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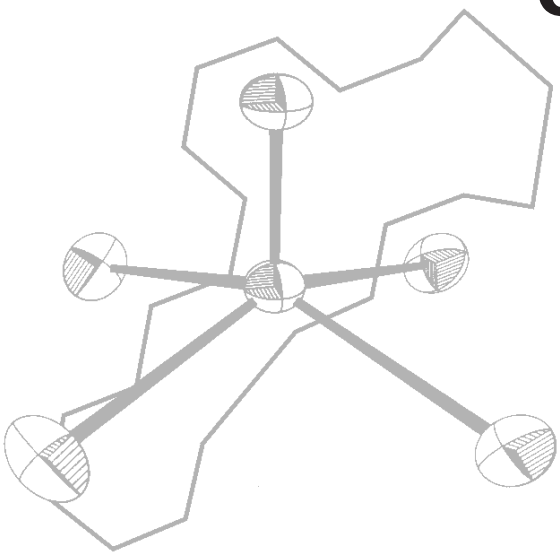

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Synthesis of Stentorin*†

Donald W. Cameron[A,B] *and Andrew G. Riches*[A]

[A] School of Chemistry, The University of Melbourne, Parkville, Vic. 3052.
[B] Author to whom correspondence should be addressed.

The two isomeric structures (2) and (3) proposed for the photodynamic pigment stentorin have both been synthesized for the first time, thereby allowing unambiguous identification of the natural material as (2). Synthesis of these highly condensed aromatic systems involved controlled oxidative couplings of the new anthrones (7) and (8), each synthesized by regiocontrolled cycloaddition.

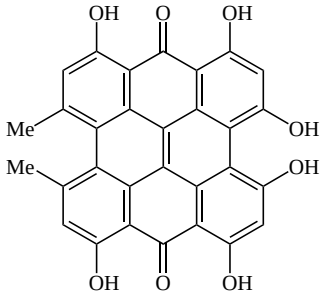
Introduction

The freshwater ciliate *Stentor coeruleus* is blue-green in colour and exhibits a characteristic red fluorescence. The name stentorin was first given to the photodynamic pigment responsible for this coloration in 1873.[1] The pigment is located in vesicles close to the cell membrane and is believed to function as the primary photoreceptor involved in the step-up photophobic and negative phototactic responses exhibited by this protozoan.[2,3] Details of the chemical structure of stentorin have remained vague until recently, with various workers noting a general resemblance to hypericin (1).[4,5] In 1993 Song and coworkers showed the pigment to consist of a naphthodianthrone core symmetrically substituted by eight hydroxy groups and further symmetrically substituted by two isopropyl groups, the relative placement of which was uncertain and the structure was assigned as one or other of the symmetrical isomers (2) or (3).[6] This makes stentorin one of the longest-known natural products not to have been assigned a unique structure.

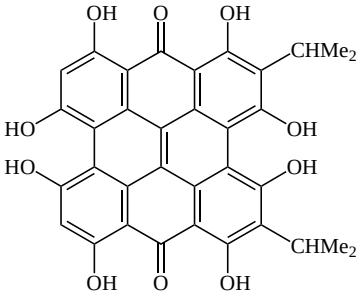
A consequence of the respective symmetries of (2) (C_{2v}) and (3) (C_{2h}) is that they are not readily differentiable by simple spectroscopic methods; for example, ^{1}H and ^{13}C n.m.r. spectra for each isomer would exhibit an identical number of resonances with identical multiplicities. Moreover, their close similarity made it likely that chemical shift values would not differ greatly or predictably from one isomer to the other.

The polyhydroxy naphthodianthrone chromophore of stentorin bears a close similarity to other photodynamic pigments such as fagopyrin,[7,8] the fringelites[9] and hypericin (1). It is believed that hypericin (1) is biosynthesized through intermediates (4) and (5) by coupling of a polyketide-derived anthrone (6)[10] (Scheme 1), and it seems reasonable to assume that stentorin is also biosynthesized in the same way. The origin of the isopropyl groups is uncertain, one suggestion being that they are incorporated via isoprene units.[6]

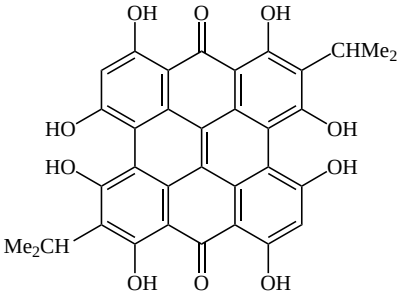
Many of these pigments are photodynamic, generating toxic concentrations of singlet oxygen upon photoexcitation.[10,11] Hypericin (1) exhibits highly specific activity against HIV and related retroviruses[12,13] in which light plays an essential role.[14] Antiviral activity was exhibited by (1) at concentrations at which photodynamic toxicity to the viral host (mouse) was not evident and was further shown to be independent of the presence of singlet oxygen.[15] It has been proposed that



(1)



(2)



(3)

* This paper is dedicated to Professor R. C. Cambie.
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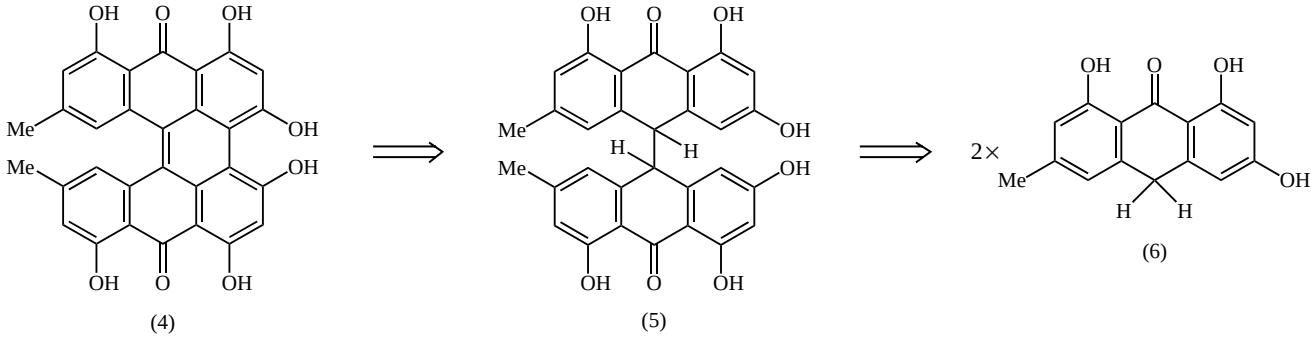


Scheme 1

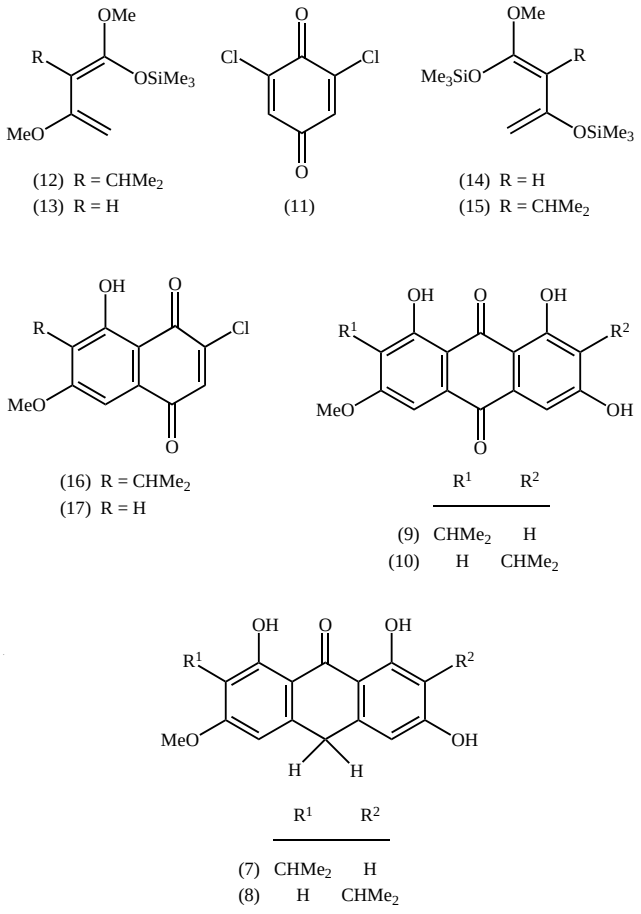
the virucidal activity of hypericin is due to its ability to acidify its environment upon optical excitation.[15] It is interesting to note that the photophobic and negative phototactic responses of *S. coeruleus* are also believed to be mediated by the generation of a proton gradient by deprotonation of excited-state stentorin.[2,3] Given that the hydroxy groups appear to be essential for antiviral activity, it is likely that analogues based on the stentorin chromophore may also exhibit this property.[14,16]

Stentorin is available only in restricted quantities, due to the slow growth rate of *S. coeruleus*.[17] Synthesis would not only achieve the primary objective of establishing its precise structure but may also provide sufficient material for more thorough evaluation of its biological activity than has so far been possible. The syntheses of (2) and (3) outlined herein were based on a biomimetic approach previously employed in this Department in the synthesis of hypericin (1)[18] (Scheme 1). This last synthesis represented an optimization of the original method of Brockmann,[19] who established the structure[20] and synthesis[21] of (1) for the first time. Regiocontrol in that synthesis was established in the oxidation (5) → (4), in which coupling occurred exclusively between the more electron-rich resorcinol rings.

Results and Discussion

It was considered unlikely that a 2-isopropyl group would have a significant enough electronic influence to exert useful regiocontrol over a parallel sequence to that of Scheme 1, starting from an otherwise symmetrical 1,3,6,8-tetrahydroxyanthrone. Such an approach would therefore not permit independent differentiated syntheses of (2) and (3), considered essential to the unambiguous identification of natural stentorin. As a more effective alternative, it was hoped that controlled placement of *O*-methyl groups would serve to differentiate the two benzenoid rings sufficiently to control the regiochemistry of coupling and thereby determine placement of the isopropyl substituents in the final condensed products. Specifically, it was hoped that bianthrone derivatives of the partially *O*-methylated polyhydroxy anthrones (7) and (8) might undergo regioselective intramolecular coupling so as to favour the dihydroxy benzene rings. It was further envisaged that these anthrones (7) and (8) would be available by regioselective reduction of the anthraquinones (9) and (10), which should themselves be amenable to synthesis by cycloaddition methodology.

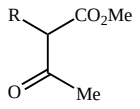
Synthesis of the isomeric anthraquinones (9) and (10) was proposed to involve initial cycloaddition of the respective 3-methoxy dienes (12) and (13) onto the bifunctional dienophile (11), followed by addition of the appropriate 3-trimethylsilyloxy dienes (14) and (15) to the resultant naphthoquinones (16) and (17). Standard workup of these additions was expected to allow retention of the *β*-methoxy and hydrolysis of



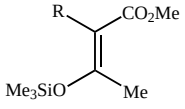
the β-trimethylsiloxy groups. Delaying establishment of 6,8(1,3)-dihydroxylation until the anthraquinonoid level, that is until after the second cycloaddition, was considered expedient because 6,8-dihydroxynaphthoquinones, that would arise as intermediates from the inverse order of addition, are relatively unstable due to their susceptibility to oxidation;[22] and their appreciably acidic β-hydroxy groups are often incompatible with the silyl ketene acetal groups in ester-derived dienes.

These projected sequences required the two known dienes (13) and (14), together with the hitherto unknown 2-isopropyl dienes (12) and (15). The former pair were each synthesized from methyl acetoacetate (18) in two steps. Thus separate enol methylation and enol silylation[23] of (18) gave, respectively, the α,β-unsaturated esters (19)[24,25] and (20),[24] both of which underwent 1,4-enolization and silylation with lithium diisopropylamide/chlorotrimethylsilane at $-78°$ to give (13)[25] and (14)[26,27] respectively.

