A Remarkable Photoreaction of 3-*O*-Benzylhypericin

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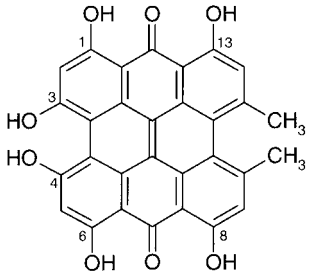
Dedicated to Prof. *Albert Eschenmoser* on the occasion of his 75th birthday

Irradiation of 3-*O*-benzylhypericin dissolved together with at least 1 equiv. of 'proton sponge' in benzene was shown, by means of UV/VIS, ^{1}H-NMR, and mass spectrometric measurements, to produce the rearranged blepharismin-analogous 11-phenyl-11*H*-benz[4,10]anthra[2,1,9,8-*nopqa*]pleiadene system. The latter compound yielded hypericin when treated with light and oxygen in acetone solution, followed by aqueous NH_4Cl. This reaction is considered to proceed *via* the oxybleopharismin-analog 3,4-benzal acetal of hypericin. The implications of the novel phototransformation for synthesis and biosynthesis of the natural products, as well as the structural peculiarities of the photoproducts, are discussed.

1. Introduction. – The investigation of the photochemistry of hypericin (=1,3,4,6,8,13-hexahydroxy-10,11-dimethylplenanthro[1,10,9,8-*opqra*]perylene-7,14-dione; **1**), a naturally occurring phenanthro-perylene quinone, as well as of its derivatives, is of primary concern with respect to their photobiological activity. Although electron, hydrogen, or proton transfer reactions and singlet oxygen sensitization are well-established photoreactions of **1** and some of its derivatives, an intra- or intermolecular photoreaction involving molecular fragments or reagents has not been encountered so far (for an overview, see [1]).

In continuation of investigations on the deprotonation capability of **1** and several of its derivatives in a variety of solvents [2][3], it has been fortuitously observed that, in presence of a certain base, the 3-*O*-benzyl derivative **2** of **1** dissolved in an aromatic solvent was photoreactive. The photochemical transformation responsible for this observation will now be reported.



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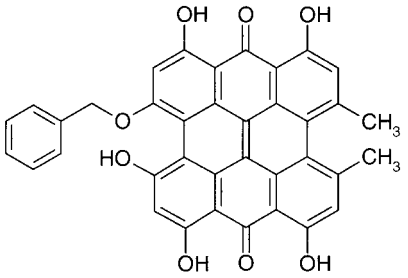

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2. Results. – Exclusively in the case of 3-*O*-benzylhypericin (**2**) dissolved in benzene together with 'proton sponge' (1,8-bis(dimethylamino)naphthalene) and in presence or absence of oxygen, irradiation with visible light led to a spectroscopic change with the educt species changing into a new one. This change was quantitative, when at least an equimolar amount or an excess of the base was applied. As can be seen in *Fig. 1*, the spectra of educt and product met in isosbestic points. It should be stressed that this phototransformation of **2** could not be observed in other solvents (*e.g.*, CH_2Cl_2, $CHCl_3$, MeCN, acetone) or with different bases (*e.g.*, *Hünig* base, 4-(dimethylamino)pyridine, *N*,*N*-dimethylaniline, pyridine, collidine, piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine). Only with benzene (or toluene) and at least an equimolar amount of 'proton sponge' could the photochemical reaction be observed so far.

