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Synthesis of Stentorin

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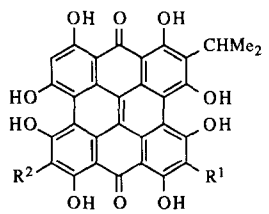
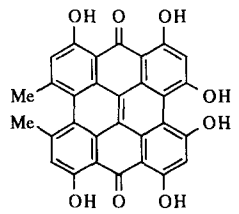
Abstract: The two symmetrical structures **1** and **2** proposed for the photodynamic pigment stentorin have both been synthesised, thereby establishing the correctness of structure **1**.

The photodynamic pigment stentorin was first reported from the protozoan *Stentor coeruleus* in 1873.[1] It is one of the longest known natural products not to have been assigned a unique structure. It is believed to function as a photoreceptor in the parent organism, in which it mediates a step-up photophobic and negative phototactic response.[2,3] In 1993 stentorin was shown to consist of a symmetrically hydroxylated naphthodianthrone core, further symmetrically substituted by two isopropyl groups. Placement of the isopropyl groups was uncertain, the structure being assigned as one of the isomers **1** or **2**.[4] Their symmetry makes differentiation between them difficult. Both structures are similar to that of hypericin **5**, a photodynamic plant and animal pigment,[5] which exhibits highly specific anti-retroviral activity, including promising activity against HIV.[6,7]



1 $R^1 = CHMe_2$, $R^2 = H$
2 $R^1 = H$, $R^2 = CHMe_2$



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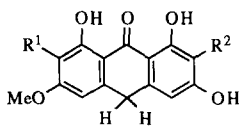
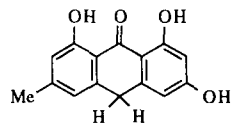


3 $R^1 = CHMe_2$, $R^2 = H$
4 $R^1 = H$, $R^2 = CHMe_2$



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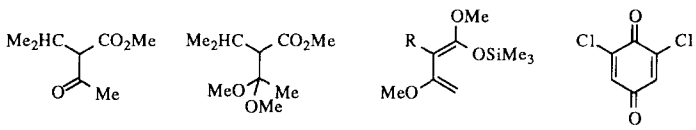
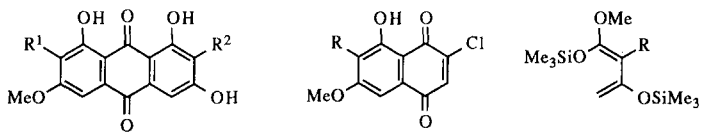
This paper describes syntheses of both **1** and **2**, thereby establishing the correctness of the former. This envisaged subjecting new regioisomeric anthrones **3** and **4** to extended oxidative coupling to form the

appropriate naphthodianthrone framework. This would parallel established coupling of emodin anthrone **6** to hypericin **5**[5] but it would also involve greater problems of regioselection, owing to the symmetrical oxy substitution pattern of **3** and **4**. It was hoped that controlled placement of the *O*-methyl group might allow these problems to be overcome.

Anthrones **3** and **4** were derived from the corresponding anthraquinones **7** and **8**, which in turn were synthesised by Diels-Alder chemistry. This required the isopropyl dienes **9** and **10**, each of which was synthesised for the first time from methyl 2-isopropylacetoacetate **11**.[8] Treatment of **11** with $(MeO)_3CH$ in MeOH in the presence of catalytic *p*-TsOH gave the dimethyl acetal **12** (δ [$CDCl_3$] 3.17, s, $(OMe)_2$; 3.67, s, CO_2Me). Concurrent enolisation, elimination and silylation of **12** at -78° (LDA/TMSCl, 2 eq.) gave the 3-methoxy diene **9** (92%) (δ [$CDCl_3$] 0.91, s, $OSiMe_3$; 0.98, d, J 7.0 Hz, Me_2; 2.73, septet, J 7.0 Hz, CH; 3.50, 3.54, s, s, 2 x OMe; 3.94, d, J 1.7 Hz, H4; 4.12, d, J 1.7 Hz, H4). The analogous 3-trimethylsilyloxy diene **10** was similarly obtained by one-pot, double enol silylation of **11** at -78° (LDA/TMSCl, 2 eq.). This gave **10** (87%) (δ [$CDCl_3$] 0.21, 0.23, s, s, 2 x $OSiMe_3$; 1.01, d, J 7.0 Hz, Me_2; 2.61, septet, J 7.0 Hz, CH; 3.55, s, OMe; 4.10, 4.28, s, s, 2 x H4).