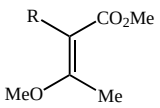
Synthesis of (15), the 2-isopropyl analogue of (14), proceeded analogously. Enol silylation of the 2-isopropyl acetoacetate (21),[28] under Danishefsky conditions,[23] gave an 8 : 1 mixture of (*E*)- and (*Z*)-isomers of the new α,β-unsaturated ester (22) in 76% yield after distillation. The ^{1}H n.m.r. spectrum of the mixture showed significant anisotropic deshielding of the methyl group of the major (*E*)-isomer (δ 2·08) relative to the minor (*Z*)-isomer (δ 1·86) by the ester carbonyl.[29] Further enolization/silylation of this geometrical isomeric mixture (22) at $-78°$ with lithium diisopropylamide/chlorotrimethylsilane proceeded as expected to give the diene (15) (81%) after bulb-to-bulb distillation. The product was a single geometrical isomer within the limits of detection of ^{1}H n.m.r. spectroscopy and was tentatively assigned (*Z*)-geometry on the basis of previous work within this Department.[24,30] Alternatively, (15) was obtained directly by a one-pot reaction of (21) with 2 equiv. of lithium diisopropylamide and of chlorotrimethylsilane at $-78°$. In this case a 4 : 1 mixture of (*E*)- and (*Z*)-isomers (15) was obtained (80%). Since work here has shown that geometrical isomerism about the 1,2-double bond has little effect either on the ability of dienes to undergo cycloaddition or on the aromatization of the resultant cycloadducts,[31] the diene was routinely generated by using this simpler one-pot procedure.



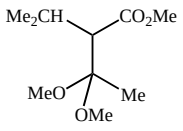
(18) R = H
(21) R = $CHMe_2$



(20) R = H
(22) R = $CHMe_2$



(19) R = H
(23) R = $CHMe_2$



(24)

Standard treatment of the 2-isopropyl acetoacetate (21) with trimethyl orthoformate in methanol and a catalytic amount of *p*-toluenesulfonic acid, instead of forming the expected enol ether (23), gave the dimethyl acetal (24). Its ^{1}H n.m.r. spectrum contained two methoxy signals, the more shielded of which (δ 3·17, 6H) was assigned to the acetal methyls, the other (δ 3·67, 3H) being assigned to the ester methyl group. Similar formation of dimethyl acetals in preference to enol methyl ethers has been observed in *O*-alkylation of other 2-substituted acetoacetate derivatives.[32,33]

The acetal (24) decomposed on attempted distillation, preventing its full characterization. No molecular ion was observed in its mass spectrum at 70 eV but an ion at *m/z* 173 was consistent with favoured loss of a methoxy radical from the molecular ion, as is characteristic of dimethyl acetals.[34] Although preliminary attempts to effect elimination of methanol from (24) to give (23) on a preparative basis were unsuccessful under acidic, basic or thermal conditions, it proved possible to convert (24) directly into the desired diene (12) by treating the former with 2 equiv. of lithium diisopropylamide and of chlorotrimethylsilane at $-78°$. The diene (12) was thereby obtained as a single isomer (95%) after distillation. Due its unconventional mode of formation, its geometry may not be in accord with that obtained by conventional enolization/silylation, and structure (12) is not intended to imply a specific geometry about the 1,2-double bond. Interestingly, attempts to effect direct conversion of (20) into (14) by a one-pot treatment with 2 equiv. of lithium diisopropylamide/chlorotrimethylsilane were unsuccessful under modified Corey internal quench conditions.[35] This contrasts with the other enol silylations (22) → (15), (21) → (15) and (24) → (12).

Treatment of the dienophile (11) with a small excess of the diene (12) in benzene resulted in smooth cycloaddition at room temperature. The crude cycloadduct was immediately aromatized, by using conditions developed within this Department,[24] by boiling in a xylene mixture, followed by brief treatment of the mixture with hydrochloric acid in tetrahydrofuran, to give naphthoquinone (16) (86%). The identity of (16) was readily established by its ^{1}H n.m.r. spectrum, which showed singlets due to the chelated hydroxy (δ 12·22), aromatic and quinonoid protons, with other signals appropriate to the methoxy and isopropyl groups. It also showed an electronic absorption maximum (λ_{max} 435 nm) appropriate to the naphthoquinone chromophore. Analogous addition of the diene (13) to (11) followed by thermal aromatization gave (17), which exhibited physical and spectroscopic characteristics in accord with those previously reported.[24,25] Aromatization and hydrolysis in this case proceeded

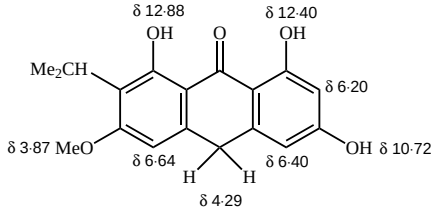
more readily than in the formation of (16), perhaps reflecting steric factors associated with the isopropyl group of the latter.

The next stage involved further cycloaddition of the respective naphthoquinone products (16) and (17), to give anthraquinones. Reaction of the isopropyl naphthoquinone (16) with the diene (14) proceeded rapidly at room temperature, with the expected regioselectivity, to give, after aromatization, the new anthraquinone (9) (90%). It was only sparingly soluble in chloroform and its ^{1}H n.m.r. spectrum was therefore acquired in (D$_6$)dimethyl sulfoxide.* The ^{1}H n.m.r. spectrum contained two chelated hydroxy signals (δ 12·71, 12·04) and aromatic proton signals appropriate to H 5 (δ 7·11) and H 7 (δ 6·57) as *meta*-coupled doublets (J 2·4 Hz), while H 4 (δ 7·28) resonated as a singlet. Parallel reaction of (17) with a threefold excess of the diene (15) was somewhat slower, furnishing after aromatization the new anthraquinone (10) (69%). Its ^{1}H n.m.r. spectrum closely resembled that of its isomer (9).

The close spectroscopic resemblance of the isomeric anthraquinones (9) and (10) is not suprising, given their structural similarity. The unambiguous synthesis of both illustrates the strong capability of cycloaddition methodology to selectively establish *C*- and *O*-alkyl substituents at positions that are otherwise chemically very similar.

Attempted reduction of the anthraquinones (9) and (10) with stannous chloride/hydrochloric acid in boiling acetic acid resulted in accompanying loss of the *O*-methyl group. Analogous demethylation has sometimes been observed for methoxyanthraquinones under strongly Lewis acidic conditions.[36] However, treatment of (9) and (10) with hydrogen over Adams' catalyst in hydrochloric acid/ethanol (5% v/v) gave the desired anthrones (7) (94%) and (8) (98%) respectively. The ^{1}H n.m.r. spectrum of each contained two chelated hydroxy signals and a broad singlet due to the new methylene group. In each case, benzylic coupling of the methylene protons with H 4 and H 5 allowed differentiation of the latter from H 7 and appropriate methoxy resonances were retained.

The main ^{1}H n.m.r. chemical shifts for the two anthrones (7) and (8) are summarized together in Fig. 1. Comparison between the two isomers suggests that the α-aromatic protons H 4 and H 5 are relatively somewhat deshielded by the *meta*-isopropyl group. This is counter to the normal hyperconjugative shielding (*c.* 0·1 ppm) of protons by a *meta*-isopropyl group[34] and might possibly reflect steric congestion, causing affected substituents to deviate from coplanarity with the ring and thereby decrease conjugative electron donation. The relative α-hydroxy shifts in the two series parallel simpler systems. In anthraquinones, *C*-methyl groups typically deshield adjacent α-hydroxy groups by *c.* 0·4 ppm.[37,38] An isopropyl group has an even stronger deshielding effect (*c.* 0·6 ppm).[39] The same deshielding effect was qualitatively observed for the anthraquinones and anthrones synthesized herein. If anything, the isopropyl groups exerted a smaller than expected deshielding influence on adjacent α-hydroxy protons in the methoxy rings. This again could be due to steric congestion leading to reduced conjugative electron donation.



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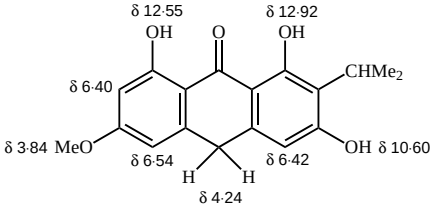

(8)

Fig. 1. ^{1}H n.m.r. chemical shifts for the anthrones (7) and (8), recorded at 400 MHz in (D$_6$)dimethyl sulfoxide.

Separate treatment of the respective anthrones (7) and (8) with iron(III) chloride, under conditions that effected oxidative dimerization of the less highly oxygenated anthrone (6),[40] gave only intractable material resulting from apparent over-oxidation. Milder conditions were therefore required, and heating (7) and (8) with potassium ferricyanide (1·1 equiv.) in a 4:3 mixture of ethanol and aqueous buffer (pH 4·5) resulted in efficient dimerization in each case. Trace amounts of the respective anthraquinones and baseline residue were easily removed by chromatography. The new bianthrones (25) (98%) and (26) (85%) were thereby each obtained as an approximately 1:1 mixture of (±)- and *meso*-diastereoisomers. Thus the ^{1}H n.m.r. spectrum of each bianthrone mixture, as isolated, exhibited four chelated hydroxy resonances, two β-hydroxy resonances and six aromatic resonances. The two signals corresponding to the 10,10′-protons resonated with half the relative intensity of the corresponding protons of the monomers. Signals corresponding to the methoxy and isopropyl groups were complicated by overlap between the two diastereoisomers. Both

* Due to the generally low solubility of these compounds in chloroform, and to facilitate spectroscopic comparison, the ^{1}H n.m.r. spectra of all tricyclic and higher polycyclic compounds described in this paper were recorded in (D$_6$)dimethyl sulfoxide, unless otherwise stated.

bianthrones (25) and (26) showed close chromophoric resemblance to the monomers (7) and (8). No molecular ion was observed in their e.i. mass spectra. In each case a relatively intense peak (*m/z* 314) arising by fission of the 10,10′-bond and H-transfer was observed, the remainder of the spectrum being similar to that of the monomer. However, f.a.b. mass spectrometry showed a weak M+H ion (*m/z* 627). In each case one recrystallization of the diastereoisomeric mixture of bianthrones gave a single diastereoisomer almost exclusively, this being the higher R_F* isomer in the case of (25) and the lower R_F isomer in the case of (26). Each diastereoisomeric mixture was also separable by careful chromatography. The ^{1}H n.m.r. spectrum of each separated diastereoisomer exhibited two chelated hydroxy resonances, a β-hydroxy resonance and three aromatic resonances, together with other appropriate signals (Fig. 2). The largest differences between the two spectra for each diastereoisomeric pair were observed in the shifts of the internuclear aromatic protons H 4(4′) and H 5(5′) (Table 1). This contrasts with the bianthrone (5) where the greatest chemical shift differences between diastereoisomers were seen in the periphery of the molecule, for the chelated hydroxy signals.[40] These diastereoisomeric differences are discussed in more detail later.

Attention was then directed to synthesizing the unsymmetrical bianthrone system (27). Subjecting an equimolar mixture of the isomeric anthrones (7) and (8) to the mild ferricyanide-mediated oxidation already developed for the formation of (25) and (26) gave rise to the expected complex mixture of products, as indicated by analytical t.l.c. and ^{1}H n.m.r. spectroscopy. The thin-layer chromatogram of this mixture was resolved into six major components, four of which corresponded to the two diastereoisomeric pairs for the symmetrical bianthrones (25) and (26). The two new bands were isolated by preparative t.l.c. As a consequence of the relatively small R_F differences between bands, only small quantities of material could be separated per plate. The sharpest separation was achieved by using a mobile phase of lower than optimal polarity and subjecting each plate to multiple, successive developments. Thus the third and fifth least polar bands each afforded a diastereoisomer of the unsymmetrical bianthrone (27) (15 and 20% respectively), each of whose ^{1}H n.m.r. spectrum contained resonances appropriate to four chelated hydroxy, two β-hydroxy and six aromatic protons. Due to their lack of regiochemical symmetry, both are (±)-diastereoisomers. While obtaining them was laborious, their combined, isolated yield of 35% made (27) the major bianthrone component of the mixture, as expected on statistical grounds.

The difficulties inherent in separating (27) from the by-products (25) and (26) notwithstanding, it was pleasing that it was possible at all, considering the small regiochemical differences between them.

The ^{1}H n.m.r. spectra of these six diastereoisomeric bianthrones (25), (26) and (27) exhibited some unusual features worthy of further comment. The relative chemical shifts of the internuclear protons H 4, H 4′, H 5 and H 5′ were found to vary unpredictably between regio- and diastereo-isomeric bianthrones (Fig. 2; Table 1). This contrasted with the relatively small differences between H 4 and H 5 for the anthrone monomers (7) and (8) (Fig. 1). For example, the shifts of these protons showed wide divergence in the low R_F isomer of (25) and in both isomers of (27). In those spectra two of the four internuclear protons resonated with an unusually high degree of shielding for aromatic systems (Table 1), while the remaining two protons were correspondingly deshielded. Also, unlike the corresponding resonances in (5), these signals showed considerable broadening at ambient temperature in dimethyl sulfoxide, to the extent that *meta*-coupling to H 7 and H 7′ was obscured (though resonances for H 7 and H 7′ were themselves observed as conventional *meta*-coupled doublets in all cases). Differentiation between the H 4, H 4′ and the H 5, H 5′ signals is described in a subsequent paragraph.