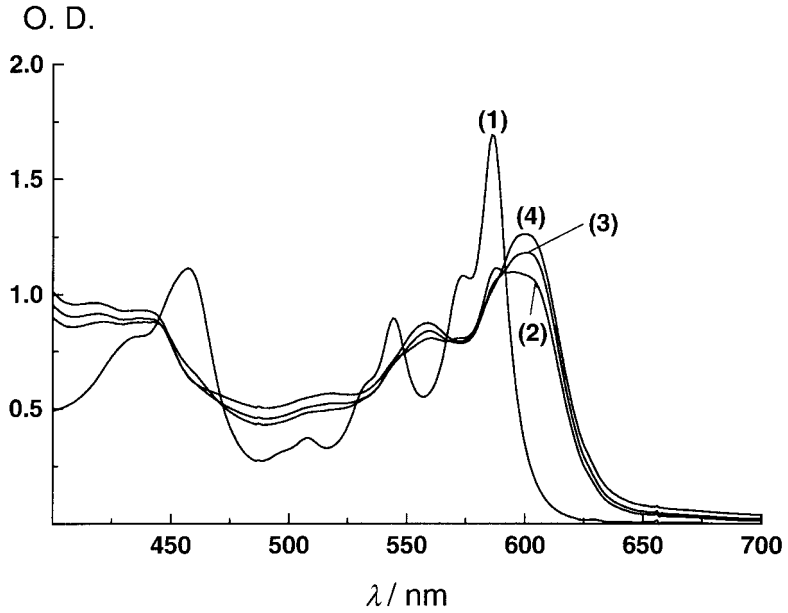


Fig. 1. *Irradiation experiment: UV/VIS spectra of a benzene solution of* **2** ($7.6 \cdot 10^{-5}$ mol dm^{-3}) *containing* $8.8 \cdot 10^{-5}$ *mol* dm^{-3} *proton sponge before* (1) *and after irradiation with a 300-W tungsten lamp at a distance of 10 cm for 3* (2), *9* (3), *and 21 minutes* (4)

At this point it was interesting to note that, in contrast to *Hünig* base (ethyldiisopropylamine; $pK_a = 9.8$ in EtOH/H_2O 80:20) the 'proton sponge' ($pK_a = 9.1$ in 80% EtOH/H_2O, however, $pK_a = 12.33$ in H_2O [4]) did not lead to a deprotonation of **2** ($pK_a^I = 8.3$, $pK_a^{II} = 11.7$ in EtOH/H_2O 80:20 [2]) dissolved in benzene. This behavior was in contrast to that observed with hypericin (**1**; ($pK_a^I = 1.6$, $pK_a^{II} = 9.4$ [5]), for which mono-deprotonation of one *bay*-OH group with the 'proton sponge' and *Hünig* base could be observed. Thus, one should be aware that, whereas in H_2O as solvent the basicity of the 'proton sponge' is higher than that of *Hünig* base, this order may become inverted in certain organic solvents.

To follow the photoreaction in more detail, the ^{1}H-NMR spectrum of the educt 3-*O*-benzylhypericin (**2**) in (D_6)benzene with an added equiv. of 'proton sponge' was measured with simultaneous recording of the same sample's UV/VIS spectrum. It displayed ^{1}H signals characteristic of the C_1-symmetrical molecule [2]. Upon irradiation of the sample, the UV/VIS spectrum changed as shown in *Fig. 1*. Depending on the sample concentration, a new set of ^{1}H-NMR signals developed synchronously, and those of **2** were diminished. This new set characteristic of $\mathbf{I}^-$ pointed to a mean molecular symmetry of C_2 at high sample concentrations, whereas at low concentrations the signal system was of formal C_1 symmetry, thus pointing to a concentration-dependent exchange phenomenon. In the high-concentration case two signals of the *peri*-OH groups, a *singlet* for one benzaldehyde-type proton signal, a *singlet* for two Me groups, and only one signal for two aromatic protons were observed. The other two could not be assigned with certainty because of overlap with reagent and educt signals.

The primary photoproduct $\mathbf{I}^-$ could be isolated from preparative runs, preferably from those that were accomplished with an excess of base to achieve complete transformation. However, its purification was found to be hampered by its rather high reactivity towards oxygen and light, and its obvious involvement in acid-base and tautomerism equilibria led to a kind of structural inhomogeneity of the product. Since the species produced was obviously involved in deprotonation equilibria, a spectrophotometric titration was performed, from which two deprotonation steps could be derived: ($pK_a^I = 7.4$, $pK_a^{II} = 11.6$ (EtOH/H_2O 80:20).

