Monatshefte für Chemie 126, 993–1000 (1995)

Monatshefte für Chemie
Chemical Monthly

On the Synthesis of ω-Appended Hypericin Derivatives

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Summary. A method for the preparation of *bis*-ω-appended hypericin derivatives bearing *n*-octyl, *n*-hexadecyl, and 2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl substituents was developed. The key step – the synthesis of appropriately ω-substituted emodin derivatives – was achieved by solvolyzing 3-bromomethyl-1,6,8-triacetyloxy-anthracene-9,10-dione (ω-bromo triacetylemodin) in an appropriate alcohol in the presence of silver perchlorate. The corresponding *bis*-ω-substituted hypericins were then prepared conventionally by dimerizing the ω-substituted emodin anthrones. The latter were prepared by reduction of the ω-appended emodins.

Keywords. ω-Appended hypericines; ω-Substituted emodin derivatives; Solvolysis; Silver perchlorate.

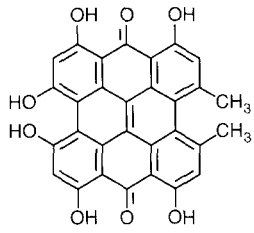
Zur Synthese von ω-substituierten Hypericinderivaten

Zusammenfassung. Eine Methode zur Darstellung von *bis*-ω-substituierten Hypericinderivaten wurde entwickelt. Der Schlüsselschritt – die Synthese der entsprechenden Emodinderivate – wurde durch die Solvolyse von 3-Bromomethyl-1,6,8-triacetyloxyanthracen-9,10-dion (ω-Bromtriacetylemodin) im entsprechenden Alkohol in Gegenwart von Silberperchlorat ermöglicht. Die entsprechenden *bis*-ω-substituierten Hypericinderivate wurden auf konventionelle Weise durch Dimerisierung der ω-substituierten Emodinanthrone dargestellt. Letztere erhielt man durch Reduktion der ω-substituierten Emodine.

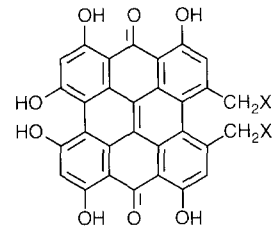
Introduction

The chemistry of hypericin (**I**) experienced a renaissance in recent years due to studies demonstrating its photodynamic, antiviral, and antiretroviral activity [1]. Moreover, it is of interest with respect to its chromophore: it is also present in the phototaxis photoreceptor pigments of organisms like *Stentor* [2] or *Blepharisma* [3]. Accordingly, the synthesis [4], photochemistry [5], and stereochemistry [6] of **I** have been thoroughly investigated.

However, all these studies suffer from the solubility problem; it is known that **I** is only very sparingly soluble in common solvents [7]. Dimethylsulfoxide and salts of **I** are exceptions. Therefore it seemed to be interesting to derivatize **I** in a way to possibly enhance its solubility in polar or apolar solvents on the one hand, and concomitantly on the other hand, leaving the functional groups of the system untouched. This led to derivatives of **I** which were functionalized or appended at the methyl groups. Thus, attaching long aliphatic chains to one or both methyl



I



II

groups should render the derivative more soluble in apolar solvents, whereas moieties consisting of oligohydroxymethyl or oligoethylene glycol units should lead to an enhanced solubility in polar or aqueous solvents. Moreover, it was desirable to provide derivatives more appropriate than hypericin itself for embedding the hypericin chromophore into matrices and vesicles or even to intercalate it with polynucleotides.

We now report on the synthesis of examples of ω-appended hypericin derivatives **II**, bearing moieties which could make the systems more soluble either in apolar or polar solvents.

Results and Discussion

First of all, it turned out that the direct derivatization of the methyl groups of **I** by means of a radical substitution reaction under a variety of reaction conditions (*e.g.*, bromination using N-bromosuccine imide) was unsuccessful. This was mostly due to an intractable product mixture of rather low stability. Therefore, the derivatization had to take place at an earlier step of the synthetic approach. Following the synthesis strategies of **I** [4], the most convenient way seemed to be the dimerization of appropriately substituted emodin anthrones. From this point of view, 3-bromomethyl-1,6,8-triacetyloxy-anthracene-9,10-dione (ω-bromo triacetylemodin **1**) [8] was chosen as the starting material to exploit the substitution of the bromine atom by a nucleophile bearing a long aliphatic chain or an otherwise appropriately substituted residue.

