could not be separated by chromatography, it was demethylated with KI in phosphoric acid [4]. On thin layer chromatography two red spots separated (silica, chloroform/methanol = 4/1; R_f = 0.11, 0.54), one of them (R_f = 0.11) showed the same R_f value as authentic **2**. However, due to the insolubility of the two reaction products, we were not able to use this separation technique on a preparative scale. Again the ^{1}H-NMR-spectrum of this demethylation reaction product resulted in two signal sets – one of them corresponded to that of **2**. On addition of N-ethyl-N,N-diisopropylamine the corresponding salts were formed [10]. However, on chromatography the difference of their R_f values was again negligible.

Therefore the product of the demethylation step was benzoylated. The resulting reaction mixture containing hexabenzoylhypericin (**11**) could then be easily separated by medium pressure chromatography on silica. Saponification of the two fractions (**11**, **12**) afforded pure hypericin (**2**) and a new hypericin colored compound, which according to its NMR data was isohypericin (**3**).

In contrast to **2** it exhibits in its ^{1}H-NMR spectrum an additional broadened deuterium exchangeable signal of intensity 2 H at 12.0 ppm which has to be assigned to the hydroxylic protons OH-3 and OH-10. Upon deprotonation by means of N-ethyl-N,N-diisopropylamine this signal gradually disappeared after considerably broadening, and after two moles of base were added. At the same time the signal assigned to CH-2 + CH-9 underwent a strong shift to lower frequencies, as well as the OH-1 + OH-8 signal was markedly shifted to higher frequencies. These shifts could be accounted for with the resonance charge delocalization shown in Scheme 1. In contrast to this behavior, only a signal at 18.4 ppm for the remaining proton

(OH-4), and only small shifts of the other signals have been observed after the first deprotonation step at OH-3 in **2** [10].



Scheme 1

Interestingly enough, the pK_a and pK_a^* values of the first deprotonation step at the hydroxylic group in position "3" of **2** (11.0, 9.8 [11]) and the first two deprotonation steps in **3** (given by the apparant values $pK_a' = 7.0$ and $pK_a^{*\prime} = 4.7$) are quite different. Whereas in **2** the ground state acidity of this phenolic group is much the same as in similar anthrone model compounds [11], it is considerably enhanced in **3**. As an interpretation we suggest, according to Scheme 1, a stabilization of the deprotonated phenolic system due to charge delocalization by means of resonance forms like II. In **2** such delocalization is improbable due to the interaction between the phenolate ion and its adjacent OH-4 group. This kind of argumentation also holds for the deprotonation of 10-OH in **3** as the "upper" and "lower" halves of **3** should be deprotonated more or less independently – accordingly a mean apparent pK_a' value is observed for **3**. It should be mentioned that the absorption band intensity of the bis-deprotonated **3** was about double the intensity of the corresponding band in the mono-deprotonated **2** [10, 11]. The differences between the pK_a and pK_a^* values of **2** and **3** are within experimental error. That means that ground and excited states are influenced by the same kind of interactions in both compounds. The third deprotonation step measured for **3** ($pK_a = 16.5$) is found to be significantly higher than the second one of **2** ($pK_a = 14$ [11]). As the latter value could not be assigned to a specific hydroxyl group for **2** [11] and we are not able to assign it for **3**, an interpretation in the present case has also to be avoided.

The protonation pK_a and pK_a^* values of **3** are estimated to amount -5.9 and -1.1. Accordingly, between the protonation and deprotonation pK_a^* values there is still a gap of nearly six pK units. Thus there is no inversion of relative acidities and basicities between ground and excited states, as also has been found in the case of **2** [11].