To corroborate the nature of the species formed upon deprotonation, electron-spray (ES) mass spectra under varied pH conditions were recorded. This method has been used recently to elucidate the nature of the deprotonated species of **1** [6]. Thus, below pH 3, no signals for negative ions were observed, whereas, in the region of pH 7, a single-charge signal at *m*/*z* 593 began to appear. Accordingly, two species could be elucidated as being involved in the photoproduct deprotonation equilibria: undissociated **I** (characterized by the main long-wavelength absorption band at 585 nm in EtOH/H_2O 80:20), and the mono-deprotonated species $\mathbf{I}^-$ (absorbing at 598 nm in EtOH/H_2O 80:20). Upon addition of further base (pH above 12) a di-deprotonated species $\mathbf{I}^{2-}$ (absorbing at 615 nm in EtOH/H_2O 80:20) occurred; the UV/VIS spectra of these three species are illustrated in *Fig. 2*.

To further probe the structural details of $\mathbf{I}^-$, and **I** (the latter could be prepared by treatment of $\mathbf{I}^-$ with acid), two-dimensional ^{1}H-NMR spectroscopy was applied, since ROESY correlations recently helped to establish the 7,14- and 1,6-tautomers of **1** [7]. Unfortunately, we were unable to achieve significant correlations, because, obviously, the photoreaction had produced paramagnetic contaminations of the system. These led to a slight signal broadening and concomittant correlation scatter. The impurities could not be cleared from the product in a series of experiments, involving radical scavengers and the like. Nevertheless, it was interesting to note that the ^{1}H-NMR spectrum of $\mathbf{I}^-$ (proton sponge · H^+) in (D_6)benzene at low concentrations, and also in (D_8)THF and other solvents (4–7 signals between 15.9 and 13.6 ppm) displayed the characteristics of an asymmetrical (C_1) molecule, and pointed even to a mixture of several mono-deprotonated species. This was in contrast to the spectrum of **I**, which was typical of a formally C_2-symmetrical molecule. Unfortunately, we were also not able to obtain

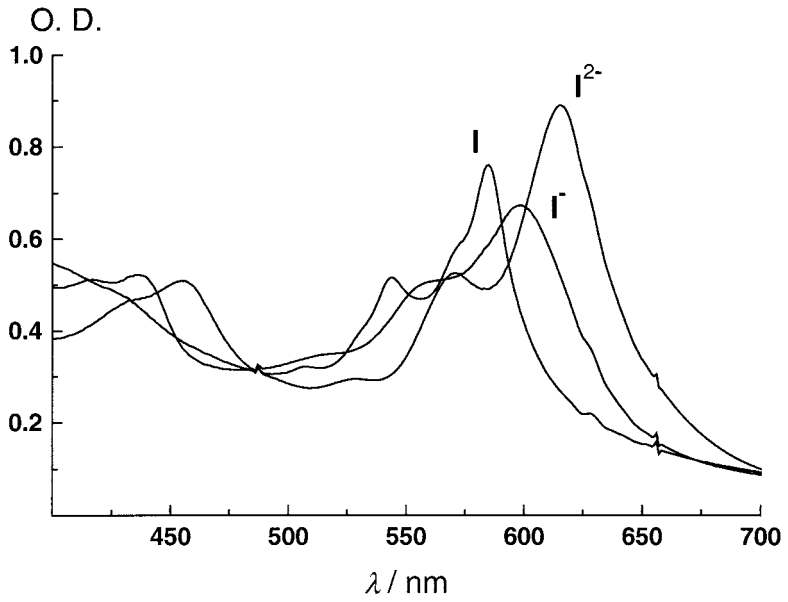


Fig. 2. *The UV/VIS spectra of the three forms* **I**, $\mathbf{I}^-$, *and* $\mathbf{I}^{2-}$, *dissolved in EtOH/H_2O 80 : 20 at pH 2.6, 7.6, and 13.7*

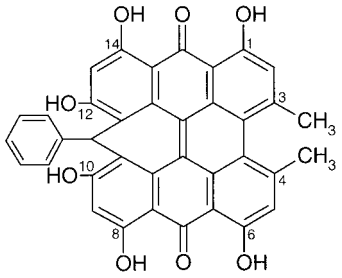
reliable ^{13}C-NMR spectra of any of the species of **I**, which would have allowed for an experimental discrimination of the various possible structural details.

Interestingly enough, treatment of **I** or $\mathbf{I}^-$ with oxygen and light in acetone solution, followed by aqueous NH_4Cl, mainly afforded hypericin (**1**), which was identified by means of its UV/VIS and ES mass spectra.