Attempts to substitute the bromine atom of **1** in basic media turned out to be unsuccessful: the reaction of **1** with sodium *n*-propylate, sodium *n*-octylate, *n*-propyl amine, benzyl amine, *n*-octadecyl amine, benzyl mercaptane, or hexadecyl mercaptane in the presence of bases (KOH, Et_3N, or N-ethyl-N,N-diisopropyl amine) resulted in product mixtures containing only trace amounts of the desired derivatives. In all these cases **1** could be partially recovered.

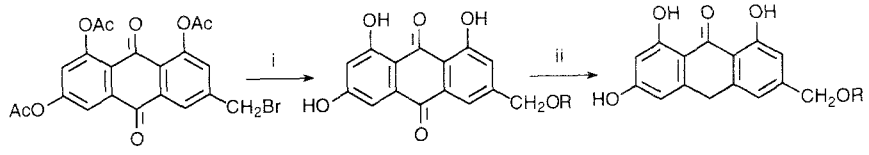
These results showed that **1** could not be considered as a classic benzyl bromide. This conclusion was also confirmed by facts from literature. Thus, the bromine in **1** could be substituted, for example, by amines only using rather long reaction times and a tremendous excess of the reagent [9]. It could also be substituted by an acetoxy group by heating **1** in an acetic anhydride-sodium acetate mixture for 10 hours, and by a hydroxy group by means of diluted acetic acid in the presence of silver acetate [8].

Continuing our efforts to substitute bromine in **1** it was found that **1** could be easily solvolyzed in alcohols such as *n*-octanol and *n*-hexadecanol in the presence

of silver perchlorate. In addition, the deprotection of the three hydroxy groups of triacetoxyemodin took place along with the substitution of the bromine atom for alkoxy groups to afford the desired ω-appended emodins **2a** and **2b** in high yields. The same results were obtained using triethylene glycol and glycerol: in these cases, emodins **2c** and **2d** were obtained.

To carry out the next step – the reduction of **2** to the corresponding anthrones **3** – the procedure described in Ref. [4] for the preparation of non-substituted emodin anthrone was adopted. Accordingly, stannous chloride in glacial acetic acid provided good yields of the ω-appended anthrones **3**.

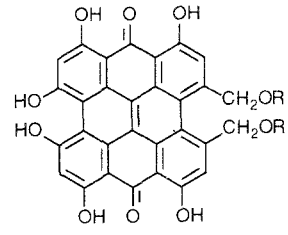
The last step – the dimerization of **3a**, **3b**, and **3c** to the *bis*-ω-appended hypericines **4a**, **4b**, and **4c** – proceeded in pyridine in the presence of piperidine, pyridine N-oxide, and ferrous sulfate, in analogy to Ref. [10]. We refrained from transforming **2d** into **4d** as this turned out to yield an unseparable mixture of stereoisomers.



1 **2 a-d** **3 a-c**

iii

a: R = *n*-C_8H_{17};
b: R = *n*-$C_{16}H_{33}$;
c: R = $CH_2CH_2(OCH_2CH_2)_2OH$;
d: R = $CH_2CHOHCH_2OH$;



4 a-c

i = $AgClO_4$/ROH; ii = $SnCl_2$/AcOH/HCl;
iii = pyridine N-oxide/piperidine/$FeSO_4$/pyridine;

The constitutions of the emodins **2a**, **2b**, **2c**, and **2d** and the emodin anthrones **3a** and **3b** were unambigiously evident from their ^1H and ^{13}C NMR, UV and IR spectroscopic data which are contained in the experimental part and do not require detailed discussion.

The constitution of the novel ω-appended hypericins was confirmed by their spectroscopic data. Thus, in the ^1H NMR spectra of **4a**, **4b**, and **4c** two high frequency signals, approximately at 14.7 and 14.1 ppm, were present. They were assigned to hydroxy protons (1-OH and 6-OH, and 8-OH and 13-OH). The signal of 10-OH and 11-OH could not be observed due to dissociation and fast proton exchange in *DMSO*-d_6 [11]. The signal of the aliphatic OH in the spectrum of **4c** could also not be observed. Another two signals were found in the aromatic region at approximately 7.5 and 6.5 ppm (2-H and 5-H, and 9-H and 13-H). In the low frequency area in the spectra of **4a** and **4b**, multiplets of

methylene groups ($2CH_3(\mathbf{CH_2})_nCH_2O$-, n = 6 and 14, respectively) at 0.83–1.15 ppm and methyl group triplets at approximately 0.69 ($J \approx 7.5$ Hz) and 0.70 ($J = 6.6$ Hz) ppm, respectively, were observed. In the spectrum of **4c** triplets at 3.99 and 3.46 ($J = 4$ Hz), and a multiplet at 3.61–3.35 ppm ($6CH_2$) were present.

