Flavonoids from *Distemonanthus benthamianus* Baillon. Methoxylated Flavones and Inter-relationships of Benthamianin, a [2]Benzopyrano-[4,3-*b*][1]benzopyran

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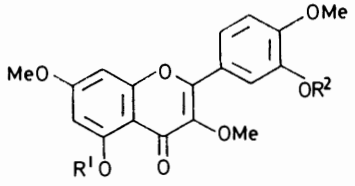
The yellow heartwood of the West African tree *Distemonanthus benthamianus* Baillon contains twelve flavonols representing the 3,3',4',5,7-, 2',3,4',5',5,7-, 3,3',4',5,6,7-, 2',3,3',5,6,7-, and 2',3',3,4',5,6,7-substitution patterns. A novel peltogynoid, benthamianin (3,4,8,10-tetrahydroxy-9-methoxy-7-oxo[2]benzopyrano[4,3-*b*][1]benzopyran) was isolated and its relationship with the 3-*O*-methylflavones and distemonanthin established chemically.

THE present reinvestigation of the yellow extracts from the heartwood of *Distemonanthus benthamianus*,[1] following on the much earlier work on the same material by King *et al.*,[2,3] has revealed a wealth of flavones and a new novel compound, which may be regarded as a 5-hydroxy-6-methoxymopanin,[4] or a deoxodistemonanthin.

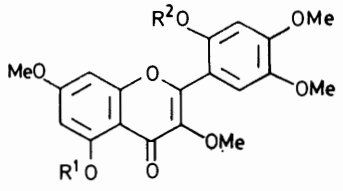
Altogether twelve flavonols (1a, b, e), (2a—e), (3a, d), and (4a, b) were isolated of which eight were partly methylated, one fully, and three unmethylated. Amongst these only oxyanin B (4a) and ayanin (1b) are known components.[1,2] In total they represent five substitution patterns which is extraordinary for any plant, matched only by *Apuleia leiocarpa*.[5]

The substitution pattern is basically that of the ubiquitous quercetin (1e) and is extended through progressive oxidation of the nucleophilic centres (2'-,



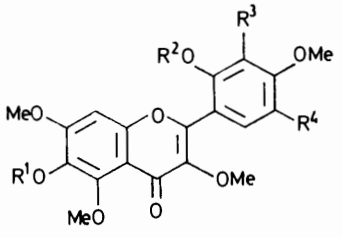
(1)

a; R^1 = H, R^2 = Me
b; R^1 = R^2 = H (ayanin)
c; R^1 = R^2 = Me
d; R^1 = Ac, R^2 = Me
e; R^1 = R^2 = H; All Me replaced by H
f; R^1 = R^2 = Ac



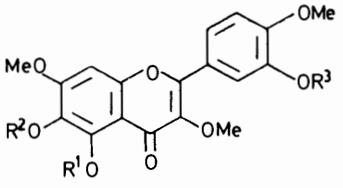
(2)

a; R^1 = H, R^2 = Me
b; R^1 = R^2 = H
c; R^1 = Me, R^2 = H
d; R^1 = R^2 = Me
e; R^1 = R^2 = H; All Me replaced by H
f; R^1 = Me, R^2 = Ac
g; R^1 = Ac, R^2 = Me
h; R^1 = R^2 = Ac
i; R^1 = H, R^2 = Ac



(3)

a; R^1 = R^2 = R^3 = H, R^4 = OMe
b; R^1 = R^2 = Me, R^3 = OMe, R^4 = H
c; R^1 = R^2 = Ac, R^3 = H, R^4 = OMe
d; R^1 = R^2 = R^4 = H, R^3 = OH; All Me replaced by H



(4)

a; R^1 = R^2 = R^3 = H (oxayanin B)
b; R^1 = R^2 = H, R^3 = Me
c; R^1 = R^2 = Ac, R^3 = Me
d; R^1 = H, R^2 = R^3 = Me
e; R^1 = R^2 = R^3 = Ac
f; R^1 = R^2 = R^3 = Me

TABLE 1

^{1}H N.m.r. spectra * of flavones and their derivatives from *Distemonanthus benthamianus*