3. Discussion. – With respect to the constitution of **I**, the molecular mass of 593 for the mono-deprotonated species, which yields a molecular mass of 594 for the unionized phototransformation product, served as the fundamental information. Thus, **I** was derived from **2** (M_r 594) by a *photorearrangement* reaction. Taken together, the formal symmetry C_2 that followed from the NMR data and the molecular mass, **I** had to be assigned the constitution **3**, which is isomeric with the educt structure **2**. Note that the formula **3** is arbitrarily drawn as the 7,15-oxo tautomer of the 11-phenyl-11*H*-benz[4,10]anthra[2,1,9,8-*nopqa*]pleiadene system.

At this point it was interesting to remember the *ca*. tenfold increase in the acidity of **3** as compared with its educt **2**. To some extent, this finding corroborated the constitution of **3**: its increased acidity might reflect the statistic effect [8] of two equal *bay*-OH groups in **3** *vs.* only one such group in **2**.

Based on the analogy of the ^{1}H-NMR and UV/VIS spectra of **1** and **2** [7], it was thought to be likely that **3** was present in the non-ionized form as the 8,14-tautomer, whereas, in the deprotonated forms, it was present as the 7,15-tautomer. Moreover, it has to be kept in mind that, in principle, **3** could also be involved in a cycloheptatriene $\rightleftharpoons$ norcaradiene valence tautomerism equilibrium [9] (for a pioneering application of the norcardiene-cycloheptatriene rearrangement to the synthesis of



I = 3

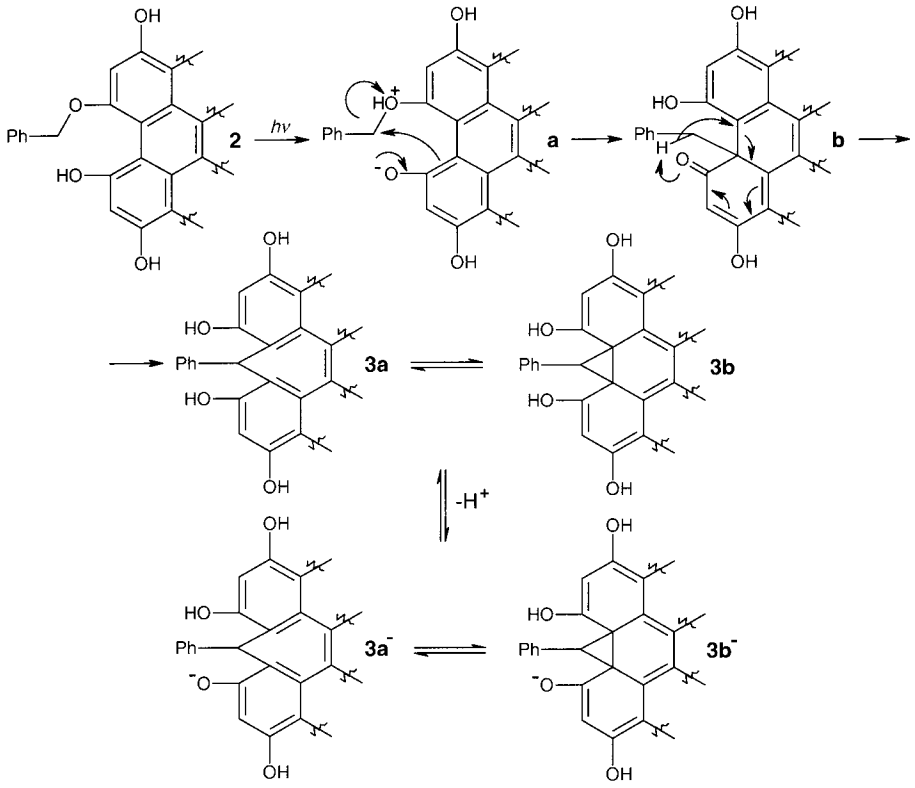
colchicine, *cf.* [9b]), as suggested recently for the blepharismins [10]. The latter equilibrium could, of course, also account to some extent for the additional proton signals. According to the experimental hints aquired so far, **3** should be thought to be amenable to being involved in equilibrium systems of a rather high structural complexity – even higher than those encountered for hypericin (**1**) [1].