The source of this shielding–deshielding is apparently the anisotropic effect of one tricyclic component on the other. This is over and above the expected effects observed for other bianthrones. For example, there is appreciable shielding (*c.* 0·5 ppm) even of α-hydroxy resonances of the bianthrone isomers (Fig. 2) relative to their monomeric counterparts (Fig. 1), despite these substituents being remote from the internuclear linkage; but this same effect has also been found for the α-hydroxy groups of (5) relative to those of monomeric emodin anthrone (6).[40] However the variable shielding–deshielding of the internuclear protons of Table 1 has no parallel in the chemistry of (5), as noted above, and it does not appear to correlate with first-order substituent patterns of the tricyclic components (7) and (8). In view of this investigation's primary aim of synthesizing stentorin, the shielding–deshielding phenomenon has not been further characterized beyond the few diagnostic experiments following.

In order to identify sharp *meta*-coupling, the ^{1}H n.m.r. spectrum of each of the bianthrone diastereoisomers [except for the low R_F diastereoisomer of (26), in which the internuclear proton signals were coincident] was acquired at increasing temperatures. In each case the broad aromatic signals progressively sharpened, a process allowing distinct *meta*-coupling (to H 7 and

* No attempts were made to identify the individual diastereoisomers as (±) or *meso* since the structural distinction between them was expected to be lost on further oxidation towards stentorin. Methodology for identifying analogous diastereoisomeric bianthrones has been achieved in a similar context by the use of chiral shift reagents.[40] Such isomers are differentiated here only by their relative R_F values as either 'high R_F' or 'low R_F'.

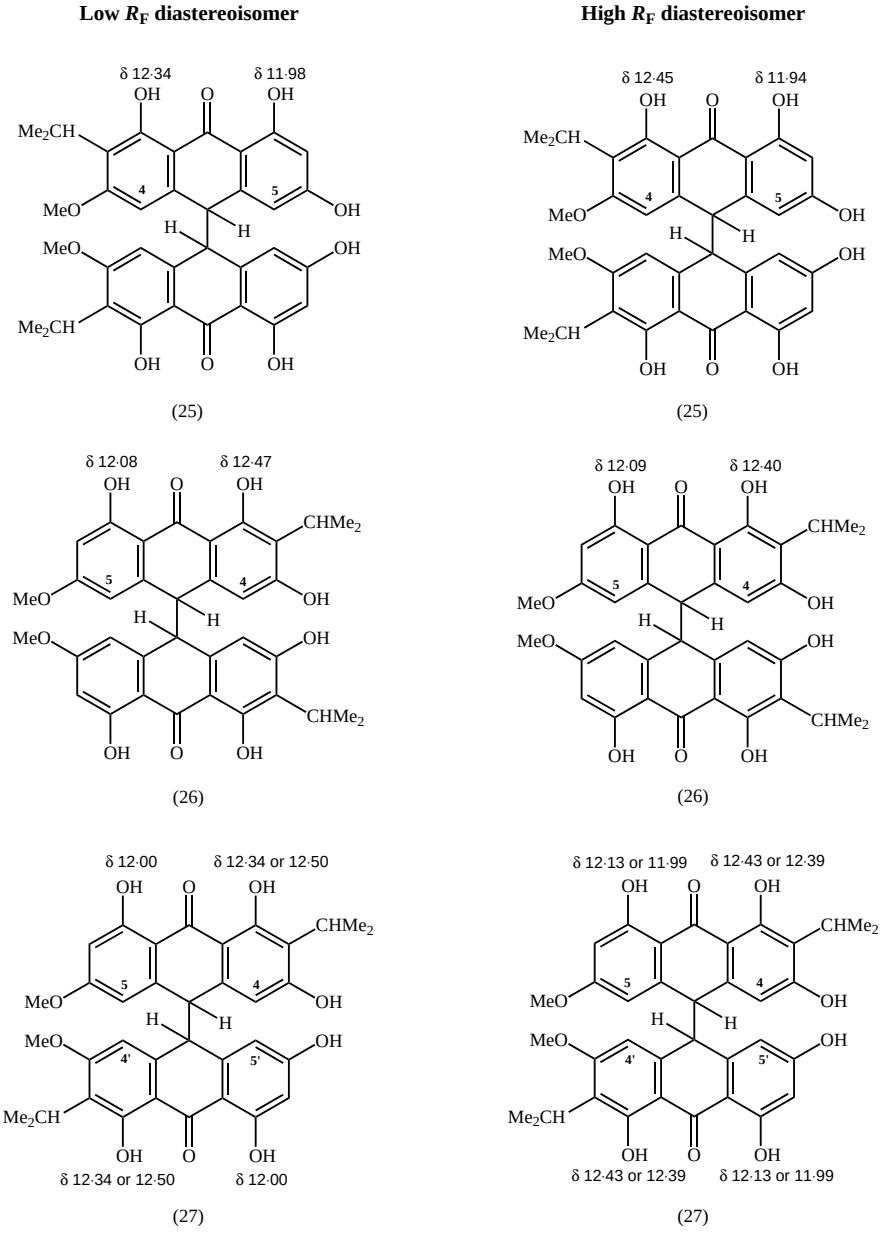

Fig. 2. Numbering and ^{1}H n.m.r. chemical shifts of the chelated hydroxy protons of the bianthrone diastereoisomers of (25), (26) and (27), recorded at 400 MHz in (D_6)dimethyl sulfoxide.

Table 1. ^{1}H n.m.r. chemical shifts of H 4, H 4′, H 5, H 5′, H 7 and H 7′ of the diastereoisomeric bianthrones (25), (26) and (27) recorded at 400 MHz in (D_6)dimethyl sulfoxide at ambient temperature and at 100° (in parentheses)

Note that IUPAC numbering of these protons (Fig. 2) must reflect 1,2,3,6,8-pentasubstitution of the parent tricycles; the isopropyl substituent always being at position 2(2′) means that H 4, for example, may represent a proton *ortho* to either a β-hydroxy or β-methoxy group, depending on the site of *O*-methylation

Compound	δ H 4, H 4′	δ H 5, H 5′	δ H 7, H 7′
(25), low R_F	5·44 (5·47)	6·79 (6·72)	6·31 (6·26)
(25), high R_F	6·19 (6·20)	6·06 (6·08)	6·17 (6·20)
(26), low R_F	5·79 (6·03)	6·39 (6·13)	6·39 (6·33)
(26), high R_F	6·02	6·02	6·36
(27), low R_F[A]	6·60, 5·60 (6·60, 5·63)	6·46, 5·52 (6·36, 5·51)	6·28, 6·27 (6·25, 6·23)
(27), high R_F	5·53, 5·51 (5·65, 5·63)	6·80, 6·67 (6·61, 6·45)	6·46, 6·27 (6·41, 6·24)

[A] No conclusion is to be drawn from the order in which the pairs of shifts are listed for each pair of protons. Thus H 4, H 5 and H 7 have not individually been differentiated from H 4′, H 5′ and H 7′ respectively.

H 7′) to be seen for one out of the two internuclear signals in the symmetrical bianthrone isomers of (25) and (26); and for two out of the four in the unsymmetrical bianthrone isomers of (27). These signals were accordingly assigned to H 5 and H 5′ (Table 1). The signals for which temperature-dependent sharpening revealed the absence of *meta*-coupling were then able to be assigned as H 4 and H 4′, although further differentiation between H 4, H 5, H 7 and H 4′, H 5′, H 7′ respectively in the two diastereoisomers of (27) was not possible. In all these cases, benzylic coupling between the internuclear protons and H 10(10′) was small, by comparison with *meta*-coupling, and did not complicate the analysis.

The low R_F diastereoisomer of (26) showed striking convergence in the shifts of the internuclear protons with increasing temperature, whereas for the other compounds these signals converged only slightly up to the maximum practical temperature of 100° (Table 1). Under these conditions the chemical shifts of the H 7 and H 7′ signals of all the bianthrones remained relatively constant at about δ 6·3. The converged internuclear values (δ 6·03, 6·13) for the low R_F diastereoisomer of (26) were comparable with chemical shifts for the internuclear protons of those isomers in which the shielding–deshielding phenomenon was not observed, for example its high R_F counterpart. This same value (*c.* δ 6·1) is also the approximate mean chemical shift for the internuclear protons of those remaining isomers which showed shielding–deshielding but which did not show appreciable coalescence on being heated.

In (D_6)dimethyl sulfoxide, the standard solvent applicable to all polycyclic compounds of this investigation, spectroscopic analysis of all the bianthrones was limited to an effective maximum temperature of 100° by the onset of considerable decomposition. The major spectroscopically discernible outcome of this process was relatively efficient conversion into the respective monomeric anthrones (7) and/or (8). This decomposition was accompanied by progressive epimerization of residual bianthrone. Analogous autoreductive decomposition has previously been observed for (5).[40] In each case, this process presumably involved homolytic cleavage of the 10,10′-bond followed by abstraction of hydrogen from the solvent, the bianthrones being effectively 1,1,2,2-tetraarylethanes.[41] Interconversion between diastereoisomers would result from some competing recombination of the radical intermediates. Interconversion between diastereoisomers has been reported for other bianthrone systems upon attempted recrystallization.[42]

The aromatic spectroscopic region for each diastereoisomer of (25) was unchanged upon addition of a drop of trifluoroacetic acid to the sample in (D_6)dimethyl sulfoxide, making it seem unlikely that these unusual internuclear shift phenomena resulted from tautomeric or conjugate-base factors. The observed broadening of signals for H 4(4′) and H 5(5′) in dimethyl sulfoxide probably derived partly from its viscosity. Acquisition of the spectrum of the low R_F isomer of (26) in either (D_6)acetone or as a very dilute solution in (D)chloroform gave sharper aromatic signals for the internuclear protons, but they nonetheless displayed the same shielding–deshielding phenomenon.

Considerably more work seems needed to characterize the relevant internuclear properties more thoroughly, a necessary preliminary to which would be independently assigning diastereoisomeric identity[40] to the respective isomers of the three systems (25), (26) and (27). This was not considered to be warranted in the present investigation, which thereupon returned to the projected synthesis of structures (2) and (3). As will be discussed, however, the regio- and diastereochemistry of the bianthrones (25), (26) and (27) does have a bearing on the effectiveness with which these bianthrones undergo the necessary oxidative coupling chemistry.

Heating the diastereoisomeric mixture of the bianthrones (25) in ethanol/aqueous ammonia for 1 h in oxygen in the absence of light pleasingly gave the deep violet helianthrone (28) (69%) with complete regioselectivity within the limits of detection. Its electronic spectrum resembled that of protohypericin (4)[43] in containing a broad visible absorption band (λ_{max} 548, 578 nm). Its symmetrical nature was confirmed by its ^{1}H n.m.r. spectrum, which showed two chelated hydroxy resonances (δ 14·34, 13·51) and two singlet aromatic resonances (δ 7·05, 6·31) (Fig. 3). The absence of splitting of the aromatic protons indicated that they were on different rings and that oxidative coupling had been selective for the resorcinol rings. The β-hydroxy protons of (28) were evidently more acidic than those of the bianthrone (25), since no signal attributable to them was observed. A strong M+H ion (*m/z* 623) was observed in the f.a.b. mass spectrum.

By analogy with the known conversion of protohypericin (4) into hypericin (1),[18] further intramolecular coupling of the helianthrone (28) occurred readily upon irradiation of its dimethyl sulfoxide solution in oxygen with a mercury vapour lamp to give the naphthodianthrone (29). Reaction was accompanied by a striking visual transformation; the colour of the solution changed from violet to bright red with an orange fluorescence, consistent with formation of the naphthodianthrone chromophore. The ^{1}H n.m.r. spectrum of (29) showed only one singlet aromatic resonance (δ 6·58). These protons, and the two pairs of chelated α-hydroxy protons (δ 15·14, 14·61) were deshielded in the more highly condensed, planar naphthodianthrone (29) relative to the corresponding protons of its helianthrone precursor (28). A strong M+H ion (*m/z* 621) in its f.a.b. mass spectrum lent support to the assignment.