The methylene group protons of the Ar-$\mathbf{CH_2}$O- and $CH_3(CH_2)_n\mathbf{CH_2}$O-type were observed as two AB systems due to their diastereotopicity. The respective chemical shifts are 4.97, 5.21 and 4.66, 4.52 ppm $J_{AB} \approx 12$ Hz) in the first case and 3.0 and 2.8 ppm for **4a** and **4b**. It should be mentioned that in the ^{1}H NMR spectra of the emodin anthrones **3a** and **3b** (the precursors of hypericins **4a** and **4b**) the Ar$\mathbf{CH_2}$O-signals were observed as singlets, and the two $CH_3(CH_2)_n\mathbf{CH_2}$O-signals as triplets ($J \approx 6$ Hz).

The ^{13}C NMR spectra of **4a**, **4b**, and **4c** were in accordance with the ^{1}H NMR data. They contained carbonyl signals at approximately 183 ppm and three signals of a pair of equivalent C-OH atoms at approximately 175, 168, and 162 ppm. The "quinoid" C-atoms appeared at 144 ppm, and nine signals in the "aromatic" area, together with two signals of ArCH_2O- and ArCH_2OCH_2- at approximately 70 and 69 ppm. The OCH_2 carbons of **4c** were also observed in the area of 60–70 ppm whereas the corresponding aliphatic carbon signals of **4a** and **4b** were observed at low frequencies.

In the IR spectra of **4a**, **4b**, and **4c** a broad band at 3421 cm^{-1} (OH) and two partially overlapped intensive bands at 1623 and 1597 cm^{-1} (C=O) were present. In addition, three bands at 2954, 2924, and 2852 cm^{-1}, corresponding to C–H vibrations of the aliphatic chains, could also be detected.

The electronic spectra of **4a**, **4b**, and **4c** contained intensive bands at 593 and 550 nm characteristic of the hypericin chromophore [4]. This type of spectra was similar to the hypericin absorption spectrum and differed significantly from the spectrum of isohypericin [6].

The fluorescence spectra of the ω-appended hypericins consisted of two bands at approximately 600 and 650 nm with relative intensities 1:0.3. The quantum yields were determined to be in the order of 0.8 and were significantly enhanced compared to that of hypericin [4].

It turned out that the solubility of **4a** and **4b** in apolar solvents, and that of **4c** in polar solvents changed only slightly as compared to hypericin. Thus, although the working hypothesis pointed in the proper direction, further investigations on the influence of chain length and substitution pattern have to be carried out.

Experimental

Melting points were measured on a Kofler hot stage microscope (Reichert, Vienna) and are uncorrected. ^{1}H and ^{13}C spectra were recorded by means of Bruker AC-200 and WM 360 spectrometers. IR spectra were obtained on a Biorad-FT-IR-45-instrument. UV/Vis spectra were measured by means of a Hitachi U-3210-spectrophotometer. Fluorescence spectra were recorded using a Hitachi-F-4010 spectrofluorimeter. Rhodamine B was used as the standard for quantum yield determinations. **1** was prepared according to Ref. [8].

1,3,8-Trihydroxy-6-octyloxymethyl-anthracene-9,10-dione (**2a**; $C_{23}H_{26}O_6$)