To obtain at least an impression of the relative stabilities of the various possible species of **3**, AM1 calculations [11] were undertaken, which have been found recently to describe the structural complexity of the various tautomers of hypericin (**1**) with some confidence [12]. Thereby, the 7,15-dioxo tautomer of the cycloheptatriene valence tautomer of **3** comprising an '*exo*'-Ph moiety was found to be the most stable species, the corresponding 8,14-dioxo tautomer and all other possible dioxo combinations being less stable by more than 40 kJ mol^{-1}. The corresponding norcaradiene valence tautomer was also found to be destabilized by *ca.* 160 kJ mol^{-1}. However, the '*endo*'-Ph cycloheptatriene valence tautomer of **3** was found to be only slightly destabilized against the '*exo*'-Ph diastereoisomer by *ca.* 5 kJ mol^{-1}. Accordingly, the equilibrium of the valence tautomer system should mainly reside in favor of the cycloheptatriene system, but with the '*exo*- and '*endo*'-Ph group introducing a potential additional source of the samples' structural heterogeneity.

The mechanistic aspects of this remarkable phototransformation may be rationalized as depicted in *Scheme 1:* upon excitation of **2** (which is non-deprotonated under the given reaction conditions), a proton shift might occur to furnish **a**, which can then rearrange *via* **b** to yield **3a**. In turn, **3a** or **3b**, which was found to be more acidic than **2** ($(pK_a^I(\mathbf{2}) = 8.3$ [2], $pK_a^I(\mathbf{3}) = 7.4)$ is then deprotonated by the 'proton sponge' to give $\mathbf{3a}^-$ or $\mathbf{3b}^-$. Of course, it is also possible that the intermolecular deprotonation of the *bay*-OH group occurs at the beginning of the reaction in the excited state of **2**. The latter was found to be acidified in the excited state by application of a *Förster* cycle [13], which yielded an estimation of the excited state (pK_a^{I*} of 6.6. This has to be compared to the ground-state pK_a^I value of 8.3 [2]. The specific role of the 'proton sponge' and the solvent might originate from the tendency of this base to extremely effectively 'catch' protons, and that its basicity in this solvent is balanced against the acidity of the substrate **2** in a way to allow deprotonation only of the more acidic product **3** or the more acidic excited state of **2**.

With respect to the reactions starting from **3** to yield hypericin (**1**), a nicely analogous transformation has been recently discovered in the realm of natural

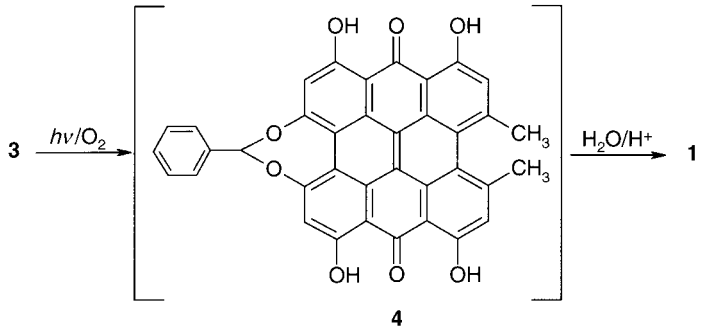
Scheme 1. *Mechanistic Aspects of the Phototransformation of* **2** *to Yield* **3**, *Which is Involved in a Coupled Complex Deprotonation, Proton and Valence Tautomer Equilibrium System, of Which only the Relevant Part is Shown*



products. Thus, it has been shown that the photosensory pigment of *Blepharisma*, blepharismin C (**5**), is related to the benzaldehyde acetal oxyblepharismin C (**6**) *via* a photooxidation reaction, and that **6**, upon acid-catalyzed hydrolysis, is converted to stentorin (**7**) [10]. Accordingly, the intermediate in the course of the photooxidation of **3** has to be assigned the benzaldehyde acetal of type **4** (*cf. Scheme 2*).