The helianthrones and naphthodianthrones isolated in the course of this work tended to tenaciously retain

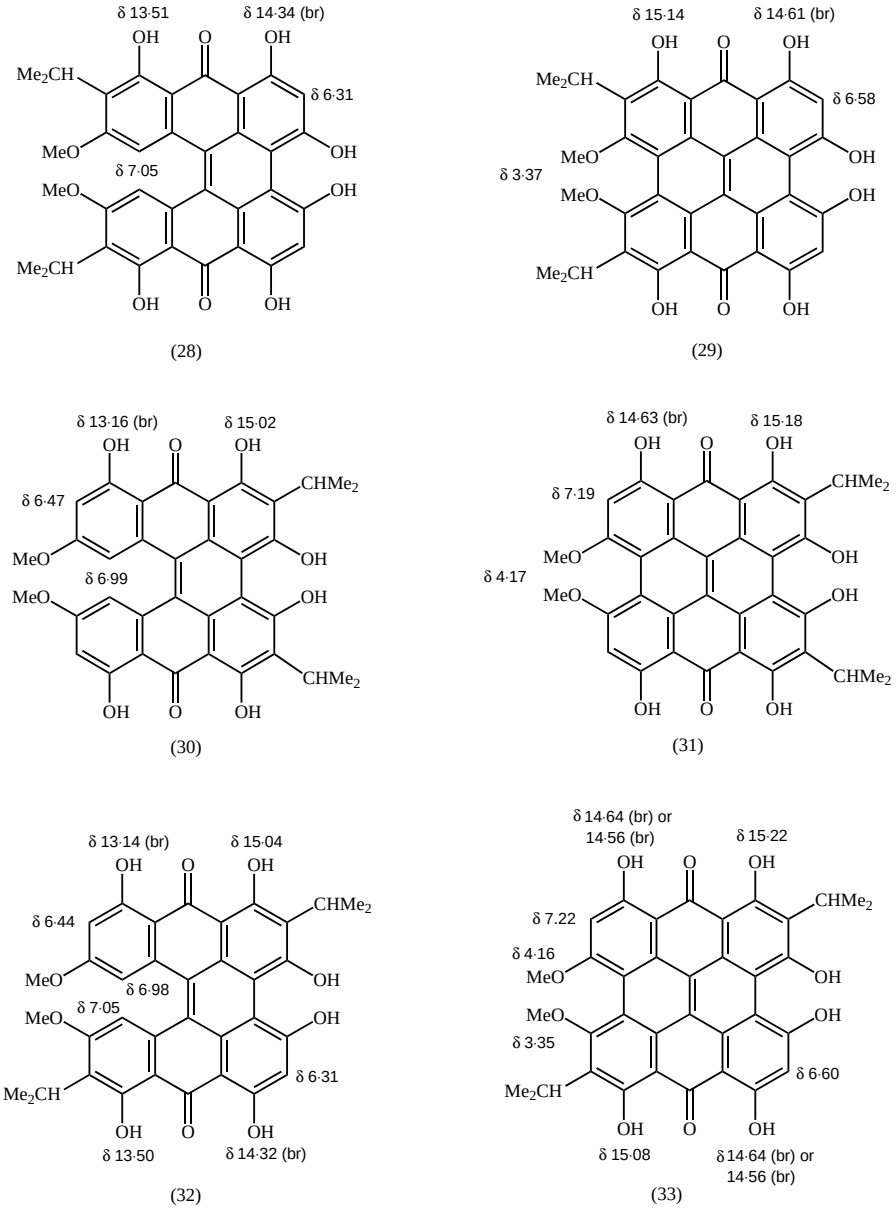

Fig. 3. Comparative ^{1}H n.m.r. data for the helianthrones (28), (30) and (32) and the naphthodianthrones (29), (31) and (33), recorded at 400 MHz in (D_6)dimethyl sulfoxide.

non-stoichiometric amounts of solvent and were insufficiently volatile to be amenable to e.i. mass spectrometry or sublimation. These factors precluded their successful combustion analysis or accurate mass determination. They were, however, generally amenable to f.a.b. mass spectrometry.

Upon treatment with oxygen in aqueous ammonia in the dark, the analogous mixture of bianthrone diastereoisomers (26) behaved somewhat differently from (25), both qualitatively and quantitatively. In relatively poor yield, the reaction gave a mixture of two coloured products which were separated by preparative thin-layer chromatography. The violet product was identified as the helianthrone (30) (7%). Its ^{1}H n.m.r. spectrum showed two α-hydroxy signals (δ 15·02, 13·16) and two *meta*-coupled aromatic resonances (δ 6·99, 6·47, J 2·2 Hz), the latter confirming that oxidative coupling had again occurred exclusively between the dihydroxylated rings. As for (28), the isopropyl methyl groups were magnetically inequivalent. The accompanying red product was identified as the corresponding naphthodianthrone (31) (15%), which was formed even when light was rigorously excluded from the reaction and subsequent workup, by using experimental conditions that were effective in suppressing naphthodianthrone formation in the isolation of (28). Its ^{1}H n.m.r. spectrum showed two α-hydroxy signals (δ 15·18, 14·63) and one aromatic singlet (δ 7·19). The f.a.b. mass spectrum of (31) exhibited an M+H ion (m/z 621). Its electronic spectrum was consistent with the naphthodianthrone chromophore (Table 2). The bulk of the oxidation mixture from (26) corresponded to intractable, decomposition products. Upon resubjecting the helianthrone (30) to oxidative treatment

with aqueous ammonia in the dark, it underwent smooth conversion into the naphthodianthrone (31). This occurred at a rate sufficient to account for the unexpected formation of (31), along with (30), when the bianthrone (26) was similarly treated. The same naphthodianthrone (31) was also obtained efficiently upon deliberate irradiation of the helianthrone (30) in air.

Table 2. Principal visible absorptions of the naphthodianthrones (29), (31) and (33) in ethanol containing 1% trifluoroacetic acid

Compound	λ_{max} (nm)	
(29)	542	584
(31)	537	577
(33)	539	580

The formation of a significant amount of a naphthodianthrone from this oxidation, together with the low overall yield of condensed products, was in marked contrast to the oxidation of the isomeric symmetrical bianthrone (25). This raised the question whether the individual diastereoisomers of (26) might have behaved differently towards further oxidation, as has been observed for the emodin bianthrone system (5).[40] Independently subjecting each separated diastereoisomer of (26) to small-scale oxidation in ammonia in the absence of light showed indeed that virtually all the condensed products (30) and (31) that were isolated from the mixed diastereoisomers apparently derived from the low R_F isomer, the high R_F isomer giving only traces of both. From a preparative standpoint, system (26) thus presents greater difficulties towards a stentorin synthesis than does the isomeric bianthrone series (25). Importantly, however, such helianthrone product as could be detected from the former system by ^{1}H n.m.r. spectroscopy corresponded to (30), the outcome of regioselective intramolecular coupling between the two resorcinol rings. Other comparative comments between the two bianthrone series (25) and (26) are deferred to a later paragraph.

In view of the difference towards intramolecular coupling between the two diastereoisomers of (26), the two diastereoisomers of (27), which necessarily were separated as part of their isolation procedure, were each independently subjected to the standard oxidation conditions. Treatment of the high R_F isomer of (27) thereby pleasingly gave rise to the violet, unsymmetrical helianthrone (32) in 88% yield. Its ^{1}H n.m.r. spectrum contained four distinct α-hydroxy signals (Fig. 3) and four aromatic signals, of which two resonated as singlets and two as *meta*-coupled doublets. The shifts and multiplicities of the aromatic protons were consistent with oxidative coupling having once again occurred exclusively between the resorcinol rings. Distinct pairs of resonances appropriate to non-equivalent methoxy and isopropyl groups were also observed. This helianthrone (32) gave an M+H ion (*m/z* 623) upon f.a.b. mass spectrometry. Treatment of the high R_F diastereoisomer of (27) under identical oxidizing conditions gave the same product (32) (30%) identical in all respects (t.l.c., and ^{1}H n.m.r., infrared and electronic spectra) to that obtained from oxidation of its high R_F counterpart. For comparison with the oxidations of (25) and (26), this represents an effective 59% conversion of a 1 : 1 mixture of the two diastereoisomers of (27) into (32). As such, it is comparably less efficient than that of the mixed isomers (25) into (28) (69%), but it further highlights the inefficient oxidation of the mixed isomers (26) into (30). No accompanying naphthodianthrone was observed upon chromatographic analysis of the crude oxidation product derived from either diastereoisomer of (27), in the absence of light.

The unsymmetrical helianthrone (32) underwent standard photooxidative ring closure, upon irradiation of its dimethyl sulfoxide solution in air, to afford the naphthodianthrone (33). Consistent with its expected lack of symmetry, its ^{1}H n.m.r. spectrum exhibited four distinct α-hydroxy resonances and two aromatic singlets. Pairs of isopropyl methine and methoxy resonances were observed, although the isopropyl methyl resonances were partly superimposed. In common with the isomeric naphthodianthrones (29) and (31), the f.a.b. mass spectrum of (33) exhibited an M+H ion at *m/z* 621.

These observed differences in intramolecular coupling of the isomeric bianthrone systems (25), (26) and (27) can partly be rationalized from earlier work in this Department on the (±)- and *meso*-diastereoisomers of emodin bianthrone (5) whose individual configurations are known independently.[40] Both diastereoisomers underwent intramolecular coupling under the standard ammonia/oxygen conditions to give the same helianthrone (4), as the first isolable product. As for the present investigation, coupling involved the two resorcinol rings exclusively. Where the connectivity of two bianthrones is the same, as is the case for two such diastereoisomers of a single regioisomer, differences in efficiency of their intramolecular oxidative coupling might be expected to reflect configuration-mediated differences in their reactive conformations. Such factors were seen to be capable of speeding or slowing the intramolecular process; but they were not so important as to change its preferred regiochemistry from resorcinol–resorcinol coupling to coupling between a resorcinol and a cresol ring.[40]

Assuming that analogous factors apply to oxidative coupling of bianthrones in the present investigation, it is not suprising that the respective diastereoisomeric components of (26) and of (27) should form the relevant helianthrones (30) and (32) with different efficiencies within each pair; and it is tempting to assign their diastereoisomeric configurations so as to parallel the observed reactivity differences for the known bianthrones (±)-(5) and *meso*-(5). However,

systems (25), (26) and (27) appear to be more complex than the bianthrone (5) in two respects. Firstly, the presence of β-methoxy rather than β-methyl substituents makes (25)–(27) more generally susceptible to competing oxidative decomposition, a problem likely to affect particularly those isomers which couple relatively slowly. When a resorcinol ring that is to undergo intramolecular coupling is substituted by a relatively bulky isopropyl group, such as for both diastereoisomers of (26), associated steric factors are inferred to disfavour close approach of the relevant components, to the point where competing decomposition supervenes. This would help account for the relative efficiencies of helianthrone formation from the three bianthrone systems (25) > (27) > (26), particularly the low yields from (26). The effect may be wholly steric or also, more indirectly, involve electronic factors arising from diminished conjugative electron donation by the oxy substituents, brought about by steric distortion.

Fortunately this adverse effect of isopropyl substitution does not handicap further intramolecular coupling of the helianthrones to give naphthodianthrones. This latter conversion presumably benefits from the conformational constraints imposed on the helianthrone system.

Importantly, the isolation of helianthrones (28), (30) and (32) has indicated that, in line with expectation, the overriding factor controlling the regiochemistry of intramolecular coupling of the bianthrones (25), (26) and (27) is linkage of the resorcinol rings in preference to rings bearing β-methoxy groups. The absence of any helianthrone product arising from coupling other than between the resorcinol rings indicates that the relative placement of the isopropyl groups does not fundamentally alter this preference, although it exerts a marked effect on the efficiency of oxidation.

The ^{1}H n.m.r. assignments of the aromatic protons of the helianthrones, in the standard solvent (D_6)dimethyl sulfoxide, together with those of the α-hydroxy protons, are summarized in Fig. 3. As for the aromatic resonances, the α-hydroxy resonances for (32) were assigned by assuming composite behaviour relative to the spectra of the two symmetrical helianthrones (28) and (30). The α-hydroxy groups adjacent to isopropyl groups were characteristically sharper than α-hydroxy groups in otherwise identically substituted rings. For the 8(15)-hydroxy groups the deshielding associated with adjacent isopropyl groups (0·36 ppm) was less than normal, as was seen in the preceding anthraquinone, anthrone and bianthrone series. In contrast, the 1(6)-hydroxy groups, in the more highly condensed part of the molecule, showed normal deshielding by an adjacent isopropyl group (*c.* 0·69 ppm).