Compound	δ Values: H 2′	3′	5′	6′	6	8	OH 5	Number of functional groups: OMe	OAc	Solvent
(1a)	7.73 (d)		7.00 (d)	7.79 (q)	6.37 (d)	6.50 (d)	12.73 (s)	4	0	$CDCl_3$
(1d)	7.77 (d)		7.07 (d)	7.80 (q)	6.66 (d)	6.89 (d)		4	1	$CDCl_3$
(1b)	7.70 (d)		7.14 (d)	7.74 (q)	6.34 (d)	6.68 (d)	12.80 (s)	3	0	[$^2H_6$]Acetone
(1f)	7.90 (d)		7.34 (d)	8.13 (q)	6.70 (d)	7.15 (d)		3	2	[$^2H_6$]Acetone
(1c)	7.75 (d)		7.00 (d)	7.73 (q)	6.36 (d)	6.53 (d)		5	0	$CDCl_3$
(2a)		6.66 (s)		7.01 (s)	6.38 (s)	6.38 (s)	12.69 (s)	5	0	$CDCl_3$
(2g)		6.70 (s)		7.04 (s)	6.79 (d)	6.66 (d)		5	1	$CDCl_3$
(2b)		6.84 (s)		6.97 (s)	6.31 (d)	6.47 (d)	12.77 (s)	4	0	[$^2H_6$]Acetone
(2h)		6.97 (s)		7.23 (s)	6.70 (d)	6.94 (d)		4	2	[$^2H_6$]Acetone
(2i)		6.73 (s)		7.17 (s)	6.37 (s)	6.37 (s)	12.68 (s)	4	1	$CDCl_3$
(2c)		6.83 (s)		6.89 (s)	6.54 (d)	6.67 (d)		5	0	[$^2H_6$]DMSO
(2f)		6.96		7.24 (s)	6.54 (d)	6.67 (d)		5	1	[$^2H_6$]DMSO
(2d)		6.68 (s)		7.04 (s)	6.39 (d)	6.51 (d)		6	0	$CDCl_3$
(3a)		6.77 (s)		7.07 (s)		6.67 (s)		5	0	$CDCl_3$
(3c)		6.73 (s)		7.18 (s)		6.67 (s)		5	2	$CDCl_3$
(4a)	7.67 (d)		7.07 (d)	7.60 (q)		6.84 (s)	12.43 (s)	3	0	[$^2H_6$]DMSO
(4e)	7.87 (d)		7.37 (d)	8.10 (q)		7.47 (s)		3	3	[$^2H_6$]DMSO
(4f)	7.77 (d)		7.02 (d)	7.77 (q)		6.79 (s)		6	0	$CDCl_3$
(4e)	7.82 (d)		7.09 (d)	8.05 (q)		6.92 (s)		3	3	$CDCl_3$
(4b)	7.73 (d)		7.02 (d)	7.78 (q)		6.56 (s)	12.70 (s)	4	0	$CDCl_3$
(4c)	7.73 (d)		7.03 (d)	7.77 (q)		6.93 (s)		4	2	$CDCl_3$
(4d)	7.74 (d)		7.05 (d)	7.76 (q)		6.55 (s)		5	0	$CDCl_3$
(3b)			6.80 (d)	7.24 (d)		6.73 (s)		7	0	$CDCl_3$

s = singlet, d = doublet, q = quartet, m = multiplet.

* Coupling constants for benzenoid protons, where applicable, are as follows: $J_{6,8}$ 2.0, $J_{2',6'}$ 2.0, $J_{3',6'} < 1$, $J_{5',6'}$ 9.0 Hz.

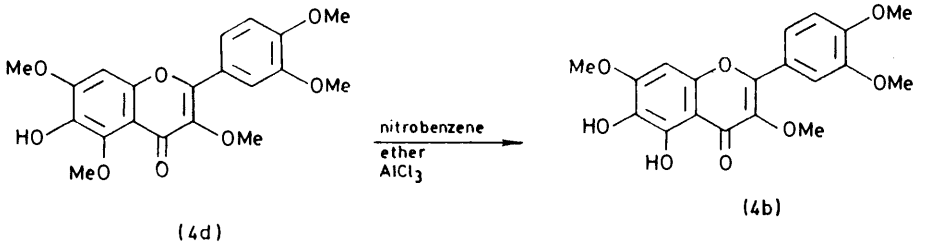
6-, and 6′-positions) and subsequent *O*-methylation. In eight of the partly methylated flavones either one or both of the 2′- or 5-hydroxys were unmethylated [(1a, b), (2a—c), (3a), (4a, b)]. This could be attributed to the ability of the 5-hydroxy group to form a hydrogen bond with the adjacent ketone (4-position) or of the 2′-hydroxy to form a similar bond with the 3-methoxy group.[6]

3,3′,4′,5,7-Substituted Flavones.—All three (1a, b, and e) yielded penta-*O*-methylquercetin (1c) on vigorous methylation and their relationship to an authentic specimen of penta-*O*-methylquercetin was confirmed. In the case of 5-hydroxy-3,3′,4′,7-tetramethoxyflavone (1a) the ^{1}H n.m.r. spectrum showed the low-field proton, δ 12.73 (Table 1), representing the hydrogen-bonded 5-hydroxy group, while the molecular mass was confirmed by mass spectral analysis (M^+ 358). Ayanin (1b) and quercetin (1e) are known compounds.