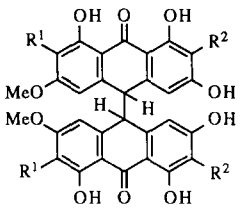
11 **12** **9** R = $CHMe_2$, **17** R = H **13**



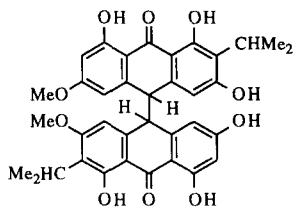
7 $R^1 = CHMe_2$, R^2 = H; **8** R^1 = H, $R^2 = CHMe_2$ **14** R = $CHMe_2$, **16** R = H **10** R = $CHMe_2$, **15** R = H

Addition of diene **9** (1 eq.) to the bifunctional dienophile **13** (benzene/room temperature) and aromatisation of the intermediate cycloadduct by treatment with boiling xylene followed by HCl/THF, gave the naphthoquinone **14** (86%) (δ [$CDCl_3$] 1.32, d, J 7.1 Hz, Me_2; 3.66, septet, J 7.1 Hz, CH; 3.97, s, OMe; 7.10, s, H3; 7.21, s, H5; 12.22, s, β-OH). This product underwent cycloaddition of the known diene **15**[9] and subsequent aromatisation (HCl/THF then NaOAc/EtOH), to give the new anthraquinone **7** (90%) (δ [$(CD_3)_2SO$] 3.97, s, OMe; 6.57, d, J 2.4 Hz, H7; 7.11, d, J 2.4 Hz, H5; 7.28, s, H4; 10.10, brs, β-OH; 12.21, 12.70, s, s, 2 x α-OH). The second new anthraquinone **8** was obtained by analogous cycloaddition of diene **10** to the naphthoquinone **16**, itself derived by cycloaddition/aromatisation of the known diene **17** to **13**.[10] Compound **8** (69%) showed δ [$(CD_3)_2SO$] 3.90, s, OMe; 6.84, d, J 2.6 Hz, H7; 7.15, d, J 2.6 Hz, H5; 7.24, s, H4; 11.20, s, β-OH, 12.24, 12.77, s, s, 2 x α-OH. Selective reduction of **7** and **8** was effected by hydrogenation (EtOH, 5% HCl, H_2, 1 atm, PtO_2) to give the respective anthrones **3** (98%) (δ [$(CD_3)_2SO$] 4.29, brs, CH_2; 12.40, 12.88, s, s, 2 x α-OH) and **4** (94%) (δ [$(CD_3)_2SO$] 4.24, brs, CH_2; 12.55; 13.10, s, s, 2 x α-OH). The expected regiochemistry of cycloaddition and of quinone reduction was confirmed by the presence of two chelated α-hydroxy resonances in the ^1H NMR spectra of both **3** and **4**.

Separate treatment of the anthrones **3** and **4** with $FeCl_3$, which was effective in oxidative coupling of the less highly oxygenated emodin anthrone **6**,[5] gave only intractable material resulting from apparent overoxidation. However, controlled oxidative dimerization of **3** and **4** was successfully brought about under milder conditions. Thus treatment with $K_3Fe(CN)_6$ in 1:1 ethanol/aqueous buffer (pH 4-5) gave the corresponding bianthrones **18** (98%) and **19** (85%) respectively. Each product showed chromophoric similarity (λ_{max} [EtOH+1% HCO_2H] 362 nm) to its parent anthrone monomer, while in their ^1H NMR spectra the 10,10'-protons resonated with half the relative intensity; each bianthrone was seen as an approximately 1:1 mixture of (±) and *meso* diastereoisomers, in common with the coupling product from emodin anthrone **6**.[5] Treatment of an equimolar mixture of **3** and **4** under these same oxidative conditions gave, in addition to **18** and **19**, the new mixed bianthrone **20** as statistically the major product.[5] This mixed bianthrone also was obtained as two diastereoisomers, which were separated by preparative TLC in a combined yield of 35%. The ^1H NMR spectrum of each diastereoisomer of **20** exhibited four chelated hydroxy signals and six aromatic proton resonances.