The behaviour of (30) is anomalous in that, of the three helianthrones (28), (30) and (32), it is the only one that underwent further oxidation under the conditions of its formation in the absence of light. The ability of (30) to couple in the absence of light may be due to relatively smaller steric interactions in the absence of a neighbouring isopropyl group, allowing carbons 11 and 12 to approach one another sufficiently closely in the ground state. The β-methoxy groups in such a situation could be coplanar with the aromatic system to which it is attached and thus be more effectively electron donating, also facilitating oxidative coupling.

As was seen in the helianthrone series, the α-hydroxy groups adjacent to the isopropyl groups exhibited markedly sharper signals than those adjacent to a proton. The unsymmetrical compound (33) gave a ^{1}H n.m.r. spectrum approximating a composite of the spectra of the two symmetrical species (29) and (31). For all these products, the aromatic protons and methoxy groups resonated with different chemical shifts depending on their two possible environments. Where the aromatic proton was part of a resorcinol ring [(29), (33)] it showed a 'normal' value, *c.* δ 6·6, but when part of a β-methoxy substituted ring [(31), (33)] it was appreciably deshielded (*c.* δ 7·2). This effect presumably reflected deviation of the methoxy groups from coplanarity with the ring system and resultant reduced resonance electron donation; this was particularly pronounced in the naphthodianthrones by virtue of their highly condensed nature. The greater shielding of the methoxy groups *ortho* to isopropyl groups was similarly attributed to their decreased conjugation with the aromatic nucleus associated with the additional crowding.

Examination of the electronic spectra of the naphthodianthrones (29), (31) and (33) showed a discernible trend in the wavelengths of their principal visible absorptions (Table 2). Compound (29), in which steric congestion of the naphthodianthrone chromophore was expected to be the greatest of the three, with both methoxy groups being flanked by isopropyl groups, showed the longest wavelength absorptions. Congestion would be least in (31), where neither methoxy has an adjoining isopropyl group, and it exhibits the shortest wavelength absorptions. The unsymmetrical (33) represents an intermediate case and its absorptions were at intermediate wavelengths. Such increase in absorption wavelength with increasing steric distortion of the chromophore, though possibly counterintuitive, has been observed in related systems.[43] It was attributed to the differential effects of distortion on the ground- and excited-state energy levels of quinones.

As was hoped at the outset, controlled placement of the *O*-methyl groups at the anthrone level and their retention through successive stages of oxidative coupling, which they themselves influenced, translated effectively into controlled placement of the *C*-isopropyl groups in the naphthodianthrones.

Optimal demethylation (56%) of (29) to the octahydroxy naphthodianthrone (2) was achieved with 47% hydriodic acid in boiling acetic acid. The absence of any methoxy resonance in the ^{1}H n.m.r. spectrum of

the product, together with an ion at *m/z* 593 (M+H) in its f.a.b. mass spectrum, confirmed that both *O*-methyl groups had been lost. Analogous demethylation of the isomeric dimethyl ether (31) gave rise to a product (64%) identical in all respects (t.l.c., and ^{1}H n.m.r., infrared and electronic spectra) to (2). The unsymmetrical dimethyl ether (33), on treatment with hydriodic acid in acetic acid in the same way, afforded an octahydroxy naphthodianthrone product (3) (61%), which exhibited the same coloration as (2). Again, the loss of both *O*-methyl groups was inferred from the absence of a methoxy resonance in the ^{1}H n.m.r. spectrum and the presence of an M+H ion (*m/z* 593) in the f.a.b. mass spectrum. Consistent with expectation, the ^{1}H n.m.r. spectrum of the centrosymmetric (3) closely resembled that of (2) (Table 3).

Table 3. Comparative ^{1}H n.m.r. spectroscopic data for synthetic (2) and (3) and natural stentorin, recorded at 400 MHz in (D_6)dimethyl sulfoxide containing added trifluoroacetic acid

Compound	α-OH	ArH	C**H**Me$_2$	CH**Me**$_2$
(2)	15·32, 14·64 (br)	6·92	4·01	1·47
(3)	15·28, 14·67 (br)	6·84	4·01	1·46
Native stentorin[A]	15·3, 14·7 (br)	6·9	4·0	1·5

[A] As reported.[6]

Like hypericin (1),[44] both (2) and (3) were appreciably acidic. This factor, until recognized, was manifested as a lack of reproducibility in their ^{1}H n.m.r. spectra in different batches of commercial (D_6)dimethyl sulfoxide. Addition of a small amount of trifluoroacetic acid to the n.m.r. samples conveniently suppressed ionization. Under these conditions, the spectrum observed for (2) was reproducible and in good agreement with that reported for natural stentorin[6] (Table 3). While the spectroscopic differences between (2) and (3) were small, as expected, the availability of authentic stentorin* put the assignment beyond doubt. Its spectrum proved to be indistinguishable from that of (2) and differed from that of (3). Pleasingly, the two compounds were also chromatographically separable. Authentic stentorin cochromatographed with (2) on GF_{254} silica, whereas (3) exhibited a discernibly greater R_F.

The difference in the shifts of the α-hydroxy signals is again readily rationalized in terms of the deshielding effect of the *ortho* alkyl groups.[34] Thus, for each compound (2) and (3), the more deshielded (and sharper) of the two α-hydroxy resonances was assigned to the α-hydroxys *ortho* to the isopropyl groups.

The two alternative structures (2) and (3) advanced for stentorin[6] have thus each been independently synthesized for the first time, by controlled coupling of anthrones. Controlled placement of the isopropyl groups in each was facilitated by differentiation of the β-oxy substituents; this involved selective placement of *O*-methyl groups in the anthrone precursors (7) and (8). In the two independent syntheses of (2), considerable differences were noted in the relative efficiency with which the conversion of the respective bianthrones (25) and (26) into more highly condensed systems proceeded. Spectroscopic and chromatographic comparison of (2) and (3) with an authentic sample of stentorin has allowed structural assignment of the natural material to be made in favour of (2). Subsequent to our preliminary communication of these results, a further, different synthesis of (2) has also been reported.[45]

Experimental

General

Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were carried out by National Analytical Laboratories, Melbourne, or Chemical and Microanalytical Services, Geelong. Electronic spectra were recorded in ethanol containing 1% formic acid (v/v), unless otherwise stated, by using a Varian Superscan 3 spectrophotometer. Infrared spectra were recorded by using a Perkin–Elmer 983-G grating spectrophotometer. Solids were recorded as potassium bromide disks and liquids as films between sodium chloride plates. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded at 399·65 MHz with a JEOL JNM-GX400 spectrometer. The solvent was (D)chloroform unless otherwise stated. High- and low-resolution mass spectra were recorded by using a V.G. Micromass 7070F instrument or a JEOL JMS-AX505H mass spectrometer at 70eV, unless otherwise stated. The mass of each ion is given, followed by its relative intensity. In general, only peaks greater than 20% are quoted. Analytical and preparative thin-layer chromatography (t.l.c.) were carried out on glass plates coated with a layer of silica gel [Merck Kieselgel 60 GF_{254} or Merck Kieselgel 60 GF_{254} containing 2% oxalic acid (oxalated silica)]. The separated components were extracted from the silica with ethyl acetate or dichloromethane. Oxalic acid was removed by washing the extracts with water and then drying over magnesium sulfate prior to evaporation of the solvent. Flash chromatography was carried out by using Merck Kieselgel No. 9385. Short-column chromatography refers to chromatography carried out on a packed column of Merck Kieselgel GF_{254} of height no greater than its diameter in a sintered glass funnel, generally by means of gradient elution. All solvents were of A.R. grade or were redistilled prior to use. Dry tetrahydrofuran was distilled from potassium benzophenone ketyl under nitrogen immediately prior to use. Dry methanol was distilled from magnesium methoxide. Petrol refers to the hydrocarbon fraction boiling in the range 60–80° and light petrol refers to the hydrocarbon fraction boiling in the range 40–60°. All diene preparations and cycloadditions were performed under dry nitrogen in flame-dried glassware. Highly acid-sensitive cycloadditions were performed in glassware which had been previously washed with aqueous ammonia solution followed by distilled water. Organic extracts were generally dried over magnesium sulfate before evaporation at reduced pressure.

Methyl 2-Isopropyl-3-oxobutanoate (21)

To a suspension of sodium hydride (15·2 g, 60% dispersion) in tetrahydrofuran (300 cm^3) was added dropwise methyl aceto-

* An authentic sample of stentorin from *S. coeruleus* was kindly provided by Professor P.-S. Song.

acetate (18) (44·0 g). The mixture was boiled for 1 h and cooled before careful addition of 2-iodopropane (129·4 g). The mixture was heated at reflux for 20 h, cooled, diluted with water (600 cm^3) and extracted into ethyl acetate (3×100 cm^3). The combined extracts were washed with water (300 cm^3) and brine (300 cm^3), then dried and evaporated. Distillation gave methyl 2-isopropyl-3-oxobutanoate (21) (50·3 g, 84%) as a colourless oil, b.p. 78–80°/10 mm. δ 3·74, s, CO_2CH_3; 3·19, d, J 9·5 Hz, H 2; 2·41, doublet of septet, J 9·5, 6·7 Hz, C**H**$(CH_3)_2$; 2·22, s, $COCH_3$; 0·96, d, J 6·7 Hz, $(CH_3)_ACH(CH_3)_B$; 0·92, d, J 6·7 Hz, $(CH_3)_ACH(CH_3)_B$. *m/z* 158 (M, 2%), 116 (49), 101 (100), 85 (39), 69 (5), 58 (55), 57 (27).

Methyl 2-Isopropyl-3,3-dimethoxybutanoate (24)

A solution of the ester (21) (11·97 g) in dry methanol (18 cm^3), trimethyl orthoformate (8·3 cm^3) and *p*-toluenesulfonic acid (15 mg) was boiled for 8 h. The mixture was poured into saturated aqueous sodium bicarbonate solution (150 cm^3) and extracted into ethyl acetate (2×50 cm^3). The combined extracts were washed with water (100 cm^3) and brine (100 cm^3), then dried and evaporated to give the crude *dimethoxy ester* (24) (13·91 g, 98%) as a pale yellow oil. Attempted distillation resulted in decomposition (Found: $M^{+\bullet} - OCH_3$, 173·1181. $M^{+\bullet} - OCH_3$ requires 173·1178). δ 3·67, s, 3H, CO_2CH_3; 3·17, s, 6H, $(OCH_3)_2$; 2·62, d, J 10·0 Hz, H 2; 2·03, doublet of septet, J 10·0, 6·6 Hz, C**H**$(CH_3)_2$; 1·46, s, 4-Me; 1·03, d, J 6·6 Hz, $(CH_3)_ACH(CH_3)_B$; 0·87, d, J 6·6 Hz, $(CH_3)_ACH(CH_3)_B$. *m/z* 173 (M − OCH_3, 18%), 130 (35), 113 (23), 99 (68), 98 (23), 89 (100).

(E)- *or* (Z)-*2-Isopropyl-1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene (12)*

To a solution of diisopropylamine (2·18 cm^3) in tetrahydrofuran (10 cm^3) at 0° was added butyllithium (5·76 cm^3, 2·7 M in hexane). The mixture was cooled to −78° and chlorotrimethylsilane (1·84 g) was added dropwise, followed, after 15 min, by dropwise addition of the acetal (24) (3·66 g). The mixture was stirred at −78° for a further 15 min and then allowed to warm to room temperature over 1 h. The solvent was evaporated and the residue diluted with dry pentane (20 cm^3), filtered, concentrated and distilled to give the (E)- or (Z)-*butadiene* (12) (4·83 g, 100%) as a colourless oil, b.p. 40–42°/0·1 mm (Found: C, 58·7; H, 10·2. $C_{12}H_{24}O_3Si$ requires C, 59·0; H, 9·9%). λ_{max} (hexane) (log ϵ) 229 inf. nm (3·73). ν_{max} 1690sh, 1664br, 1598br cm^{-1}. δ 4·12, d, J 1·7 Hz, H 4; 3·94, d, J 1·7 Hz, H 4; 3·50, 3·54, s, s, 2×OMe; 2·73, septet, J 7·0 Hz, C**H**$(CH_3)_2$; 0·98, d, J 7·0 Hz, $CH(CH_3)_2$; 0·91, s, $OSiMe_3$. *m/z* 244 (M, 15%), 233 (34), 229 (23), 125 (68), 97 (34), 89 (32), 73 (100), 58 (29).