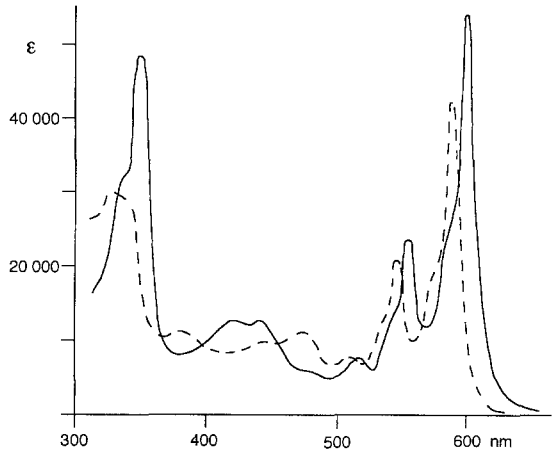
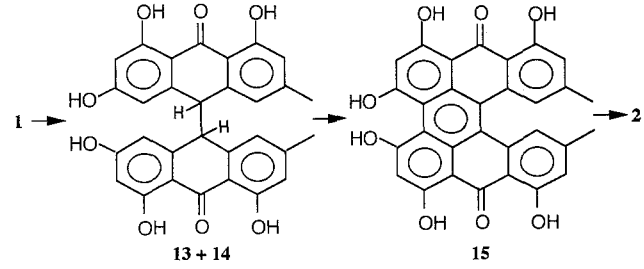


Fig. 1. UV-Vis spectra of **2** (dashed line) and **3** in ethanol

As shown in Fig. 1 the long wavelength bands in the absorption spectrum of **3** are bathochromically shifted by about 12 nm as compared to **2**, and there is a significant difference in the absorption region between 300 and 500 nm. The bathochromic shift of the long wavelength absorption bands could indicate a slightly planarized chromophoric system in **3** as compared to **2**.

The fluorescence spectrum of **3** is similar to that of **2**: the fluorescence band system is mirror symmetric to the long wavelength absorption bands, its Stokes shift is only 4 nm, and its quantum yield is 0.25.

Bearing in mind the spectroscopic properties of **3** advanced so far, the synthesis of **2** from **1** as described in Ref. [1, 2] was revisited. Indeed, following the procedure described in Ref. [1, 2], and modifying it to achieve higher yields, did not result in the formation of even a trace of **3** when proceeding from **1** via the bianthraquinoyls (**13** + **14**) and protohypericin (**15**). Obviously, the free phenolic groups are needed to ensure regioselectivity by enhancing the reactivity of the 4 and 4′ positions in the second oxidative coupling step.



Experimental Part

Melting points were taken by means of a Kofler hot stage microscope (Reichert, Vienna). ^{1}H-, ^{13}C-, IR-, UV-VIS-, and fluorescence-spectra were recorded using the Bruker-WM-360-, and AC-200-, Biorad-FT-IR-45-, Hitachi-U-3210-, and F-4010-instruments. For fluorescence spectroscopy 95% ethanol of "für die Fluoreszenzspektroskopie" grade (Merck) was used. The pK_a and pK_a* values of **3** were determined spectrophotometrically using 80% aqueous dimethylsulfoxide and tetrabutylam-

monium hydroxide as the base and by means of a Förster cycle calculation as reported recently [11] for **2**.

(meso+racem)1,1',3,3',9,9'-Hexamethoxy-7,7'-dimethylbianthraquinoyl [**6**+**7**; $C_{36}H_{34}O_8$]

In analogy to Ref. [8] 209 mg (0.70 mmol) **11** were dissolved in 5 ml refluxing ethanol (p.a.). During 30 min 24 ml $FeCl_3$-solution (1% $FeCl_3 \cdot 6$ aq. in ethanol, 0.70 mmol) were dropped into this mixture and the solution was refluxed for additional 30 min. The green solution was poured into 1 000 ml 5% HCl and extracted twice with chloroform. The organic phase was washed with saturated NaCl solution, dried over Na_2CO_3 and evaporated on a rotavapor. Chromatography (silica, chloroform/methanol = 10/1) resulted in 189 mg (91%) white crystals of the two diastereomeres **6** and **7**; m.p. = 253 – 263°C (dec.). ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): 6.67, 6.65, 5.78, 5.75 (4 s, 2 × H 5 + H 5', 2 × H 7 + H 7'), 6.39, 6.37, 5.44, 5.38 (4 d, J = 2.08 Hz, 2 × H 2 + H 2', 2 × H 4 + H 4'), 3.939, 3.930, 3.920, 3.907 (4 s, 4 × 2 *Me*O), 3.504, 3.470 (2 s, 2 × 2*Me*O), 3.492, 3.485 (2 s, 2 × H 10 + H 10'), 2.11, 2.07 (2 s, 2 × 2 *Me*) ppm. UV-Vis (ethanol) λ = 324 (15 600) nm (ε). IR (KBr): ν = 1 670, 1 620, 1 590 cm^{-1}.