A mixture of 950 mg **1** (2 mmol), 15 ml of octanol, and 950 mg $AgClO_4$ (4.6 mmol) was stirred for 6 h at 100 °C. The precipitate was filtered off and washed with acetone. Filtrate and washings were combined and subjected to water steam distillation to remove acetone and excess octanol. The remaining solid was extracted with chloroform, dried over Na_2SO_4, evaporated, and chromatographed on a silica gel column using $CHCl_3$:MeOH = 20:1 as eluent. The first fraction was collected, evaporated and chromatographed again on a silica gel column (eluent $CHCl_3$:tetrahydrofuran = 20:1). Again, the first fraction was collected, evaporated to dryness, and suspended in petroleum ether (50–70 °C). The precipitate was filtered off and dried. Yield 688 mg (86%); m.p.: 162–164 °C; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 12.03 (s, OH), 12.02 (s, OH), 11.43 (s, OH), 7.56 (m, $1H_{arom}$), 7.19 (m, $1H_{arom}$), 7.09 (m, $1H_{arom}$), 6.57 (m, $1H_{arom}$), 4.53 (s, $ArCH_2O$), 3.46 (t, $J = 6.5$ Hz, OCH_2CH_2), 1.59–1.49 (m,

OCH_2CH_2), 1.23 (m, 10H, -$(CH_2)_5CH_3$)), 0.83 (t, $J = 6.5$ Hz, CH_3) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 189.7 (C=O), 181.3 (C=O), 165.7, 164.5, 161.4, 149.0, 135.2, 133.1, 121.6, 117.6, 114.6, 109.1, 108.9, 108.0 ($12C_{arom}$), 70.5 (OCH_2), 70.1 (OCH_2), 31.3, 29.2, 28.8, 28.7, 25.7, 22.1 ($6CH_2$), 14.0 (CH_3) ppm; IR (KBr): $\nu = 3386$, 2928, 2855,1671, 1624 cm^{-1}; UV (*DMSO*): $\lambda_{max} = 441$ (8900), 347 (3800), 290 (17200), 270 (15300) nm (ε).

3-Hexadecyloxymethyl-1,6,8-trihydroxy-anthracene-9,10-dione (**2b**; $C_{31}H_{42}O_6$)

To a melt of 9.5 g *n*-hexadecanol 950 mg **1** (2 mmol) and 950 mg $AgClO_4$ (4.6 mmol) were added. The mixture was stirred for 6 h at 100 °C and poured into 400 ml of petroleum ether (b.p.: 50–70 °C) to give a suspension which was left standing overnight. The precipitate formed was filtered off and suspended again in 150 ml of petroleum ether. The suspension was kept overnight and the formed precipitate was isolated and chromatographed on a silicagel column (eluent $CHCl_3$:methanol = 20:1). The first fraction was collected, evaporated, and recrystallized from $CHCl_3$ to yield 565 mg **2b**. The filtrate was evaporated and the resulting solid chromatographed on a silica gel column (eluent $CHCl_3$:tetrahydrofuran = 20:1). Again, the first fraction was collected and evaporated to give additional 300 mg of **2b**. Yield 865 mg (85%); m.p.: 145–146 °C ($CHCl_3$); ^1H NMR (350 K, *DMSO*-d_6, δ, 360 MHz): 12.01 (s, 2OH), 7.63 (m, $1H_{arom}$), 7.23 (m, $1H_{arom}$), 7.16 (m, $1H_{arom}$), 6.60 (m, $1H_{arom}$), 4.56 (s, $ArCH_2O$), 3.50 (t, $J = 6.4$ Hz, OCH_2), 1.62–1.54 (m, OCH_2CH_2), 1.37–1.10 (m, 26H, -$(CH_2)_{13}CH_3$)), 0.85 (t, $J = 6.7$ Hz, CH_3) ppm; IR (KBr): $\nu = 3369$, 2921, 2849, 1667, 1620 cm^{-1}; UV (*DMSO*): $\lambda_{max} = 442$(7700), 348(4000), 288 (16300), 269(14800) nm (ε).

1,3,8-Trihydroxy-6-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-anthracene-9,10-dione (**2c**; $C_{21}H_{22}O_9$)