Methyl (E)- *and* (Z)-*2-Isopropyl-3-trimethylsilyloxybut-2-enoate (22)*

Methyl 2-isopropyl-3-oxobutanoate (21) (6·15 g) was added to a stirred solution of triethylamine (9·0 cm^3), chlorotrimethylsilane (8·2 cm^3) and fused zinc chloride (50 mg) in benzene (100 cm^3) under nitrogen. The mixture was stirred at 50° for 48 h, filtered (Supercel) and then concentrated. Pentane was added to the residue and the mixture refiltered and then reconcentrated to a yellow oil. Distillation gave an 8 : 1 mixture of the (E)- and (Z)-*butenoates* (22) (6·85 g, 76%) as a colourless oil, b.p. 62–63°/3·0 mm (Found: C, 57·4; H, 9·8. $C_{11}H_{22}O_3Si$ requires C, 57·4; H, 9·6%). λ_{max} (log ϵ) 204 (3·90), 232 nm (3·97). ν_{max} 2955, 1708, 1664 cm^{-1}. δ (*E*)-Isomer 3·70, s, CO_2Me; 3·03, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 2·08, s, 4-Me; 1·07, d, J 7·1 Hz, $CH(CH_3)_2$; 0·24, s, $OSiMe_3$. δ (partial) (*Z*)-Isomer 1·86, s, 4-Me; 1·08, d, J 7·1 Hz, $CH(CH_3)_2$. *m/z* (of mixture) 230 (M, 8%), 215 (31), 130 (20), 111 (5), 99 (47), 89 (100), 73 (39).

2-Isopropyl-1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (15)

(A) To a stirred solution of diisopropylamine (0·7 cm^3) in tetrahydrofuran (10 cm^3) at 0° was added dropwise a solution of butyllithium in hexane (2·2 cm^3, 2·2 M). The mixture was cooled to −78° and chlorotrimethylsilane (0·7 cm^3) was added dropwise, followed, after 15 min, by dropwise addition of the ester (22) (1·00 g). The mixture was stirred at −78° for a further 15 min and then allowed to warm to room temperature over 1 h. The solvent was evaporated and dry pentane (20 cm^3) was added to the residue. The mixture was filtered, concentrated and distilled to give the (Z)-*butadiene* (15) (1·07 g, 81%) as a colourless oil, b.p. 58–60°/0·05 mm (Found: C, 55·4; H, 10·0. $C_{14}H_{30}O_3Si_2$ requires C, 55·6; H, 10·0%). λ_{max} (hexane) (log ϵ) 244 nm (3·96). ν_{max} 1699sh, 1651, 1610, 1439 cm^{-1}. δ 4·28, s, H 4; 4·10, s, H 4; 3·55, s, OMe; 2·61, septet, J 7·0 Hz, C**H**$(CH_3)_2$; 1·01, d, J 7·0 Hz, $CH(CH_3)_2$; 0·22, 0·21, s, s, 2×$OSiMe_3$. *m/z* 302 (M, 9%), 287 (30), 183 (22), 155 (28), 73 (100).

(B) To a stirred solution of diisopropylamine (2·14 cm^3) in tetrahydrofuran (10 cm^3) at 0° was added dropwise a solution of butyllithium (5·10 cm^3, 2·4 M). The mixture was cooled to −78° and chlorotrimethylsilane (2·11 cm^3) was added dropwise, followed, after 15 min, by dropwise addition of methyl 2-isopropyl-3-oxobutanoate (21) (1·00 g). The mixture was stirred at −78° for a further 15 min and allowed to warm to room temperature over 30 min. The solvent was evaporated and the residue diluted with dry pentane (20 cm^3), filtered and then concentrated. Distillation gave a 4 : 1 mixture of the (E)- and (Z)-*butadienes* (15) (1·67 g, 80%) as a colourless oil, b.p. 57–60°/0·05 mm. The ^{1}H n.m.r. spectrum of the (*E*)-isomer partially overlapped that of the (*Z*)-isomer synthesized as in (A), with additional resonances as follows: δ (partial) 4·24, d, J 0·5 Hz, H 4; 4·11, d, J 0·5 Hz, H 4; 3·53, s, OMe; 2·69, septet, J 7·0 Hz, C**H**$(CH_3)_2$.

2-Chloro-8-hydroxy-7-isopropyl-6-methoxy-1,4-naphthoquinone (16)

To a solution of 2,6-dichloro-1,4-benzoquinone (11) (103 mg) in benzene (5 cm^3) was added the diene (12) (220 mg) and the mixture stirred at room temperature for 4 h. It was then poured into hot xylenes and refluxed for 2 h. The solvent was evaporated and the mixture treated with concentrated hydrochloric acid (1 cm^3) in tetrahydrofuran (10 cm^3) for 30 min. It was then poured into water (100 cm^3) and extracted with ethyl acetate (2×50 cm^3). The combined extracts were washed successively with water (100 cm^3) then brine (100 cm^3), and dried and evaporated to give an orange residue. Short-column chromatography, with an ethyl acetate/petrol (0 : 100 → 5 : 95) solvent gradient as eluent, gave the *naphthoquinone* (16) (138 mg, 86%) as orange needles from ether/petrol, m.p. 150–151° (Found: C, 59·9; H, 4·5. $C_{14}H_{13}ClO_4$ requires C, 59·9; H, 4·7%). λ_{max} (log ϵ) 240 (4·02), 268 (2·24), 283sh (4·02), 435 nm (3·75). ν_{max} 1668, 1598, 1568sh cm^{-1}. δ 12·22, s, 8-OH; 7·21, s, H 3 or H 5; 7·10, s, H 3 or H 5; 3·97, s, OMe; 3·66, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 1·32, d, J 7·1 Hz, $CH(CH_3)_2$. *m/z* 282 (M[^{37}Cl], 14%), 280 (M[^{35}Cl], 40), 267 (35), 265 (100).

A sample obtained by short-column chromatography prior to the acidic treatment showed a ^{1}H n.m.r. spectrum as for (16) with additional resonances attributable to 2-chloro-7-isopropyl-6-methoxy-8-trimethylsilyloxy-1,4-naphthoquinone as follows: δ 7·30, s, H 3 or H 5; 7·08, s, H 3 or H 5; 3·95, s, OMe; 3·65, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 1·31, d, J 7·1 Hz, $CH(CH_3)_2$; 0·33, s, $OSiMe_3$.

2-Chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone (17)

To a solution of the dichlorobenzoquinone (11) in benzene (10 cm^3) was added the diene (13) and an exothermic reaction was noted. After 5 min starting material was absent (t.l.c. analysis), and the reaction mixture was poured into boiling xylenes and allowed to reflux for 2 h. Evaporation and crystallization from ethyl acetate/petrol gave the naphthoquinone (17) as orange needles, m.p. 176–177° (lit.[25] 177°). δ 11·93, s, 8-OH; 7·19, d, J 2·6 Hz, H 5; 7·14, s, H 3; 6·67, d, J 2·6 Hz, H 7; 3·92, s, OMe.

1,6,8-Trihydroxy-2-isopropyl-3-methoxy-9,10-anthraquinone (9)

To a stirred solution of the naphthoquinone (16) (580 mg) in dry benzene (10 cm^3) was added the diene (14) (810 mg) and an exothermic reaction was noted as the solution darkened, then faded to pale green. The solvent was evaporated and the residue dissolved in tetrahydrofuran (30 cm^3) and concentrated hydrochloric acid (3 cm^3), and stirred overnight. The mixture was poured into water (100 cm^3) and extracted with ethyl acetate (2×50 cm^3). The combined extracts were washed with water (100 cm^3), brine (100 cm^3), and then dried and evaporated. Petrol (20 cm^3) was added to the residue and the resulting suspension filtered to give the *anthraquinone* (9) (611 mg, 90%) as an orange solid which was used without further purification. An analytical sample was recrystallized from ethyl acetate to give orange needles, m.p. 271–273° (Found: C, 65·8; H, 4·9. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). λ_{max} ($\log\epsilon$) 286 (4·45), 326 (3·99), 451 nm (3·96). ν_{max} 3360, 1619, 1600, 1563 cm^{-1}. δ [$(CD_3)_2SO$] 12·71, s, 1-OH; 12·04, s, 8-OH; 11·32, br s, 6-OH; 7·28, s, H 4; 7·11, d, J 2·4 Hz, H 5; 6·57, d, J 2·4 Hz, H 7; 3·97, s, OMe; 3·60, septet, J 7·1 Hz, CH; 1·28, d, J 7·1 Hz, CH($C\mathbf{H}_3$)$_2$. m/z 328 (M, 52%), 314 (21), 313 (100), 299 (38).

1,3,8-Trihydroxy-2-isopropyl-6-methoxy-9,10-anthraquinone (10)

To a stirred suspension of the naphthoquinone (17) (0·76 g) in dry benzene (7 cm^3) was added the diene (15) (3·67 g) and the mixture stirred at room temperature for 3 days. The solvent was evaporated and the residue was dissolved in tetrahydrofuran (10 cm^3). Concentrated hydrochloric acid (5 drops) was added and the mixture was stirred for 15 h. Ethanol (20 cm^3) and sodium acetate (50 mg) were added and the mixture was heated under reflux for a further 2 h. The mixture was poured into water (150 cm^3) and extracted with ethyl acetate (2×70 cm^3). The combined extracts were washed with water (2×100 cm^3) then brine (150 cm^3), and dried and evaporated to give an orange residue. Crystallization of the residue from ethyl acetate gave the *anthraquinone* (10) (0·72 g, 69%) as orange plates, m.p. 335–337° (Found: C, 65·5; H, 4·9. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). λ_{max} ($\log\epsilon$) 289 (4·31), 319 (3·80), 451 nm (3·85). ν_{max} 3389, 1660, 1618, 1599, 1580 cm^{-1}. δ [$(CD_3)_2SO$] 12·77, s, 1-OH; 12·24, s, 8-OH; 11·20, br s, 3-OH; 7·24, s, H 4; 7·15, d, J 2·6 Hz, H 5; 6·84, d, J 2·6 Hz, H 7; 3·90, s, OMe; 3·55, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 1·29, d, J 7·1 Hz, CH($C\mathbf{H}_3$)$_2$. m/z 328 (M, 63%), 313 (100), 300 (29), 299 (52).

1,6,8-Trihydroxy-2-isopropyl-3-methoxyanthracen-9-one (7)

To a solution of the quinone (9) (72 mg) in ethanol (25 cm^3) was added concentrated hydrochloric acid (5 cm^3) and PtO_2 (15 mg) and the mixture stirred vigorously under an atmosphere of hydrogen for 3 h, filtered through Supercel into water (150 cm^3) and extracted into ethyl acetate (2×75 cm^3). The organic extract was washed with water (2×150 cm^3), brine (150 cm^3), and then dried and evaporated. The brown residue was subjected to short-column chromatography, with an ethyl acetate/petrol (30 : 70 → 50 : 50) solvent gradient as eluent, to give the *anthracenone* (7) (65 mg, 94%) as pale yellow plates, m.p. >215° (dec.), from ethyl acetate/petrol (Found: C, 68·5; H, 6·0. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%). λ_{max} ($\log\epsilon$) 239 (4·04), 278 (4·09), 356 nm (4·38). ν_{max} 3312, 1602, 1564 cm^{-1}. δ [$(CD_3)_2SO$] 12·88, s, 1-OH; 12·40, s, 8-OH; 10·72, s, 6-OH; 6·64, br s, H 4; 6·40, br d, J 2·2 Hz, H 5; 6·20, d, J 2·2 Hz, H 7; 4·29, br s, CH_2; 3·87, s, OMe; 3·53, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 1·25, d, J 7·1 Hz, CH($C\mathbf{H}_3$)$_2$. m/z 314 (M, 34%), 299 (100).

1,3,8-Trihydroxy-2-isopropyl-6-methoxyanthracen-9-one (8)

The quinone (10) (542 mg) was reduced with hydrogen over PtO_2 (90 mg) as for the formation of (7). Chromatography of the crude product, with an ethyl acetate/petrol (20 : 80 → 40 : 60) solvent gradient as eluent, gave the *anthracenone* (8) (510 mg, 98%) as pale yellow needles, m.p. 190–192°, from ethyl acetate/petrol (Found: C, 68·6; H, 6·0. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%). λ_{max} ($\log\epsilon$) 240 (4·02), 277 (4·01), 354 nm (4·31). ν_{max} 3371, 1619, 1597 cm^{-1}. δ [$(CD_3)_2SO$] 12·92, s, 1-OH; 12·55, s, 8-OH; 10·60, s, 3-OH; 6·54, br d, J 2·6 Hz, H 5; 6·42, br s, H 4; 6·40, d, J 2·6 Hz, H 7; 4·24, br s, CH_2; 3·84, s, OMe; 3·48, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 1·26, d, J 7·1 Hz, CH($C\mathbf{H}_3$)$_2$. m/z 314 (M, 45%), 313 (30), 300 (20), 299 (100), 285 (20).