3,3′,4′,5,6,7-Substituted Flavones.—The previously known constituent, 3′,5,6-trihydroxy-3,4′,7-trimethoxyflavone (4a) was isolated along with another similarly substituted tetra-*O*-methylflavone (4b).

The ^{1}H n.m.r. pattern (Table 1) of their acetylated derivatives (4c and e) respectively, was identical, except for the chemical shifts of the ring B protons which were less shielded for (4e), indicating the absence of an *O*-acyl group on ring B. The position of the two hydroxy groups in the new flavone (4b) was confirmed by *O*-ethylation and subsequent alkaline degradation which yielded 3,4-dimethoxybenzoic (veratric) acid and 2′,3′-diethoxy-6′-hydroxy-2,4′-dimethoxyacetophenone. Synthesis of 5,6-dihydroxy-3,3′,4′,7-tetramethoxyflavone (4b) was effected by using 3′,6′-dihydroxy-2,2′,4′-trimethoxyacetophenone, veratric anhydride, and potassium 3,4-dimethoxybenzoate in an Allan–Robinson procedure to give 6-hydroxy-3,3′,4′,5,7-pentamethoxyflavone (4d). The latter intermediate was demethylated with $AlCl_3$ in nitrobenzene and dry ether to afford the desired flavonol, thus placing its structure (4b) beyond doubt.

2′,3,4′,5′,5,7-Substituted Flavones.—The 2′,5,5′-trihydroxy-3,4′,7-trimethoxyflavone (oxyayanin A) isolated by King *et al.*[3] could not be traced during the present investigation but one unmethylated (2e), three partly methylated (2a—c), and one fully methylated (2d) flavones with the same 2′,3,4′,5′,5,7-oxygenated pattern were isolated. The fully *O*-methylated derivatives of (2a—c and e) were identical with the isolated analogue (2d). The ^{1}H n.m.r. spectrum of the 2′,3,4′,5′,5,7-hexamethoxyflavone (2d) (Table 1) showed two doublets with chemical shifts and coupling constant typical of



(4d) (4b)

meta-coupled protons at C-6 and -8 (ring A) and two singlets representing *para*-coupled protons of ring B.

The position of the hydroxy group in 5-hydroxy-2',3,4',5,7-pentamethoxyflavone (2a) (Table 1) was obvious from the deshielded sharp hydroxy proton resonance at δ 12.69.

The ^{1}H n.m.r. spectrum of the acetylated derivative (2f) (Table 1) of 2'-hydroxy-3,4',5',5,7-pentamethoxyflavone compared with that of the natural phenol (2c) showed deshielding of the 3' and 6' protons only, which indicated the hydroxy group on ring B. Mass-spectral analysis of (2c) showed loss of 17 (*m/e* 371, 16%) and 31 (*m/e* 357, 100%) mass units from the molecular ion which confirmed that the hydroxy group is at the 2'-position.[7]

Comparison of the ^{1}H n.m.r. spectra of the isolated 2',5-dihydroxyflavone (2b) (Table 1) and its acetylated derivative (2h) (Table 1) showed deshielding of all the benzenoid protons (3', 6', 6, and 8) which indicated the presence of one hydroxy group on each ring. The presence of a low-field proton signal at δ 12.77 in the ^{1}H n.m.r. spectrum of (2b) establishes the hydroxy at C-5 in ring A. Use of 50% of the amount of acetic anhydride–pyridine required for complete acetylation of the two hydroxys, resulted in the partially acetylated 2'-acetoxy-5-hydroxy-3,4',5',7-tetramethoxyflavone (2i), (Table 1). Its ^{1}H n.m.r. spectrum confirmed the presence of a hydroxy at C-5 (δ 12.68) and the 2'-acetoxy on ring B, judged from the deshielding of 3'- and 6'-H when compared with the spectrum of (2b). Degradation of the di-*O*-ethylated derivative in alkaline medium led to 2'-ethoxy-6'-hydroxy-2,4'-dimethoxyacetophenone and 2-ethoxy-4,5-dimethoxybenzoic acid which were isolated and compared with authentic samples. The degradation products confirm the position of the two hydroxys at C-2' and -5 in (2b).