A mixture of 250 mg **1** (0.526 mmol), 6 ml of triethylene glycol, and 250 mg $AgClO_4$ (1.20 mmol) was stirred for 6 h at 100 °C, quenched with brine and extracted with ethyl acetate. The extract was dried over Na_2SO_4, evaporated, and the remaining amorphous residue was chromatographed on a silica gel column (eluent $CHCl_3$:methanol = 20:1) to yield crude **2c** which afforded 157 mg (72%) **2c** after crystallization from ethyl acetate. M.p.: 128–130 °C; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 12.02 (s, 2OH), 11.4 (s, OH), 7.55 (m, $1H_{arom}$), 7.21 (m, $1H_{arom}$), 7.07 (m, $1H_{arom}$), 6.55 (m, $1H_{arom}$), 4.59 (s, $ArCH_2O$), 3.61–3.35 (m, 13H, $6CH_2$ + OH) ppm; ^{13}C NMR (*DMSO*)-d_6, δ, 50 MHz): 189.7 (C=O), 181.2 (C=O), 165.7, 164.5, 161.4, 148.9, 135.1, 133.0, 121.6, 117.5, 114.5, 109.0, 108.8, 107.9 ($12C_{arom}$), 72.4, 70.7, 69.9, 69.8, 69.7, 60.2 (only six side chain carbon signals were observed due to signal overlap) ppm; IR (KBr): $\nu = 3502$, 3053, 2908, 1677, 1628 cm^{-1}; UV (*DMSO*): $\lambda_{max} = 548$(600), 441(8400), 347(4300), 289(17000) nm (ε).

3-(2,3-Dihydroxy-propoxymethyl)-1,6,8-trihydroxy-anthracene-9,10-dione (**2d**; $C_{18}H_{16}O_8$)

A mixture of 300 mg **1** (0.632 mmol), 7 ml of glycerol, and 300 mg $AgClO_4$ (1.44 mmol) was stirred for 4 h at 100 °C, quenched with brine ane extracted with ethyl acetate. The extract was dried over Na_2SO_4, evaporated, and the remaining solid was chromatographed on a silica gel column (eluent $CHCl_3$: methanol = 20:1) to yield crude **2d** which afforded 150 mg (66%) **2d** after crystallization from methanol. M.p.: 198–201 °C; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 12.01 (s, 2OH), 11.38 (s, OH), 7.55 (m, $1H_{arom}$), 7.24 (m, $1H_{arom}$), 7.07 (m, $1H_{arom}$), 6.55 (m, $1H_{arom}$), 4.81 (broad s, OH), 4.58 (s, $ArCH_2O$), 3.50–3.35 (m, 5H, $2CH_2$ + CH), 2.07 (s, OH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 189.7 (C=O), 181.2 (C=O), 165.6, 164.5, 161.4, 148.9, 135.1, 133.0, 121.7, 117.6, 114.4, 109.0, 108.9, 107.9 ($12C_{arom}$), 72.5, 71.0, 70.6, 63.0 (4 side chain C) ppm; IR (KBr): $\nu = 3250$ (broad band), 1675, 1627 cm^{-1}; UV (*DMSO*): $\lambda_{max} = 557$(800), 441(7400), 348(5000), 288(16500) nm (ε).

1,3,8-Trihydroxy-6-octyloxymethyl-10H-anthracene-9-one (**3a**; $C_{23}H_{28}O_5$)

To a solution of 196 mg of **2a** (0.492 mmol) in 50 ml glacial acetic acid, 1.13 g of $SnCl_2 \times 2H_2O$ (5.0 mmol) in 5 ml conc. HCl were added under heating. The resulting solution was refluxed for 3 h, cooled, and poured into 300 ml of brine, extracted with ethyl acetate, dried with Na_2SO_4, and evaporated. The residue was chromatographed on a short silica gel column (eluent $CHCl_3$:tetrahydrofuran = 20:1). The first fraction was collected, evaporated to dryness, suspended in petrol ether (b.p.: 50–70 °C), and filtered to give 159 mg (84%) of **3a** M.p.: 161–165 °C; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 12.33 (s, OH), 12.25 (s, OH), 10.85 (s, OH), 6.86 (m, $1H_{arom}$), 6.74 (m, $1H_{arom}$), 6.41 (m, $1H_{arom}$), 6.22 (m, $1H_{arom}$), 4.45 (s, Ar–CH_2O or Ar–CH_2–Ar), 4.32 (s, Ar–CH_2–Ar or Ar–CH_2O), 3.43 (t, J = 6.3 Hz, OCH_2), 1.57–1.48 (m, OCH_2CH_2), 1.23 (broad s, 10H, -(CH_2)$_5CH_3$)), 0.83 (t, J = 6.4 Hz, CH_3) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 50 MHz): 191.1 (C=O), 165.1, 164.6, 161.7, 147.8, 145.1, 142.2, 117.1, 114.0, 112.6, 108.5, 107.4, 101.0 ($12C_{arom}$), 7.10 (OCH_2), 70.1 (OCH_2), 32.4 ($ArCH_2Ar$), 31.3, 29.2, 28.8, 28.7, 25.7, 22.1 ($6CH_2$), 14.0 (CH_3) ppm; IR (KBr): ν = 3296, 2926, 2854, 1629, 1601 cm^{-1}; UV (*DMSO*): λ_{max} = 363(15300), 272(17700) nm (ε).