In conclusion, the remarkable photoreaction of 3-*O*-benzylhypericin (**2**) leading to the pleiadene derivative **3** and its transformation to the 3,4-benzaldehyde acetal **4** could pave the way to the synthesis of blepharismin- and oxyblepharismin-type chromophores. As can be seen from the molecular formulae of the natural pigments, blepharismin C (**5**) and oxyblepharismin C (**6**), they also involve the pleiadene and *bay*-acetal moieties. This option is of more interest, since it turned out meanwhile that, on the one hand, experiments to synthesize the condensed pleiadene skeleton by means of electrophilic substitution of, *e.g.*, protohypericin or protofringelit D (**8**) with HCHO or PhCHO catalyzed by a variety of acids like TsOH, CF_3COOH, chlorosulfuric acid, or $AlCl_3$ failed. On the other hand, experiments to introduce the acetal functionality into the OH-substituted *bay*-region of OH-substituted phenanthro-perylene quinones

Scheme 2. *Photoxidation of* **3** *to Yield the Intermediate* bay-*Benzaldehyde Acetal* **4** *and, after Hydrolysis, Hypericin* (**1**)



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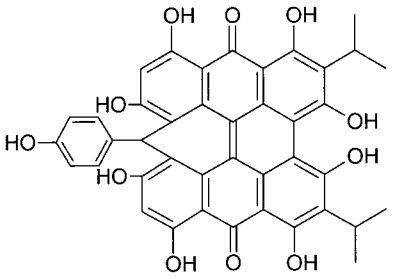

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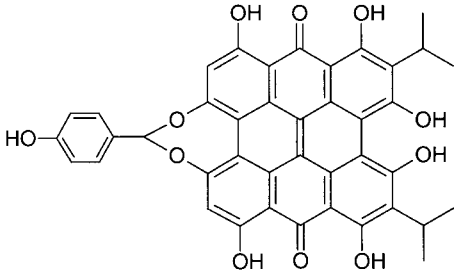

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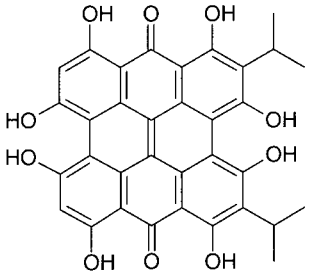

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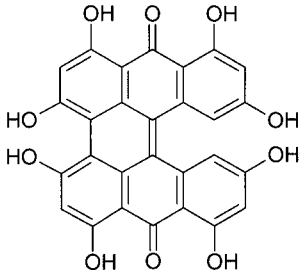

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such as hypericin (**1**) or fringelite D by means of conventional techniques to prepare the oxyblepharismin-type molecules have also failed so far. Thus, attempts to acetalize **1** under various conditions (PhCHO/TsOH in THF; PhCHO/chlorosulfonic acid; CH_2I_2/K_2CO_3 or *Hünig* base in MeCN; PhCOCl/pyridine reflux, or pyridine/NaI, or MeCN/K_2CO_3, or *Hünig*'s base) were unsuccessful.

Of course, the results of this study could also shed some light on the biosynthesis of blepharismins and oxyblepharismins such as **5** and **6**, relating them to the hypericin-analog stentorins like **7**; the latter could undergo, after benzylation of one of its *bay*-OH

groups, the photorearrangement to the blepharismins, which then could be photooxidized to the oxyblepharismins.

The recording of the electron-spray mass spectra and IR spectra by Dipl. Ing. *W. Ahrer* and Mrs. *B. Hager* (Institute of Chemistry, Johannes Kepler University, Linz) is gratefully acknowledged. We are also grateful to Prof. Dr. *K. Grubmayr* for continuos stimulating discussions.

Experimental Part

General. Hypericin (**1**) was prepared and purified according to [14] and [3]. Its benzylation to yield **2** was achieved according to [2]. Irradiations of solns. in *Pyrex* glass or quartz cuvettes were performed with a 300-W tungsten lamp without additional filters. The solns. were either air-saturated or percolated with Ar. Solvents and bases were of commercial origin and of the best qualities available. UV/VIS [λ_{max} (nm), ε(M^{-1} cm^{-1})]: *Hewlett Packard 8453 UV/VIS*; spectrophotometric titrations were executed also with this instrument and the *WTW pH 530* instrument together with a glass electrode. The latter combination was also used for the electrometric estimations of the pK_a values of *Hünig* base and 'proton sponge' in EtOH/H_2O 80:20. Fluorescence spectra [λ_{em}/nm (relative intensity)]: *Hitachi F-4010* at a concentration of 10^{-6}M dm^{-3}; quantum yields were estimated using the fluorescence of $\mathbf{1}^-$ ($\Phi_f = 0.2$ [15]) as the standard. IR Spectra [cm^{-1}]: *Bio-Rad FTS 45*. NMR Spectra: *Bruker DRX 500* with TMS as the internal standard at 300 K; 2D ROESY experiments on Ar-purged solns. of **3** ($c \approx 10^{-4}$ mol dm^{-3}) in (D_6)DMSO and (D_8)THF were performed with the spectrometer's standard setup. ES-MS: as described in [6] with a *Hewlett Packard 59987* quadrupole instrument.