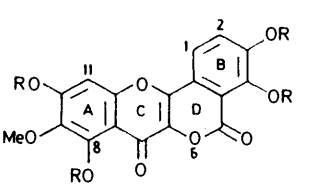
Heptaoxygenated Flavones.—The two heptasubstituted flavones (3a and d) did not yield the same fully *O*-methylated ether under conditions of drastic methylation.

The heptahydroxyflavone (3d) was isolated as 2',3',-3,4',5,6,7-heptamethoxyflavone (3b) after methylation of a mixture and subsequent separation. The ^{1}H n.m.r. spectrum of (3b) showed *ortho*-coupled doublets, δ 6.8 (5'-H) and 7.24 (6'-H), attributed to ring B and the singlet, δ 6.73 (8-H), to ring A. On addition of [$^2H_6$] benzene to the $CDCl_3$ solution (1 : 1) substantial shifts of two methoxy proton resonances were observed (Δδ *ca.* 0.4) which supported this assignment. Degradation with alkali results in 6'-hydroxy-2,2',3',4'-tetramethoxyacetophenone and 2,3,4-trimethoxybenzoic acid. The above and other physical data are in accord with those of a derivative prepared by Gottlieb *et al.*[5]

The second heptaoxygenated flavone (3a) showed five *O*-methyl and two *O*-acyl groups in the ^{1}H n.m.r. spectrum of the acetylated derivative (3c) (Table 1). Three prominent singlets in the benzenoid region were tentatively assigned to 3'-, 6'-, and 8-H (δ 6.73, 7.18, and 6.67) by comparison with other flavones isolated. The mass-spectral analysis of (3a) showed loss of 17 (*m/e* 387, 18%) and 31 (*m/e* 373, 100%) mass units, indicative of a hydroxy at the 2'-position.[7] The $M^+ - 1$ (*m/e* 403, 41%) fragment was prominent, which corresponds to loss of hydrogen from 6-OH to give the stable quinonoid ion.[8]

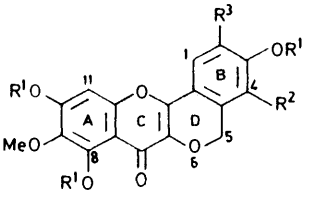
Although a statement has been made to the effect that ' flavones with four or more oxygen substituents do not give meaningful RDA-fragments ',[9] the flavone (3a) has proved to be an exception, RDA-fragments representing rings A (*m/e* 197, 29%) and B (*m/e* 181, 14%) being obtained. Mass-spectral evidence supports a 2',6-dihydroxy-3,4',5',5,7-pentamethoxyflavone (3a) structure. Alkaline degradation of the *O*-ethylated derivative produced 3'-ethoxy-6'-hydroxy-2,2',4'-trimethoxyacetophenone and 2-ethoxy-4,5-dimethoxybenzoic acid, representative of rings A and B, respectively, thus confirming the proposed structure (3a).

Benthamianin and Distemonanthin.—A novel peltogynoid, benthamianin (6a), was isolated as the tetra-*O*-acyl



(5)

a; R = H
b; R = Ac
c; R = Me



(6)

a; $R^1 = R^3 = H$, $R^2 = OH$
b; R^1 = Ac, R^2 = OAc, $R^3 = H$
c; R^1 = Me, R^2 = OMe, $R^3 = H$
d; R^1 = Me, $R^2 = H$, R^3 = OMe

derivative (6b) (Table 2). The ^{1}H n.m.r. spectrum of the derivative (6b) showed two *ortho*-coupled doublets, δ

TABLE 2

Chemical shifts of distemonanthin, benthamianin and their derivatives

Compound	δ Values: OH 8	H 1	H 2	H 4	H 11	CH_2	Number of functional groups: OMe	OAc	Solvent	$J_{1,2}$/Hz
(5a)	12.37 (s)						1	0	[$^2H_6$]DMSO	
(5b)		8.06 (d)	7.74 (d)		7.34 (d)		1	4	$CDCl_3$	
(5c)		7.67 (d)	7.08 (d)		6.66 (s)		5	0	$CDCl_3$	8.5
(6a)	12.37 (s)						1	0	[$^2H_6$]DMSO	
(6b)		7.79 (d)	7.40 (d)		7.48 (s)	5.17 (s)	1	4	[$^2H_6$]Acetone	8.5
(6c)		7.55 (d)	7.00 (d)		6.84 (s)	5.36 (s)	5	0	$CDCl_3$	8.5
(6d)		7.28 (s)		6.84 (s)	6.71 (s)	5.21 (s)	5	0	$CDCl_3$	