3-Hexadecyloxymethyl-1,6,8-trihydroxy-10H-anthracene-9-one (**3b**; $C_{31}H_{44}O_5$)

To a solution of 204 mg of **2b** (0.4 mmol) in 40 ml glacial acetic acid 950 mg of $SnCl_2 \times 2H_2O$ (4.2 mmol) in 4 ml conc. HCl were added under heating. The resulting solution was refluxed for 3 h, cooled, diluted with 20 ml of methanol, and kept in a refrigerator overnight. The precipitate formed was isolated and dried to yield 142 mg (72%) of **3b** M.p.: 148–149 °C; ^{1}H NMR 355 K, *DMSO*-d_6, δ, 360 MHz): 12.28 (s, OH), 12.20 (s, OH), 10.59 (broad s, OH), 6.89 (m, $1H_{arom}$), 6.77 (m, $1H_{arom}$), 6.43 (m, $1H_{arom}$), 6.24 (m, $1H_{arom}$), 4.47 (s, Ar–CH_2O or Ar–CH_2–Ar), 4.32 (s, Ar–CH_2–Ar or Ar–CH_2O), 3.47 (t, J = 6.4 Hz, OCH_2), 1.59–1.53 (m, OCH_2CH_2), 1.34–1.23 (m, 26H, -(CH_2)$_{13}CH_3$)), 0.85 (t, J = 6.8 Hz, CH_3) ppm; IR (KBr): ν = 3567, 2918, 2850, 1630, 1600 cm^{-1}; UV (*DMSO*): λ_{max} = 388(12800), 369(9700), 279(30700) nm (ε).

1,3,8-Trihydroxy-6-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-10H-anthracene-9-one (**3c**)

To a solution of 190 mg of **2c** (0.45 mmol) in 35 ml glacial acetic acid 1 g of $SnCl_2 \times 2H_2O$ (4.4 mmol) in 5 ml conc. HCl were added under heating. The resulting solution was refluxed for 4 h, cooled, and quenched with brine. The formed precipitate was dried, dissolved in acetone and chromatographed on a silica gel column (eluent $CHCl_3$:methanol = 40:1) to yield 102 mg **3c**, which – due to its sensitivity – was used for the hypericin synthesis without characterization.

General procedure for the synthesis of hypericines **4**

A solution containing 0.27 mmol of the appropriate anthrone **3a**, **3b**, or **3c**, 140 mg pyridine N-oxide (1.62 mmol), 140 µl piperidine and several crystals of ferrous sulfate heptahydrate in 1.5 ml pyridine in the dark was stirred for 2 h at 100 °C, cooled, and quenched with a solution of 5 ml conc. HCl in 40 ml water. The precipitate formed was collected, suspended in 250 ml acetone and subjected to sunlight irradiation for 3 days. The resulting suspension was filtered through a silicagel column, the raspberry colored filtrate was evaporated, and the remaining solid was dissolved in 5 ml of 10% methanolic KOH (**4a**, **4b**) or in 5 ml methanol (**4c**). The resulting solutions of appropriate hypericins were chromatographed on a Sephadex LH-20 column with methanol as eluent, the fraction of the first (most intensive) bands of the hypericines **4a**, **4b**, and **4c** were collected and evaporated. The remaining solids were dissolved again in 10% methanolic KOH (**4a**, **4b**) or in 5 ml methanol (**4c**) and again chromatographed on a Sephadex LH-20 column with methanol as the eluent. Again the fractions of the most intensive bands were collected and in the case of **4c** evaporated to dryness, or partially evaporated and treated with a solution of 1 ml conc. HCl in 50 ml water (in the case of **4a** and **4b**). The acidic solutions of **4a** and **4b** were extracted with 50 ml $CHCl_3$ and the extracts were evaporated to yield **4a** and **4b**.