Phototransformation of **2** *in Benzene*. A soln. of 1.5 mg (2.5 μmol) of **2** and 0.57 (2.5 μmol) of 1,8-bis(dimethylamino)naphthalene (z. S., *Merck*) in 0.7 cm^3 of (D_6)benzene was placed in a NMR sample tube, bubbled with Ar, and its ^{1}H-NMR and UV/VIS spectra were recorded as the reference. ^{1}H-NMR (500 MHz): 14.8 (*s*, OH); 14.6 (*s*, OH); 14.2 (*s*, OH); 14.1 (*s*, OH); 7.3 (*s*, 1 arom. H); 7.2 (br. *s*, 5 H, Ph); 7.06 (*s*, 1 arom. H); 7.04 (*s*, 1 arom. H); 6.9 (*s*, 1 arom. H); 4.5 (*AB*, $J = 10$, PhCH_2); 2.24 (*s*, 1 Me); 2.22 (*s*, 1 CH_3); the signal of the *bay*-OH could not be localized in this system, probably due to exchange phenomena, and, in addition to the signals of **2**, the appropriate neutral 'proton sponge' signals were observed. For the UV/VIS spectrum, *cf. Fig. 1*, trace *1*. Irradiation of this sample for the time intervals given in the legend of *Fig. 1* resulted eventually in the transformation characterized by the UV/VIS spectrum given in *Fig. 1*, trace *4*, and the following ^{1}H-NMR (500 MHz): 15.04 (br. *s*, 2 OH); 14.38 (br. *s*, 2 OH); 7.92 (*s*, 2 arom. H); 7.6–6.5 (*m*, 5 + 2(+6) arom. H); 5.59 (*s*, Ph); 2.39 (*s*, 2 Me). In addition, the corresponding signals of the protonated 'proton sponge' were observed. The same procedure was repeated with 0.05 mg (0.08 μmol) of **2** and 0.18 mg of 'proton sponge' in 0.7 cm^3 of (D_6)benzene to result in the UV/VIS spectrum given in *Fig. 1*, trace *1*, and the following ^{1}H-NMR (500 MHz): 17.10 (br. *s*, OH); 16.52 (br. *s*, OH); 15.09 (br. *s*, OH); 16.06 (br. *s*, OH); 14.37 (br. *s*, OH); 7.90 (*s*, 1 arom. H); 7.64 (*s*, 1 arom. H); 7.43 (*s*, 1 arom. H); 7.32–6.6. (*m*, 5 + 1(+6) arom. H); 5.59 (*s*, Ph); 2.385 (*s*, 1 Me); 2.380 (*s*, 1 Me).