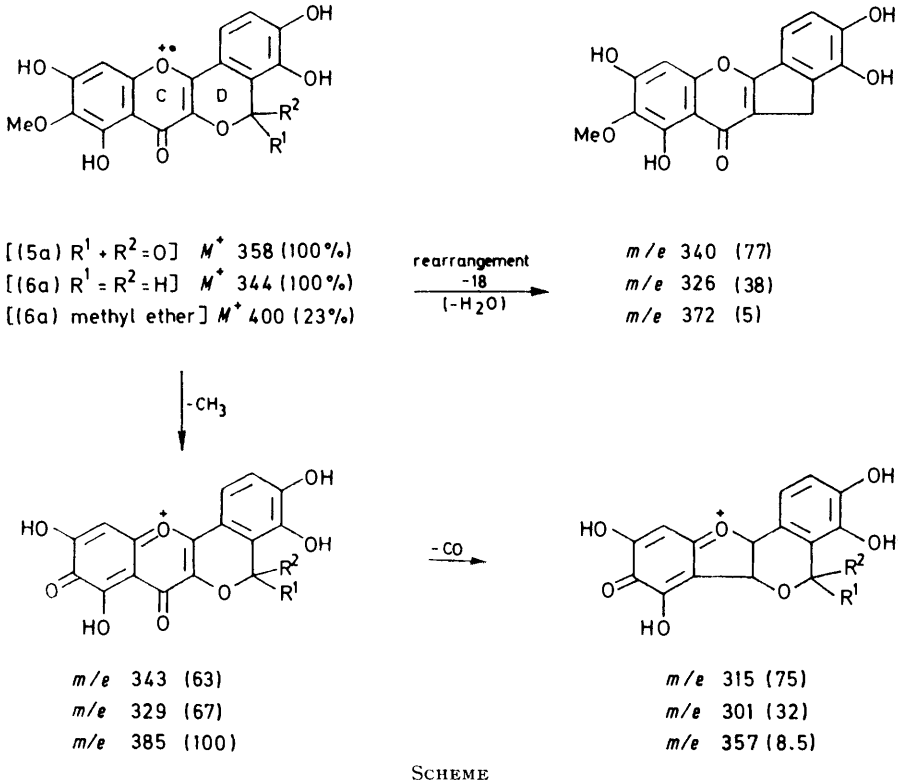
7.63 and 7.28 ($J_{1,2}$ 8.5 Hz), and a singlet, δ 7.35, in the benzenoid range. A singlet at δ 5.14 represented two protons, obviously a strongly deshielded methylene group. One *O*-methyl group, δ 3.89, and four *O*-acyl groups, δ 2.52, 2.39, 2.32, and 2.27, completed the spectrum. The ^{1}H n.m.r. spectrum of distemonanthin [3] tetra-acetate (5b) (Table 2) exhibited the same proton pattern, except for the absence of the singlet at δ 5.14. In addition to the above evidence, mass-spectral analysis showed a difference of 14 mass units in the molecular ions of tetra-acetates (M^+ 512 and 526) of benthamianin (6a) and of distemonanthin (5a) respectively. This led to the surmise that the carbonyl group in ring D of distemonanthin (5a) was replaced by a methylene group in benthamianin (6a).

The mass spectra of benthamianin, distemonanthin, and their *O*-methyl and *O*-acyl derivatives were in accord with fragmentations proposed for 6-*O*-methylflavones [9] and for the C_{16} flavonoid analogue mopanin,[10] but differ from the latter by showing prominent water loss and also a reversed sequence of methyl and CO loss from the molecular ion (Scheme).

The structural relationship became evident when the tetra-acetate of benthamianin (6b) in acetone solution showed slow autoxidation to distemonanthin tetra-acetate (5b), a conversion more readily achieved (14% yield) with MnO_2 in chloroform. The reverse of the above oxidation was carried out by reducing distemonanthin (5a) to benthamianin (6a) with BF_3–$NABH_4$–diglyme [11] in MeOH–pyridine–dioxan solution (17% yield). Since the structure of distemonanthin tetramethyl ether [3] (5c) has been confirmed by synthesis,[12] the structure of benthamainin (6a) is conclusively established as 3,4,8,10-tetrahydroxy-9-methoxy-7-oxo[2]benzopyrano[4,3-*b*][1]benzopyran.