1,3,4.6,8,13-Hexahydroxy-10,11-bis-octyloxymethyl-phenanthro[1,10,9,8-o,p,q,r,a]perylene-7,14-dione (**4a**; $C_{46}H_{48}O_{10}$)

Yield: 13%; m.p.: not up to 340 °C; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 14.69 (s, 2OH), 14.11 (s, 2OH), 7.54 (s, $2H_{arom}$), 6.53 (s, $2H_{arom}$), 4.97 (A-part of an AB system, $J_{AB} = 12.2$ Hz, 2Ar–**H**CH–OCH_2), 4.52 (B-part of an AB system, $J_{AB} = 12.1$ Hz, 2Ar–HC**H**–OCH_2), 3.03–2.99 (m, 2H, 2O–**H**CH–CH_2), 2.87–2.81 (m, 2H, 2O–HC**H**–CH_2), 1.16–0.83 (m, 24H, $2(CH_2)_6CH_3$), 0.69 (t, $J = 7.5$ Hz, $2CH_3$) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 90 MHz): 183.3 (C=O), 174.7, 168.4, 161.7, 144.0, 127.0, 125.6, 121.3, 119.6, 119.0, 117.9, 109.6, 105.6, 102.2, ($13\,C_{arom}$), 70.4 (OCH_2), 69.4 (OCH_2), 31.1, 28.7, 28.6, 28.5, 25.4, 22.0 ($6CH_2$), 13.8 (CH_3) ppm; IR (KBr): $\nu = 3421$, 2955, 2924, 2852, 1623, 1597 cm^{-1}; UV (ethanol): $\lambda_{max} = 593(40000)$, 550(19500), 512(7300), 478(10600), 384(9300), 329(23400), 287(30300) nm (ε); Fluorescence (ethanol): $\lambda_f = 599(1)$, 647(0.3) nm (relative intensity) $\Phi_f = 0.98$.

3,4-Bis-hexadecyloxymethyl-1,6,8,10,11,13-hexahydroxy-phenanthro[1,10,9,8-o,p,q.r,a]perylene-7,14-dione (**4b**; $C_{62}H_{80}O_{10}$)

Yield: 8%; m.p.: not up to 340 °C; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 14.71 (s, 2OH), 14.12 (s, 2OH), 7.57 (s, $2H_{arom}$), 6.56 (s, $2H_{arom}$), 4.99 (A-part of an AB system, $J_{AB} = 12.1$ Hz, 2Ar–**H**CH–OCH_2), 4.55 (B-part of an AB system, $J_{AB} = 12.0$ Hz, 2Ar–HC**H**–CH_2), 3.05–2.99 (m, 2H, 2O–**H**CH–CH_2), 2.88–2.82 (m, 2H, 2O–HC**H**–CH_2), 1.15–0.83 (m, 56H, $2(CH_2)_{14}CH_3$), 0.70 (t, $J = 6.6$ Hz, $2CH_3$) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 90 MHz): 183.4 (C=O), 174.7, 168.4, 161.8, 144.1, 127.0, 125.6, 121.3, 119.6, 119.1, 118.0, 109.6, 105.6, 102.2 ($13C_{arom}$), 70.4 (OCH_2), 69.4 (OCH_2), 31.1, 28.7, 28.55, 28.5, 25.4, 22.0 ($6CH_2$ signals were observed instead of $14CH_2$ due to signal overlap), 13.8 (CH_3) ppm; IR (KBr): $\nu = 3421$, 2955, 2924, 2852, 1623, 1597 cm^{-1}; UV (ethanol): $\lambda_{max} = 593(43300)$, 550(21400), 512(8300), 478(11800), 384(10600), 329(26500), 287(33800) nm (ε); Fluorescence (ethanol): $\lambda_f = 600(1)$, 648(0.3) nm (relative intensity), $\Phi_f = 0.63$.

1,3,4,6,8,13-Hexahydroxy-10,11-bis-(2-(2-(2-hydroxyethoxy)-ethoxy)-ethoxymethyl)-phenanthro[1,10,9,8-o,p,q,r,a]perylene-7,14-dione (**4c**; $C_{42}H_{40}O_{16}$)