*1,8-Bis(dimethylamino)naphthalene Salt of 1,6,8,10,12,14-Hexahydroxy-3,4-dimethyl-11-phenyl-11*H*-benz[4,10]anthra[2,1,9,8*-nopqa*]pleiadene-7,15-dione* ($\mathbf{3}^- \cdot BDMN^+$). A soln. of 1.85 mg (3 μmol) of **2** and 0.73 mg (3.4 μmol) of 1,8-bis(dimethylamino)naphthalene in 1 cm^3 of benzene was purged with Ar and then irradiated in a *Pyrex* flask under Ar protection by means of a 300-W tungsten lamp placed at a distance of 10 cm. After completion of the reaction (20 min), the meanwhile precipitated black photoproduct was centrifuged, sonicated three times with 1 cm^3 of benzene, and then dried *in vacuo* over P_2O_5. Yield 2.1 mg (87%). M.p. > 320°. UV/VIS (EtOH/H_2O 80:20): 598 (33800), 436 (26200), 417 (25800), 329 (47500). Fluorescence (EtOH/H_2O; λ(excit.) = 559 nm): 602 (1.0), 633 (0.6); $\Phi_f = 0.02$. IR (KBr): 1620 (sh), 1590*s*, 1471*m*, 1457*m*, 1418*w*, 1388*w*, 1370*w*, 1312*w*, 1256*s*, 1234*m*, 1192*m*, 1119*w*. ^{1}H-NMR (500 MHz, (D_8)THF): 18.3 (*s*, H^+); 15.5 (*s*, OH); 14.3 (*s*, OH); 14.2 (*s*, OH); 13.8 (*s*, OH); 13.7 (*s*, OH); 8.6 (*d*-like, 2 naphth. H); 8.3 (*s*, 1 arom. H); 7.8 (*d*-like, 2 naphth. H); 7.33 (*t*-like, 2 naphth. H); 7.6 (*m*, Ph); 7.3 (*s*, 1 arom. H); 7.1 (*s*, 1 arom. H); 6.8 (*s*, 1 arom. H); 5.62 (*s*, Ph); 2.81 (*s*, Me); 2.78 (*s*, Me); 2.3 (*s*, 2 Me_2N). ES-MS (MeOH/NH_3): 593.

*1,6,8,10,12,9,14-Hexahydroxy-3,4-dimethyl-11-phenyl-11*H*-benz[4,10]anthra[2,1,9,8*-nopqa*]pleiadene-7,15-dione* (**3**). The black salt $\mathbf{3}^- \cdot BDMN$ (1 mg, 1.2 μmol) was treated (sonication) three times with 5 cm^3) of 1N HCl and then carefully washed with deionized H_2O. The resulting red solid was then dried *in vacuo* over P_2O_5. Yield 0.7 mg (95%). M.p. > 320°. UV/VIS (EtOH/H_2O 80:20): 585 (38200), 544 (25900), 507 (16200), 456 (25600), 317 (46600). Fluorescence (EtOH/H_2O 80:20; λ(excit.) = 541 nm): 584 (1.0), 632 (0.3); $\Phi_f = 0.12$. IR (KBr): 1622 (sh), 1599*s*, 1541*w*, 1472*m*, 1417*w*, 1387*w*, 1328*w*, 1259*s*, 1235*s*, 1192*m*, 1117*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 14.38 (*s*, 2 OH); 13.73 (*s*, 2 OH); 8.0–6.9 (*m*, 4 + 5(+6) arom. H); 5.4 (*s*, Ph); 2.75 (*s*, 2 Me).

Spectrophotometric Titration. EtOH/H_2O 80:20; $\lambda(\mathbf{3}) = 585$ nm; $\lambda(\mathbf{3}^-) = 598$ nm; $\varepsilon(\mathbf{3})/\varepsilon(\mathbf{3}^-) = 1.15$; $pK_a^I(\mathbf{3}) = 7.4 \pm 0.1$; $\lambda(\mathbf{3}^{2-}) = 615$ nm; $\varepsilon(\mathbf{3}^-)/\varepsilon(\mathbf{3}^{2-}) = 0.73$; $pK_a^{II}(\mathbf{3}) = 11.6 \pm 0.1$.

Förster-*Cycle Estimates* [13]. $pK_a^*(\mathbf{2}) = pK_a^I(\mathbf{2}) - 1.7 = 6.6$ (from [2]: $pK_a^*(\mathbf{2}) = 8.3$; $\lambda(\mathbf{2}) = 581$ nm; $\lambda(\mathbf{2}^-) = 610$ nm); $pK_a^*(\mathbf{3}) = pK_a^I(\mathbf{3}) - 0.8 = 6.6$.

Transformation of **3** *to* **1**. Salt $\mathbf{3}^- \cdot$ BDMN (1 mg, 1.2 μmol) was dissolved in 1 cm^3 of acetone. The mixture was bubbled under daylight conditions with O_2 for 3 h. Then, 10 cm^3 of sat. aq. NH_4Cl soln. was added, and, after 1 h, the precipatate was centrifuged, washed with H_2O, and dried *in vacuo*. According to its UV/VIS and ES-MS [6], this material consisted mainly of hypericin (**1**).

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