β-Sitosterol accompanies the above flavones and their mopanoid analogues.

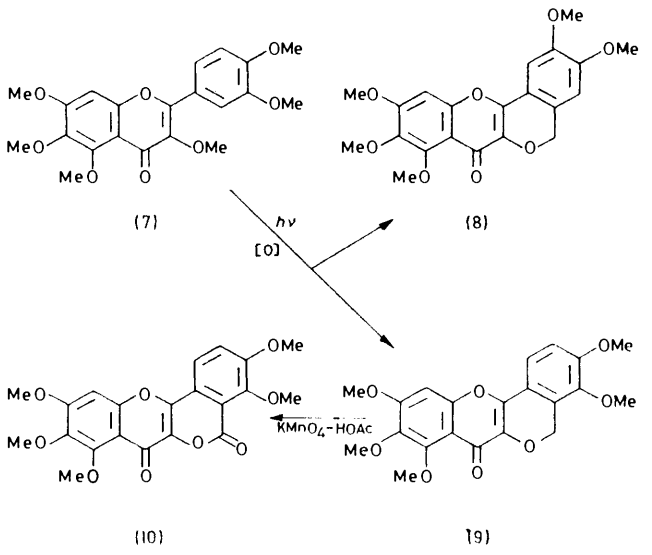
Inter-relationships.—The relationship between benthamianin (6a), distemonanthin (5a), and 3-*O*-methylflavonols, for example oxyayanin B (4a), is demonstrated by the sequence of conversions (7) ⟶ (10). Oxidative photolysis of oxyayanin B trimethyl ether (7) for 7 h at 350 nm gave the anticipated [13] new peltogynin



SCHEME

The association of peltogynoids in species of the Caesalpiniaceae (*Trachylobium verrusocum*,[14] *Peltogyne pubescens*, and *P. venosa* [15]) and Mimosaceae (*Acacia peuce* [16] and *A. carnei* [17]) with 3-*O*-methyldihydroflavonols and the prevalence of the 3-*O*-methyl function in the flavonols with the structures (1a and b) and (4a and b) related to both benthamianin (6a) and distemonanthin (5a), support the premise that the conversions (7) ⟶ (9) ⟶ (10) may also represent the immediate biogenetic pathway in *D. benthamianus* leading to distemonanthin *via* benthamianin as the key intermediate. The absence of the 5,6-disubstituted peltogynin analogue (8) from the heartwood permits the interesting conjecture

that the initial oxidative cyclization leading only to the mopanin analogue, benthamianin, may be enzymic rather than photolytic.



Of the two batches of *D. benthamianus* (Gabon and Cameroons) which were investigated the absence of distemonanthin in the sample from the Cameroons was obvious, a similar observation being reported by King *et al.*[3] Although both benthamianin and distemonanthin are present in the sample from the Gabon in the ratio of 2 : 1, and benthamianin may be regarded as a key intermediate leading to distemonanthin, the probability of this final conversion being either enzymic or autoxidative (*i.e.* distemonanthin possibly representing an artefact) could not be established conclusively.

EXPERIMENTAL

Authenticated heartwood samples were kindly supplied by Professor D. Normand, Centre Technique Forestier Tropical, Norgent sur Marne, France. *Distemonanthus benthamianus* Baillon was from both the Gabon (CTFT 15 000 vicinity of Libreville, Cap Esterias) and Cameroons (CTFT 18 863, vicinity of E. Yaoundé).

Spectra were recorded on a double focusing AEI MS-9 mass spectrometer, a Varian T-60 n.m.r. spectrometer with tetramethylsilane as an internal standard, a Beckman DB-G u.v. spectrophotometer, and a Unicam SP 1 000 i.r. spectrophotometer.

M.p.s were determined with a Kofler hot-stage microscope and are uncorrected. Separations by column chromatography were carried out using Merck Kieselgel 60 (120—230 mesh) and the fractions collected with an ISCO model 273 fraction collector.

T.l.c. was on Kieselgel PF_{254} (0.25 mm) and on preparative scale using the same substrate (1.00 mm). Plates were air-dried and sprayed with H_2SO_3–40% formaldehyde (40 : 1).