1,1′,6,6′,8,8′-Hexahydroxy-2,2′-diisopropyl-3,3′-dimethoxy-10,10′-bianthrone (25)

To a solution of the anthrone (7) (138 mg) in ethanol (20 cm^3) was added a 1% w/v solution of $K_3Fe(CN)_6$ in pH 4·5 phthalate buffer (15 cm^3) and the mixture was heated gently over a steam bath until starting material was no longer observed by t.l.c. The reaction mixture was poured into 1 M HCl and extracted with ethyl acetate (2×50 cm^3). The combined organic phases were dried and evaporated and the resultant residue was subjected to column chromatography, with an ethyl acetate/petrol (20 : 80 → 40 : 60) solvent gradient as eluent, to give the *bianthrone* (25) as a pale green solid (135 mg, 98%) containing an approximately 1 : 1 mixture of (±)- and *meso*-diastereoisomers. Recrystallization from ethyl acetate/petrol gave the high R_F diastereoisomer as pale yellow needles, m.p. >240° (dec.) (Found: C, 65·3; H, 5·7. $C_{36}H_{34}O_{10}.2H_2O$ requires C, 65·2; H, 5·8%). λ_{max} ($\log\epsilon$) 241 (4·24), 287 (4·28), 362 nm (4·25). ν_{max} 3416br, 1698, 1622sh, 1608, 1566sh cm^{-1}. δ [$(CD_3)_2SO$] 12·45, s, 1-OH, 1′-OH; 11·94, s, 8-OH, 8′-OH; 10·66, s, 6-OH, 6′-OH; 6·19, brs, H 4,4′; 6·17, d, J 2·4 Hz, H 7,7′; 6·06, br s, H 5,5′; 4·49, s, H 10,10′; 3·77, s, OMe; 3·47, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·21, d, J 7·1 Hz, 2×CH($C\mathbf{H}_3$)$_2$. For ^{1}H n.m.r. data at 100° see Table 1. m/z 314 (37%), 299 (100), 88 (27), 73 (33), 70 (54), 69 (27), 60 (86), 56 (29), 54 (22). m/z (f.a.b.) 627 (M+1, 5%), 315 (32), 314 (100), 313 (70), 219 (17).

A portion of the liquor of crystallization was subjected to preparative t.l.c., eluting with ethyl acetate/petrol (2 : 5). The lower pale yellow band gave the low R_F isomer of (25) as a pale yellow solid. δ [$(CD_3)_2SO$] 12·34, s, 1-OH, 1′-OH; 11·98, s, 8-OH, 8′-OH; 10·89, s, 6-OH, 6′-OH; 6·79, br s, H 5,5′; 6·31, d, J 2·4 Hz, H 7,7′; 5·44, br s, H 4,4′; 4·47, s, H 10,10′; 3·56, s, 2×OMe; 3·38, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·17, d, J 7·1 Hz, 2×($C\mathbf{H}_3$)$_A$CH(CH_3)$_B$; 1·18, d, J 7·1 Hz, 2×(CH_3)$_A$CH($C\mathbf{H}_3$)$_B$. δ ($CDCl_3$) 12·38, s, 1-OH, 1′-OH; 12·22, s, 8-OH, 8′-OH; 6·62, br d, J 2·3 Hz, H 5,5′; 6·38, d, J 2·3 Hz, H 7,7′; 5·64, br s, exchanged with D_2O, 6-OH, 6′-OH; 5·31, s, H 4,4′; 4·27, br s, H 10,10′; 3·59, s, OMe; 3·48, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·25, d, J 7·1 Hz, 2×CH($C\mathbf{H}_3$)$_2$. For ^{1}H n.m.r. data at 100° see Table 1.

An unseparated mixture of diastereoisomers of (25) showed the following data. δ (partial) [$(CD_3)_2CO$] 6·89, d, J 2·4 Hz, H 7,7′; 6·38, d, J 2·4 Hz, H 7,7′; 6·29, br s, H 4,4′ or H 5,5′;

6·24, br d, J 2·4 Hz, H 5,5′; 6·13, br s, H 4,4′ or H 5,5′; 5·54, s, H 4,4′.

1,1′,3,3′,8,8′-Hexahydroxy-2,2′-diisopropyl-6,6′-dimethoxy-10,10′-bianthrone (26)

The anthrone (8) was oxidized with $K_3Fe(CN)_6$ as for (7) and the resultant residue subjected to short-column chromatography, with an ethyl acetate/petrol/acetic acid (16 : 83 : 1 → 29 : 70 : 1) solvent gradient as eluent, to give the bianthrone (26) (84 mg, 85%) as an approximately 1 : 1 mixture of (±)- and *meso*-diastereoisomers. Recrystallization from ethyl acetate/petrol gave the low R_F diastereoisomer, m.p. >250° (dec.) λ_{max} ($\log\epsilon$) 241 (4·32), 287 (4·34), 362 nm (4·51). ν_{max} 3436br, 1610 cm^{-1}. δ [$(CD_3)_2SO$] 12·47, s, 1-OH, 1′-OH; 12·08, s, 8-OH, 8′-OH; 10·40, s, 3-OH, 3′-OH; 6·39, d, J 2·4 Hz, H 7,7′; 6·39 (overlapping) br s, H 5,5′; 5·79, s, H 4,4′; 4·35, s, H 10,10′; 3·80, s, 2×OMe; 3·40, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·24, d, J 7·1 Hz, 2×$(CH_3)_ACH(CH_3)_B$; 1·22, d, J 7·1 Hz, 2×$(CH_3)_ACH(CH_3)_B$. For ^{1}H n.m.r. data at 100° see Table 1. *m/z* 626 (M, 0·3%), 625 (0·6), 314 (58), 313 (70), 299 (100), 298 (24), 285 (28).

A portion of the liquor of crystallization was subjected to preparative t.l.c., with ethyl acetate/petrol (2 : 5) as eluent. The upper pale yellow band gave the high R_F isomer of (26) as a pale yellow solid. δ [$(CD_3)_2SO$] 12·40, s, 1-OH, 1′-OH; 12·09, s, 8-OH, 8′-OH; 10·37, s, 3-OH, 3′-OH; 6·36, d, J 2·4 Hz, H 7,7′; 6·02, br s, H 4,4′, H 5,5′; 4·36, s, H 10,10′; 3·76, s, OMe; 3·39, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·25, m, 2×$CH(CH_3)_2$.

1,1′,3,6′,8,8′-Hexahydroxy-2,2′-diisopropyl-3′,6-dimethoxy-10,10′-bianthrone (27)

A mixture of the anthrones (7) (61 mg) and (8) (61 mg) was oxidized with $K_3Fe(CN)_6$ as for (7). The crude product was subjected to preparative thin-layer chromatography, developing twice with ethyl acetate/petrol/acetic acid (38 : 61 : 1). Six major bands were observed. The third least polar band was eluted from the silica with ethyl acetate and the solvent evaporated to yield a single diastereoisomer of the bianthrone (27) (18 mg, 15%), m.p. >260° (dec.). λ_{max} ($\log\epsilon$) 237 (4·34), 283 (4·28), 361 nm (4·46). ν_{max} 3401br, 1608 cm^{-1}. δ [$(CD_3)_2SO$] 12·43, s, 1-OH or 1′-OH; 12·39, s, 1-OH or 1′-OH; 12·13, s, 8-OH or 8′-OH; 11·99, s, 8-OH or 8′-OH; 10·71, s, 3-OH or 6′-OH; 10·31, s, 3-OH or 6′-OH; 6·80, br s, H 5 or H 5′; 6·67, br s, H 5 or H 5′; 6·46, d, J 2·4 Hz, H 7 or H 7′; 6·27, d, J 2·0 Hz, H 7 or H 7′; 5·53, br s, H 4 or H 4′; 5·51, br s, H 4 or H 4′; 4·41, ABq, J_{AB} 2·5 Hz, H 10,10′; 3·88, 3·58, s, s, 2×OMe; 3·40, m, 2×C**H**$(CH_3)_2$; 1·20, m, 2×$CH(CH_3)_2$. For ^{1}H n.m.r. data at 100° see Table 1. *m/z* (f.a.b.) 627 (M+H, 12%), 315 (32), 314 (100), 313 (74), 91 (62), 73 (27), 57 (30).

The fifth least polar band gave a second diastereoisomer of the bianthrone (27) (24 mg, 20%), m.p. >255° (dec.). λ_{max} ($\log\epsilon$) 237 (4·29), 286 (4·26), 361 nm (4·39). ν_{max} 3412br, 1603 cm^{-1}. δ [$(CD_3)_2SO$] 12·50, s, 1-OH or 1′-OH; 12·34, s, 1-OH or 1′-OH; 12·00, s, 8-OH, 8′-OH; 10·89, s, 3-OH or 8′-OH; 10·74, s, 3-OH or 8′-OH; 6·60, br s, H 4 or H 4′; 6·46, br s, H 5 or H 5′; 6·28, d, J 2·4 Hz, H 7 or H 7′; 6·27, d, J 2·4 Hz, H 7 or H 7′; 5·60, br s, H 4 or H 4′; 5·52, br s, H 5 or H 5′; 4·45, d, J 2·9 Hz, H 10 or H 10′; 4·43, m, H 10 or 10′; 3·60, 3·67, s, s, 2×OMe; 3·49, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 3·41, septet, J 7·1 Hz, C**H**$(CH_3)_2$; 1·27, d, J 7·1 Hz, $(CH_3)_ACH(CH_3)_B$; 1·26, d, J 7·1 Hz, $(CH_3)_ACH(CH_3)_B$; 1·19, d, J 7·1 Hz, $CH(CH_3)_2$. For ^{1}H n.m.r. data at 100° see Table 1. *m/z* (f.a.b.) 627 (M+H, 14%), 315 (30), 314 (100), 313 (65), 91 (25).

Bands 1 and 2 were chromatographically indistinguishable from the high and low R_F isomers of bianthrone (26). Similarly, bands 4 and 6 were indistinguishable from the high and low R_F isomers of bianthrone (25).

1,3,4,6,8,15-Hexahydroxy-9,14-diisopropyl-10,13-dimethoxydibenzo[a,o]perylene-7,16-dione (28)

The mixed bianthrone diastereoisomers (25) (41 mg) were dissoved in ethanol (2 cm^3), ammonia solution was added and, in the absence of light, the mixture heated on a steam bath while a stream of oxygen was passed through it for 1 h. The resulting violet solution was poured into 2 M hydrochloric acid (10 cm^3). The precipitate was collected by centrifugation and filtration, washed, dried and subjected to short-column chromatography, with an acetone/toluene/acetic acid (19 : 40 : 1 → 32 : 66 : 1) solvent gradient as eluent, to give the helianthrone (28) (28 mg, 69%) as a violet solid, m.p. >350°. λ_{max} (EtOH and 1% HCO_2H) ($\log\epsilon$) 257 (4·67), 287 (4·46), 380 (4·17), 548 (4·21), 578sh nm (4·17). ν_{max} 3460br, 1590 cm^{-1}. δ [$(CD_3)_2SO$] 14·34, br s, 1-OH, 6-OH; 13·51, s, 8-OH, 15-OH; 7·05, s, H 11,12; 6·31, s, H 2,5; 3·56, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 3·38, s, 2×OMe; 1·27, 2×overlapping d, J 7·1, J 7·1 Hz, 2×$CH(CH_3)_2$. *m/z* (f.a.b.) 623 (M+H, 18%), 237 (38), 131 (23), 91 (56), 90 (40), 75 (23), 73 (87), 59 (48), 58 (24), 56 (100).

1,3,4,6,8,15-Hexahydroxy-2,5-diisopropyl-10,13-dimethoxydibenzo[a,o]perylene-7,16-dione (30)

A mixture of the diastereoisomers (26) (48 mg) was oxidized under the same conditions as for (25). The precipitated residue was subjected to preparative t.l.c. on oxalated silica, with acetone/toluene (1 : 9) as eluent. A violet band and a red band were each eluted from the silica with acetone, the eluates were poured into water and the respective precipitates collected, washed and dried. The violet band gave the helianthrone (30) (4 mg, 7%) as a black powder, m.p. >350°. λ_{max} (EtOH and 1% CF_3CO_2H) ($\log\epsilon$) 254 (4·56), 278sh (4·43), 330sh (4·00), 384 (4·01), 411 (3·96), 450sh (3·73), 536 (4·11), 561 (4·12), 576 nm (4·15). ν_{max} 3411br, 1594 cm^{-1}. δ [$(CD_3)_2SO$] 15·02, s, 1-OH, 6-OH; 13·16, br s, 8-OH, 15-OH; 6·99, d, J 2·2 Hz, H 11,12; 6·47, d, J 2·2 Hz, H 9,14; 3·52, s, 2×OMe; 3·84, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·39, d, J 7·1 Hz, 2×$(CH_3)_ACH(CH_3)_B$; 1·38, d, J 7·1 Hz, 2×$(CH_3)_ACH(CH_3)_B$. *m/z* (f.a.b.) (partial) 506 (23%), 253 (50), 351 (100).