(Z+E)1,1',3,3',9,9'-Hexamethoxy-7,7'-dimethylbianthrone [**8**+**9**; $C_{36}H_{32}O_8$]

In analogy to Ref. [9] 0.7 g KOH were dissolved in 5 ml ethanol (p.a.). 58 mg (97.6 μmol) of the above described mixture of **7**+**9** was added and the mixture refluxed for 30 min under exclusion of light. The yellow-red solution was dropped into the vigorously stirred solution of 60.8 mg (225 μmol) potassium peroxodisulfate in 20 ml water. After 2 h the residue was centrifuged off, washed three times with water and dried. Chromatography on silica using chloroform yielded 52 mg (90%) yellow crystals; m.p. = 312 – 328°C. ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): signals of diastereomer I: 6.65, 6.48 (2 s, *ar*-H 6 + *ar*-H 6', *ar*-H 8 + *ar*-H 8'), 6.37, 6.10 (2 d, J = 2.10 Hz, *ar*-H 2 + *ar*-H 2', *ar*-H 4 + *ar*-H 4'), 3.930, 3.920 (2 s, *Me*O-1 + *Me*O-1'', *Me*O-9 + *Me*O-9'), 3.41 (s, *Me*O-3 + *Me*O-3'), 2.09 (s, 6H, 2*Me*) ; signals of diastereomer II: 6.65, 6.40 (2 s, *ar*-H 6 + *ar*-H 6', *ar*-H 8 + *ar*-H 8'), 6.37, 6.18 (2 d, J = 2.10 Hz, *ar*-H 2 + *ar*-H 2', *ar*-H 4 + *ar*-H 4'), 3.942, 3.907 (2 s, *Me*O-1 + *Me*O-1', *Me*O-9 + *Me*O-9'), 3.46 (s, 6 H, *Me*O-3 + *Me*O-3'), 2.04 (s, 6 H, 2 *Me*) ppm. UV-Vis (ethanol) λ = 353 (10 400), 297 (20 300) nm (ε). IR (KBr): ν = 1 690, 1 600 cm^{-1}.

Hexamethylhypericin + Hexamethylisohypericin [**5**+**10**; $C_{36}H_{28}O_8$]

50 mg **8**+**9** were dissolved in 380 ml ethanol, and under agitation in the presence of air the solution was irradiated by means of a low pressure mercury vapor lamp (500 W) for 100 min. The orange colored solution was evaporated on a rotavapor and chromatographed on silica (chloroform/methanol = 20/1), yield 34.8 mg (70%) of orange crystals; m.p. = 340°C (dec.). ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): 7.33, 7.27, 6.98, 6.94 (4 s, 4 × 2 *ar*-H), 4.218, 4.217, 4.186, 4.171, 4.156, 4.099 (6 s, 6 × 2 *Me*O), 2.68, 2.64 (2 s, 2 × 2 *Me*) ppm. UV-Vis (ethanol) λ = 532 (13 900), 420 (13 800), 307 (34 600) nm (ε). IR (KBr) ν = 1 690, 1 600 cm^{-1}.

Hypericin + Isohypericin [**2**+**3**; $C_{30}H_{16}O_8$]

Demethylation of **5**+**10** in analogy to [4]: 132 mg (224 μmol) **5**+**10** were dissolved in 13.2 ml phosphoric acid (95%) at 140 – 150°C. 660 mg (4 000 μmol) KI were added and the reaction mixture was stirred for 30 min. After addition of 660 mg KI the mixture was stirred for another 30 min at 140 – 150°C. The cold solution was poured into 130 ml water, the precipitate centrifuged off, washed with water (3 ×), and dried in high vacuum. Yield 104 mg (92%) **2**+**3**. Tlc (silica, chloroform/Methanol = 4/1): R_f (**2**) = 0.11, R_f (**3**) = 0.54. Due to the rather very low solubility of this mixture in common solvents preparative chromatography could not be achieved.