Preparation of Derivatives.—Methylation (ethylation) of the phenolic groups was carried out using dimethyl or diethyl sulphate in dry acetone over anhydrous potassium carbonate and refluxing at 60 °C. One mole of $(CH_3)_2SO_4$ $[(C_2H_5)_2SO_4]$ was used per mole of hydroxy methylated.

Additional phenolic groups were introduced into the ring by potassium persulphate (Elbs) oxidation during preparation of synthetic starting materials (oxygenated 2-methoxyacetophenones and benzaldehydes) and reference compounds (oxygenated 2-methoxyacetophenones and benzoic acids) for the products of alkaline degradation. Separate solutions of persulphate (3%, w/w) and NaOH (3%, w/w) were prepared. The phenolic compound (1 g) was dissolved in pyridine (10 ml) and cooled to *ca.* 0 °C in water–ice. NaOH solution (20 ml) was first added, and while the solution was stirred constantly, persulphate solution (50 ml), simultaneously with NaOH solution (20 ml) were introduced slowly over *ca.* 3 h. After another 6 h at 0 °C the mixture was left at room temperature for an additional 16 h. The mixture was cooled to 0 °C and 2M-HCl solution added to pH 3. Unchanged phenolic material was removed by ether extraction (4 × 50 ml). At 96 °C, Na_2SO_3 (2 g) was added followed by HCl (20 ml). After another 30 min on a water-bath the mixture was cooled to room temperature and extracted with ether (4 × 50 ml). Removal of the ether under vacuum resulted in the *para*-oxidized phenolic product which was purified either by crystallization or t.l.c.

A saturated solution of potassium permanganate in water at 50 °C was used to oxidize aldehydes to the corresponding acids.

Phenolic material was acetylated in dry pyridine with acetic anhydride at 60 °C for 2 h. The mixture was added to finely divided ice and the precipitate recovered.

Acetates in $CHCl_3$ or ethanol were hydrolysed by addition of concentrated HCl (*ca.* 0.5 ml for 100 mg samples) and maintaining the solution at 75 °C for 45 min.

Alkaline degradation of *O*-ethylated methoxyflavones was carried out in ethanol (10 ml)–potassium hydroxide (5 ml; 50% aqueous) under nitrogen on a steam-bath for 2 h. Ethanol was removed by distillation while water was added simultaneously. The aqueous solution was acidified (1M-HCl) and extracted with ether. The ether solution was successively extracted with concentrated aqueous $NaHCO_3$ and with a 1M-NaOH solution. The $NaHCO_3$ solution was acidified (1M-HCl) and extracted with $CHCl_3$, the latter solution being evaporated and the residue either recrystallized from a solvent mixture or purified by t.l.c. From the $NaHCO_3$ solution was obtained the substituted benzoic acid representing ring B. The NaOH solution was treated in the same way and from this was recovered the substituted 2-methoxyacetophenone, representing ring A.

Extraction and Preliminary Separation.—Drillings (935 g) from each of the heartwoods of both samples (Gabon and Cameroons) were successively extracted with solvents as indicated in Table 3.

β-Sitosterol. Evaporation of the hexane extract and separation of the residue by t.l.c. in a benzene–ethyl acetate–acetone (7 : 2 : 1 v/v) mixture afforded β-sitosterol (80 mg), R_F 0.60, m.p. 138—139° (lit.,[18] 136—139°), M^+ 414 (100%), identified by comparison with an authentic sample (Merck).

TABLE 3

Yields from successive extractions of the heartwood of *D. benthamianus*

Solvent (extractions)	Time (days)	Quantity (gram, %)
Hexane (2)	2	1.3 (0.13)
Ether (2)	4	8.8 (0.94)
Acetone (3)	6	37.5 (4.0)
Methanol (1)	2	21.0 (2.2)
Dioxan (2)	4	14.2 (1.5)

The acetone extract was chromatographed through a column [Merck Kieselgel 60 (120—230 mesh)] with benzene–ethyl acetate–acetone (7 : 2 : 1 v/v) and four fractions F_1—F_4 were collected.

Fraction F_1 was separated by t.l.c. using the same solvent mixture as above and the following four compounds were isolated: 5-hydroxy-3,3′,4′,7-tetramethoxyflavone (1a), R_F 0.61, 3′,5-dihydroxy-3,4′,7-trimethoxyflavone [2] (1b), R_F 0.54, 5-hydroxy-2′,3,4′,5′,7-pentamethoxyflavone (2a), R_F 0.58, and 2′,5-dihydroxy-3,4′,5′,7-tetramethoxyflavone (2b), R_F 0.48.