The red band afforded 1,3,4,6,8,13-hexahydroxy-2,5-diisopropyl-10,11-dimethoxyphenanthro[1,10,9,8-*opqra*]perylene-7,14-dione (31) (8 mg, 15%) as a dark solid, m.p. >350°. λ_{max} (EtOH and 1% CF_3CO_2H) ($\log\epsilon$) 240 (4·64), 285 (4·60), 333 (4·48), 428 (4·05), 453 (4·13), 499 (3·92), 537 (4·22), 577 nm (4·49). ν_{max} 3425br, 1590, 1554 cm^{-1}. δ [$(CD_3)_2SO$] 15·18, s, 1-OH, 6-OH; 14·63, br s, 8-OH, 13-OH; 7·19, s, H 9,12; 4·17, s, 2×OMe; 4·00, septet, J 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·47, d, J 7·1 Hz, 2×$CH(CH_3)_2$. *m/z* (f.a.b.) 621 (M+H, 86%), 605 (29), 237 (37), 147 (22), 131 (100), 126 (24), 102 (96), 91 (82), 90 (2), 89 (22), 77 (38), 73 (75), 61 (53), 69 (54), 57 (100), 55 (27).

A solution of (30) (6 mg) in dimethyl sulfoxide (30 cm^3) was irradiated as for the formation of (29) (below). The crude product was subjected to preparative t.l.c., with toluene/acetone/acetic acid (89 : 10 : 1) as eluent. The major red band gave the naphthodianthrone (31) (8 mg, 15%), identical in all respects to that obtained above.

The helianthrone (30) (6 mg) was dissolved in ethanol (1 cm^3) and heated over a steam bath in conc. ammonia solution (5 cm^3, 0·88 g cm^{-3}) while a stream of oxygen was passed through, for 40 min in the absence of light. It was then poured into 1 M aqueous hydrochloric acid (100 cm^3). The precipitate (5 mg, 80%) was identical to the naphthodianthrone (31) obtained above.

*1,3,4,6,8,15-Hexahydroxy-2,9-diisopropyl-10,13-dimethoxydibenzo[*a,o*]perylene-7,16-dione (32)*

The high R_F diastereoisomer of the bianthrone (27) (16 mg) was subjected to oxidation as for (25). The precipitated residue was subjected to short-column chromatography, with acetone/toluene/acetic acid (20 : 79 : 1 → 33 : 65 : 1) as eluent, to give the helianthrone (32) (14 mg, 88%) as a purple solid, m.p. >350°. λ_{max} (EtOH and 1% HCO_2H) (log ϵ) 254 (4·54), 282sh (4·37), 380 (4·03), 548 (4·05), 582 nm (4·04). ν_{max} 3424br, 1648sh, 1591, 1555 cm^{-1}. δ [$(CD_3)_2SO$] 15·04, s, 1-OH; 14·32, br s, 6-OH; 13·50, s, 8-OH; 13·14, br s, 15-OH; 7·05, s, H 11; 6·98, d, *J* 2·2 Hz, H 12; 6·44, d, *J* 2·2 Hz, H 14; 6·31, s, H 5; 3·40, 3·47, s, s, 2×OMe; 3·84, septet, *J* 7·1 Hz, C**H**$(CH_3)_2$; 3·56, septet, *J* 7·1 Hz, C**H**$(CH_3)_2$; 1·38, d, *J* 7·1 Hz, CH(C**H**$_3)_2$; 1·27, 2×overlapping d, *J* 7·1 Hz, CH(C**H**$_3)_2$. *m/z* (f.a.b.) 623 (M+H, 19%), 237 (22), 217 (21), 216 (21), 131 (32), 109 (28), 91 (100), 73 (40), 56 (2).

Analogous oxidation of the low R_F isomer of the bianthrone (27) (17 mg) gave, after chromatography, an identical (t.l.c., ^{1}H n.m.r., electronic spectrum) product (5 mg, 30%).

*1,6,8,10,11,13-Hexahydroxy-2,5-diisopropyl-3,4-dimethoxyphenanthro[1,10,9,8-*opqra*]perylene-7,14-dione (29)*

A solution of the helianthrone (28) (19 mg) in dimethyl sulfoxide (30 cm^3) in air was irradiated with a mercury vapour lamp for 40 min, during which time the purple colour became red with an orange fluorescence. The crude product was subjected to preparative t.l.c. on oxalated silica, with toluene/acetone (9 : 1) as eluent, to yield the naphthodianthrone (29) (13 mg, 69%) as a dark solid, m.p. >350°. λ_{max} (EtOH and 1% CF_3CO_2H) (log ϵ) 239 (4·71), 287 (4·68), 320sh (4·53), 331 (4·55), 434sh (4·23), 458 (4·43), 507 (3·86), 542 (4·33), 584 nm (4·62). ν_{max} 3423, 1648sh, 1582, 1554sh cm^{-1}. δ [$(CD_3)_2SO$] 15·14, s, 1-OH, 6-OH; 14·61, br s, 8-OH, 13-OH; 6·58, s, H 9,12; 3·96, septet, *J* 7·1 Hz, 2×C**H**$(CH_3)_2$; 3·37, s, 2×OMe; 1·56, d, *J* 7·1 Hz, 2×(C**H**$_3)_A$CH$(CH_3)_B$; 1·46, d, *J* 7·1 Hz, 2×$(CH_3)_A$CH(C**H**$_3)_B$. *m/z* (f.a.b.) 621 (M+H, 25%), 282 (21), 237 (32), 217 (21), 215 (22), 162 (65), 150 (36), 148 (32), 133 (36), 131 (73), 91 (100), 90 (34), 89 (28), 77 (25), 73 (76), 61 (46), 59 (5), 57 (100).

*1,3,4,6,8,13-Hexahydroxy-2,9-diisopropyl-10,11-dimethoxyphenanthro[1,10,9,8-*opqra*]perylene-7,14-dione (33)*

The helianthrone (32) (17 mg) was photooxidized as for (28). The crude product was subjected to preparative t.l.c. on oxalated silica, with toluene/acetone (9 : 1) as eluent. The bright red band afforded the naphthodianthrone (33) (11 mg, 65%) as a dark solid, m.p. >350°. λ_{max} (log ϵ) 237 (4·54), 285 (4·50), 330 (4·38), 434sh (3·98), 455 (4·10), 503 (3·83), 539 (4·15), 580 nm (4·43). ν_{max} 3427, 1642sh, 1590, 1554sh cm^{-1}. δ [$(CD_3)_2SO$] 15·22, s, 1-OH; 15·08, s, 8-OH; 14·64, br s, 6-OH or 13-OH; 14·56, br s, 6-OH or 13-OH; 7·22, s, H 12; 6·60, s, H 5; 4·16, s, 11-OMe; 3·35, s, 10-OMe; 3·99, septet, *J* 7·1 Hz, C**H**$(CH_3)_2$; 3·92, septet, *J* 7·1 Hz, C**H**$(CH_3)_2$; 1·46, d, *J* 7·1 Hz, 2×CH(C**H**$_3)_2$. *m/z* (f.a.b.) (partial) 621 (M+H, 16%), 412 (27), 237 (25), 216 (30), 215 (31), 131 (72).

*1,3,4,6,8,10,11,13-Octahydroxy-2,5-diisopropylphenanthro-[1,10,9,8-*opqra*]perylene-7,14-dione (Stentorin) (2)*

(A) The dimethyl ether (29) (27 mg) was dissolved in acetic acid (5 cm^3) with heating and sodium hypophosphite (100 mg) and hydriodic acid (47%, 10 drops) were added and the mixture refluxed for 32 h, over which time three more additions of hydriodic acid (10 drops) were made. The mixture was cooled and poured into water (70 cm^3). The precipitate was collected, washed with water, dried and subjected to preparative t.l.c., with acetone/toluene/acetic acid (43 : 56 : 1) as eluent. The major maroon band was eluted from the silica with acetone and evaporated to give stentorin (2) (15 mg, 56%) as a dark solid, m.p. >350°. λ_{max} (EtOH and 1% CF_3CO_2H) (log ϵ) 235 (4·55), 283 (4·51), 319sh (4·37), 330 (4·39), 432sh (4·01), 456 (4·24), 503 (3·67), 538 (4·14), 565sh (4·15), 579 nm (4·45). ν_{max} 3413s(br), 3120s(br), 2933, 1602, 1536 cm^{-1}. δ [$(CD_3)_2SO$] 15·32, s, 1-OH, 6-OH; 14·64, br s, 8-OH, 13-OH; 6·92, s, H 9,12; 4·01, septet, *J* 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·47, d, *J* 7·1 Hz, 2×CH(C**H**$_3)_2$. δ [$(CD_3)_2SO$ (saturated with $NaHCO_3$)] 17·58, 16·68, s, s, 2×'bay'-OH; 15·45, s, 1-OH, 6-OH; 14·92, s, 8-OH, 13-OH; 6·56, s, H 9,12; 4·02, septet, *J* 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·47, d, *J* 7·1 Hz, 2×CH(C**H**$_3)_2$. *m/z* (f.a.b.) 593 (M+H, 5%), 217 (38), 216 (29), 131 (34), 109 (25), 91 (100), 73 (2), 57 (34). This product was indistinguishable from a sample of natural stentorin[5] by ^{1}H n.m.r. spectroscopy with added CF_3CO_2H, electronic absorption spectroscopy and analytical thin-layer chromatography [acetone/toluene/acetic acid (43 : 56 : 1)].

(B) The dimethyl ether (31) (23 mg) was treated with hydriodic acid in acetic acid as for (29). This yielded stentorin (2) (14 mg, 64%), identical (^{1}H n.m.r., t.l.c.) to that obtained in (A) above.

*1,3,4,6,8,10,11,13-Octahydroxy-2,9-diisopropylphenanthro[1,10,9,8-*opqra*]perylene-7,14-dione (3)*

The dimethyl ether (33) (12 mg) was demethylated with hydriodic acid in acetic acid as for (29), and the crude product subjected to preparative t.l.c. on GF_{254} silica, with acetone/toluene/acetic acid (43 : 56 : 1) as eluent. The major maroon band gave the naphthodianthrone (3) (7 mg, 61%) as a dark solid, m.p. >350°. λ_{max} (EtOH and 1% CF_3CO_2H) (log ϵ) 238 (4·69), 284 (4·65), 320sh (4·48), 330 (4·51), 434sh (4·18), 456 (4·31), 503 (3·91), 538 (4·25), 567 inf. (4·31), 578 nm (4·53). ν_{max} 3435br, 1648sh, 1599, 1554 cm^{-1}. δ [$(CD_3)_2SO$] 15·28, s, 1-OH, 8-OH; 14·67, br s, 6-OH, 13-OH; 6·84, s, H 5,12; 4·01, septet, *J* 7·3 Hz, 2×C**H**$(CH_3)_2$; 1·46, d, *J* 7·1 Hz, 2×CH(C**H**$_3)_2$. δ [$(CD_3)_2SO$ (saturated with $NaHCO_3$)] 17·12, s, 2×'bay'-OH; 15·47, s, 1-OH, 8-OH; 14·89, s, 6-OH, 13-OH; 6·58, s, H 5,12; 4·01, septet, *J* 7·1 Hz, 2×C**H**$(CH_3)_2$; 1·46, d, *J* 7·1 Hz, 2×CH(C**H**$_3)_2$. *m/z* (f.a.b.) 593 (M+H, 6%), 237 (100), 232 (38), 215 (71), 214 (50), 197 (48), 181 (38), 131 (88), 109 (2), 105 (2), 91 (100), 90 (47), 73 (94), 61 (3), 57 (96).

In addition to spectroscopic differences implicit in the foregoing data, this product (3) was separable from a sample of natural stentorin[6] on cochromatography in acetone/toluene/acetic acid (43 : 56 : 1).

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