Hypericinhexabenzoate + Isohypericinhexabenzoate [**11** + **12**; $C_{72}H_{40}O_{14}$]

120 mg (238 μmol) **5** + **10** was dissolved in 4 ml pyridine, cooled to ice temperature, and 1 ml benzoylchloride was added during 10 min. After stirring for 2 h at 20°C the mixture was cooled again and quenched by addition of 1 ml water. After stirring for 20 min 100 ml chloroform was added and the solution was washed three times with 5% HCl, saturated $NaHCO_3$ solution, and saturated NaCl solution. The organic layer was dried over Na_2CO_3 and evaporated on a rotavapor. Medium pressure chromatography (silica, benzene/ethylethanoate = 20/1) resulted in two fractions:

Hypericinhexabenzoate (**11**): Tlc (silica, benzene/ethylethanoate = 20/1): R_f = 0.30; yield 83 mg (31%), m.p. 303 – 304°C, yellow crystals; compare Ref. [4]. ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): 8.16 – 7.27 (m, 6 *Ph*CO + 4 *ar*-H), 2.81 (s, 2 *Me*) ppm. UV-Vis (ethanol): λ = 425 (28 300), 290 (51 800) nm (ε). IR (KBr): ν = 1 745, 1 650 cm^{-1}.

Isohypericinhexabenzoate (**12**): Tlc (silica, benzene/ethylethanoate = 20/1): R_f = 0.34; yield 70 mg (26%) yellow crystals of m.p. 314 – 322°C, yellow crystals. ^{1}H-NMR ($CDCl_3$, 360 MHz, δ) 8.15 – 7.29 (m, 6 *Ph*CO + 4 *ar*H), 2.78 (s, 2 *Me*) ppm. UV-Vis (ethanol): λ = 424 (28 600), 289 (54 600) nm (ε). IR (KBr): ν = 1 750, 1 650 cm^{-1}.

Isohypericin [**3**; $C_{30}H_{16}O_8$]

Saponification of **12** was achieved by dissolving 70 mg (62 μmol) **12** in 20 ml 2 *N* methanolic KOH and refluxing this mixture for 20 min. The green solution was poured into 40 ml 2 *N* HCl, the precipitate centrifuged off, washed four times with water of 90°C, and dried for 2 days at room temperature and 2 h at 60°C in high vacuum. Yield 29 mg (93%) of black-violet crystals, m. p. > 350°C. ^{1}H-NMR (*DMSO-d_6*, 360 MHz, δ): 13.85 (broadened s, OH-6 + OH-13), 13.61 (broadened s, OH-1 + OH-8), 12.0 (broadened s, OH-3 + OH-10), 7.07 (s, CH-5 + CH-12), 6.64 (s, CH-2 + CH-9), 2.34 (s, 2 *Me*) ppm; NOE: (CH_3-4 + CH_3-11) → (H-5 + H-12). The ^{13}C-NMR spectrum could not be recorded due to the insufficient solubility of **3**. UV-VIS (ethanol): λ = 604 (54 500), 558 (24 400), 519 (7 700), 442 (12 500), 420 (12 600), 352 (49 800) nm (ε). Fluorescence (ethanol): λ = 608 (1.00), 656 (0.37) nm (relative intensity); fluorescence quantum yield Φ_F = 0.25 (Rhodamine B was used as the fluorescence quantum yield standard); the excitation spectrum proved to be superimposable on the absorption spectrum. IR (KBr): ν = 1 620, 1 600 cm^{-1}. The mass spectrum could not be obtained. Elemental analysis: calculated for $C_{30}H_{16}O_8 \cdot H_2O$ 3.60% H, 69.00% C; found 3.48% H, 68.61% C; as observed earlier [1, 4], these compounds show a strong tendency to retain solvents. Spectrophotometric pK_a determinations (solvent, 80% aqueous dimethylsulfoxide; base, tetrabutylammonium hydroxide): λ = 583 nm, λ_{--} = 611 nm, $\varepsilon_\lambda/\varepsilon_{\lambda--}$ = 0.64, pK_a' (I) = 7.0, pK_a*' (I) = 4.7; λ_{---} = 666 nm, $\varepsilon_\lambda/\varepsilon_{\lambda---}$ = 1.59, pK_a (II) = 16.5; (solvent aqueous sulfuric acid [11]): λ = 580 nm, λ_{H^+} = 642 nm, pK_a = – 5.9, pK_a* = – 1.1.