Yield: 11%; m.p.: not up to 340 °C; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 18.49 (broad s, 2OH), 14.73 (s, 2OH), 14.14 (s, 2OH), 7.64 (s, $2H_{arom}$), 6.56 (s, $2H_{arom}$), 5.11 (A-part of an AB system, $J_{AB} = 12$ Hz, 2Ar–**H**CH–OCH_2), 4.62 (B-part of an AB system, $J_{AB} = 12$ Hz, 2Ar–HC**H**–OCH_2), 3.96 (t, 4H, 2Ar–CH_2–OCH_2, $J = 4.5$ Hz), 3.46 (t, 4H, 2Ar–CH_2–OCH_2CH_2, $J = 4.5$ Hz), 3.49–3.13 (m, 16H, $8CH_2$) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 90 MHz): 183.4 (C=O), 174.8, 170.2, 168.4, 161.8, 143.9, 127.0, 125.9, 121.6, 119.9, 119.1, 109.9, 105.9, 102.2 ($13\,C_{arom}$), 70.9, 69.6, 69.5, 69.1, 68.2, 63.1 (only six side chain carbon signals were observed due to signal overlap) ppm; IR (KBr): $\nu = 3421$, 2955, 2924, 2852, 1623, 1597 cm^{-1}; UV (ethanol): $\lambda_{max} = 593$ (43100), 550(20300), 512(8000), 478(12500), 384(10800), 329(27300), 287(34300) nm (ε); Fluorescence (ethanol): $\lambda_f = 600(1)$, 648(0.3) nm (relative intensity), $\Phi_f = 0.78$.

Acknowledgements

A *Lise Meitner* post doc fellowship of the *Fonds zur Förderung der wissenschaftlichen Forschung* to *A. F.*, and a stipendium of the *Österreichische Akademische Austauschdienst* to *A. M. A.* (from Faculty of Science, Zagazig University, Egypt) are gratefully acknowledged. The authors are grateful to Mr. *B. Gura* and Mrs. *A. Brandstetter* for technical assistance.

References

[1] Meruelo D, Lavie G, Lavie D, (1988) Proc Natl Acad Sci USA **85**: 5230; Lavie G, Valentine F, Levin B, Mazur Y, Gallo G, Lavie D, Weiner D, Meruelo D (1989) Proc Natl Acad USA **86**:

5963; Tang J, Calacino JM, Larsen SH, Spitzer W (1990) Antiviral Res **13**: 313; Lopez-Bazzocchi I, Hudson JB, Towers HN (1991) Photochem Photobiol **54**: 95; Carpenter S, Kraus GA (1991) Photochem Photobiol **53**: 169

[2] Tao N, Orkando M, Hyon J, Grass M, Song P-S (1993) J Am Chem Soc **115**: 2526

[3] Giese AC, (1981) Photochem Photobiol Rev **6**: 139

[4] Falk H, Schoppel G (1991) Monatsh Chem **112**: 739; (1992) **123**: 931; Falk H, Meyer J, Oberreiter M (1993) Monatsh Chem **124**: 339

[5] Jakobson P, Lazortchak N, Gautron R (1987) J Chem Phys **84**: 1141; Racinet H, Jardon P, Gautron R (1988) J Chim Phys **85**: 971; Angerhofer A, Falk H, Meyer J, Schoppel G (1993) J Photochem Photobiol B **20**: 133; Pschierer H, Freidrich J, Falk H, Schmitzberger W (1993) J Phys Chem **97**: 6902; Falk H, Meyer J (1994) Monatsh Chem **125**: 753; Freeman D, Frolow F, Kapinus E, Lavie D, Lavie G, Meruelo D, Mazur Y (1994) J Chem Soc Chem Commun 891; Gai F, Fehr MJ, Petrich SW (1994) J Phys Chem **98**: 5784

[6] Etzlstorfer C, Falk H, Müller N, Schmitzberger W, Wagner UG (1993) Monatsh Chem **124**: 751; Etzlstorfer C, Falk H (1993) Monatsh Chem **124**: 1031 (1994) **125**: 955

[7] Roth L (1990) Hypericum-Hypericin, Botanik·Inhaltsstoffe·Wirkung·ecomed Verlagsgesellschaft mbH, Landsberg

[8] Thiem J, Wessel HP (1985) Z Naturforsch **40b**: 422

[9] Koyama M, Takahashi K, Chou T-C, Darzynkiewicz Z, Kapuscinski J, Kelly TR, Watanabe KJ (1989) Med Chem **32**: 1594

[10] Mazur Y, Bock H, Lavie D (1992) Can Pat Appl CA 2.029,993

[11] Falk H, Mayr E (1995) Monatsh Chem **126**: 699–710

Received January 16, 1995. Accepted February 3, 1995