18 $R^1 = CHMe_2$, $R^2 = H$
19 $R^1 = H$, $R^2 = CHMe_2$



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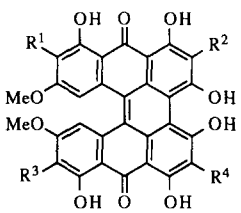
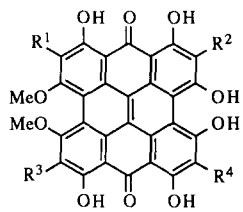


21 $R^1 = R^3 = CHMe_2$, $R^2 = R^4 = H$
23 $R^1 = R^3 = H$, $R^2 = R^4 = CHMe_2$
25 $R^1 = R^4 = H$, $R^2 = R^3 = CHMe_2$



22 $R^1 = R^3 = CHMe_2$, $R^2 = R^4 = H$
24 $R^1 = R^3 = H$, $R^2 = R^4 = CHMe_2$
26 $R^1 = R^4 = H$, $R^2 = R^3 = CHMe_2$

Diastereoisomeric mixtures of each of the three bianthrones **18**, **19**, **20** were subjected to further oxidative coupling involving passage of oxygen through their heated basic solutions (EtOH, aqueous NH_3) in the dark. Under these conditions **18** gave a deep violet product (69%). It was identified as **21** on the basis of its electronic absorbtion (λ_{max} [EtOH+1% CF_3CO_2H] 548, 580 nm) and ^1H NMR spectrum (δ [$(CD_3)_2SO$] 6.30, 7.05, s, s, 2 x ArH, 2 x ArH; 13.51, 14.34, s, s, 2 x α-OH). This was consistent with a symmetrical structure and confirmed that, as hoped, the coupling process selectively involved the two resorcinol rings of **18** rather than those containing the methyl ether groupings. The conversion (**18**→**21**) has direct parallel in hypericin chemistry,[5] as has the next stage, subjecting a DMSO solution of **21** to ultraviolet irradiation in air. This resulted in complete conversion to the naphthodianthrone **22** (δ [$(CD_3)_2SO$] 6.56, s, 2 x ArH; 14.60,

15.14, s, s, 2 x α-OH, 2 x α-OH). Similar oxidation of **19** (NH_3/O_2) in the dark gave the symmetrical **23** (δ [$(CD_3)_2SO$] 6.49, d, J 2.2 Hz, ArH; 7.01, d, J 2.2 Hz, ArH; 13.18, 14.66, s, s, 2 x α-OH), although in this relatively crowded case the yield was lower (7%) and there was concomitant further coupling to **24** (15%) (δ [$(CD_3)_2SO$] 7.19, s, 2 x ArH; 14.63, 15.17, s, s, 2 x α-OH, 2 x α-OH) even when light was carefully excluded. Conversion of **23** to **24** was effected by aeration in light, as before.

In the same way, mixed bianthrone **20** underwent coupling with selective involvement of the resorcinol rings giving the unsymmetrical violet product **25** (58%) (δ [$(CD_3)_2SO$] 6.31, s, ArH; 6.43, d, J 2.2 Hz, ArH; 6.98, d, J 2.2 Hz, ArH; 7.05, s, ArH; 13.12, 13.50, 14.33, 15.04, s, s, s, s, 4 x α-OH). Photooxidation of **25** gave the unsymmetrical naphthodianthrone **26** (δ [$(CD_3)_2SO$] 6.60, 7.22, s, s, ArH, ArH; 14.56, 14.64, 15.08, 15.22, s, s, s, s, 4 x α-OH). The naphthodianthrones **22**, **24** and **26** each gave an ion at m/z (FAB) 621 (M+1).

Boiling with 47% HI in acetic acid over 32 h effected smooth demethylation of **22** and **24** to give **1** and of **26** to give **2**, thereby providing rational syntheses for both symmetrical structures possible for stentorin.[4] **1** and **2** were chromatographically separable on GF_{254} silica. Each gave a weak (<5%) ion at m/z (FAB) 593 (M+1). Like hypericin **5**,[11] both isomers were appreciably acidic and NMR spectroscopic comparisons were accordingly made both in DMSO containing CF_3CO_2H (trace) and in DMSO saturated with $NaHCO_3$. On that basis **1** (δ 6.94, s, 2 x ArH; 14.64, 15.32, s, s, 2 x α-OH, 2 x α-OH) was found to correspond (TLC, electronic absorbtion and ^1H NMR) to an authentic sample of stentorin,[4] whereas **2** (δ 6.84, s, 2 x ArH; 14.67, 15.28, s, s, 2 x α-OH, 2 x α-OH) was clearly different.

Stentorin has thus been synthesised for the first time and its structure **1** thereby confirmed.

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