(meso + racem) 1,1',3,3',9,9'-Hexahydroxy-7,7'-dimethylbianthraquinoyl [**13** + **14**; $C_{30}H_{22}O_8$]

As described above for **6** + **7**, the mixture of **13** + **14** was prepared from 150 mg (585 μmol) **1** (dissolved in 75 ml boiling ethanol p.a.) into which during 30 min 134 ml 1% $FeCl_3 \cdot 6$ aq in ethanol (585 μmol) was dropped. After 4 h refluxing the mixture was poured into 1 000 ml 5% HCl. Extraction with three 150 ml portions of ether, washings with water, drying over Na_2CO_3, and evaporation resulted after chromatography (silica, ethylethanoate) 140 mg (94%) **13** + **14** as white crystals of m.p. 250°C (dec.). ^{1}H-NMR (acetone-d_6, 360 MHz, δ); signals of the *meso* diastereomer: 11.86, 11.78 (2 s, OH-8 + OH-8', OH-1 + OH-1'), 10.71 (s, OH-3 + OH-3'), 6.67, 6.21 (2 s, *ar*-H 5 + *ar*-H 5', *ar*-H 7 + *ar*-H 7'), 6.18, 6.03 (2 d, J = 2.1 Hz, *ar*-H 2 + *ar*-H 2', *ar*-H 4 + *ar*-H 4'), 4.47 (s, H 10 + H 10'), 2.24 (s, 2 *Me*) ppm, signals of the *racem* diastereomer: 11.92, 11.68 (2 s, OH-8 + OH-8', OH-1 + OH-1'), 10.79 (s, OH-3 + OH3'), 6.63, 6.23 (2 s, *ar*-H 5 + *ar*-H 5', *ar*-H 7 + *ar*-H 7''), 6.23, 6.03 (2 d, J = 2.1 Hz, *ar*-H 2 + *ar*-H 2', *ar*-H 4 + *ar*-H 4'), 4.47 (s, H 10 + H 10'), 2.18 (s, 2 *Me*) ppm; assignments according to [2]. UV (ethanol): λ = 280 (18 300), 375 (23 500) nm (ε). IR (KBr): ν = 1 640, 1 600 cm^{-1}.

Protohypericin [**15**; $C_{30}H_{18}O_8$]

140 mg (275 μmol) of the **13**+**14** mixture obtained above were solved in 150 ml aqueous ammonia (32%) and heated to 100°C. A vigorous stream of oxygen was bubbled through the solution during 40 min. The violet solution was poured into 300 ml water, acidified with conc. HCl and the precipitate was centrifuged off. It was washed three times with water and dried in high vacuum. Chromatography (silica, *n*-butanol/toluene/formic acid = 6/3/1; R_f = 0.8) yielded 91 mg (65%) violet crystals of m.p. >350°C. ^{1}H-NMR (acetone-d_6, 360 MHz, δ): 14.52, 13.10 (2 s, OH-1 + OH-6, OH-8 + OH-15), 7.27 (s, *ar*-H 9 + *ar*-H-14), 6.70 (s, *ar*-H 11 + *ar*-H 12), 6.37 (s, *ar*-H 2 + *ar*-H 5), 2.10 (s, 2 *Me*) ppm, assignments according to [5]. UV-Vis (ethanol): λ = 592 (25 500), 548 (21 000), 375 (18 900) nm (ε). IR (KBr): ν = 1 620, 1 600 cm^{-1}.

Hypericin [**2**; $C_{30}H_{16}O_8$]

a) A solution of 50 mg (98.7 μmol) **15** in 60 ml acetone was irradiated for 10 min with a low pressure mercury vapor lamp (500 W). Chromatography of the residue (silica, *n*-butanol/toluene/formic acid = 6/3/1) afforded 46 mg (92%) **2**. Isohypericin content as judged from ^{1}H-NMR < 0.2%.
b) Saponification of **12** in analogy to **3** afforded 91% **2** of m. p. >350°C, black-violet crystals. ^{1}H-NMR (*DMSO-d*$_6$, 360 MHz,δ): 14.63 (s, broadened, OH-1 + OH-6), 14.02 (s, broadened OH-8 + OH-13), 7.38 (s, *ar*-H 9 + *ar*H 12), 6.53 (s, *ar*-H 2 + *ar*-H 5), 2.68 (s, 2 *Me*) ppm (compare [10]). UV-Vis (ethanol): λ = 592 (41 000), 548 (20 400), 511 (7 600), 476 (10 700), 379 (10 700), 327 (29 300) nm (ε). IR (KBr): ν = 1 620, 1 600 cm^{-1}.

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