Three flavonols were isolated from fraction F_2 after acetylation and subsequent separation of the acetylated product by t.l.c. using benzene–ethyl acetate–acetone (7 : 2 : 1 v/v). Hydrolysis of the separated compounds gave: 2′,6-dihydroxy-3,4′,5,5′,7-pentamethoxyflavone (3a), R_F 0.38, 3′,5,6-trihydroxy-3,4′,7-trimethoxyflavone (4a),[3] R_F 0.43, and 5,6-dihydroxy-3,3′,4′,7-tetramethoxyflavone (4b), R_F 0.33.

T.l.c. separation of the acetylated F_3 fraction in benzene–ethyl acetate–acetone (8 : 2 : 2 v/v) produced one acetylated flavonol. Acid hydrolysis of the acetate yielded 2′-hydroxy-3,4′,5,5′,7-pentamethoxyflavone (2c), R_F 0.29. Together in the same fraction, the fully methylated flavonol, 2′,3,4′,-5,5′,7-hexamethoxyflavone was found (2d), R_F 0.21.

Fraction F_4 was dissolved in [^{2}H]methanol and subjected to ^{1}H n.m.r. analysis for *O*-methyl groups. None were observed and the fraction (670 mg) was treated with diazomethane in methanol for 48 h at −15°. T.l.c. separation of the methylated product in benzene–ethyl acetate–acetone (7 : 2 : 1 v/v) gave three flavonols, *viz.* 3,3′,4′,5,7-pentamethoxyflavone (1c), R_F 0.16, 2′,3,4′,5′,5,7-hexamethoxyflavone (2d), R_F 0.29, and 2′,3′,3,4′,5,6,7-heptamethoxyflavone (3b), R_F 0.47.

The methanol and dioxan extracts were combined and acetylated with acetic anhydride in pyridine. The acetylated product was separated by column chromatography in benzene–acetone–ethyl acetate (7 : 2 : 1 v/v) into two compounds (by t.l.c. their R_F values were 0.41 and 0.54, respectively). After acid hydrolysis of the compounds they were analysed and identified as distemonanthin,[3] 3,4,8,10-tetrahydroxy-9-methoxy-5,7-dioxo[2]benzopyrano-[4,3-*b*][1]benzopyran (5a), and benthamianin,[1] 3,4,8,10-tetrahydroxy-9-methoxy-7-oxo[2]benzopyrano[4,3-*b*][1]-benzopyran (6a).

3,3′,4′,5,7-*Substituted flavones related to quercetin.* 5-Hydroxy-3,3′,4′,7-tetramethoxyflavone (1a) gave yellow, woolly crystals (48 mg), m.p. 157—158° (from benzene–ethanol) (lit.,[19] 156—157, 159—160°, $\nu_{max.}$ ($CHCl_3$) 1 655 cm^{-1} (CO stretching), *m/e* 358 (M^+, 100%), 357 (47), 343 (35), 315 (34), 284 (12), 179 (7), 167 (6), 165 (15), and 150 (6); ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 352, 288, 272, 254, and 232 nm (ε 7 600, 3 850, 6 650, 6 650, and 16 350).

5-*O*-Acetyl-3,3′,4′,7-tetramethoxyflavone (1d) gave needles (31 mg), m.p. 168° (from benzene–ethanol) (lit.,[19] 169—170°) (Found: C, 62.8; H, 5.2. Calc. for $C_{21}H_{20}O_8$: C, 62.9; H, 5.0%); *m/e* 400 (M^+); ^{1}H n.m.r. in Table 1.

3′,5-Dihydroxy-3,4′,7-trimethoxyflavone (1b) [2] gave yellow needles (2.86 g), m.p. 173—174° (from methanol–acetone) (lit.,[2] 172—173°); ^{1}H n.m.r. in Table 1. The other physical constants were identical to those in the literature.[2]

3,3′,4′,5,7-Pentahydroxyflavone (1c) was isolated as the penta-*O*-methyl ether after methylation of the crude product, giving needles (56 mg), m.p. 152° (from acetone–ethanol) (lit.,[19] 151—152°); $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1} (CO stretching); ^{1}H n.m.r. in Table 1.

3,3′,4′,5,6,7-*Substituted flavones.* 3′,5,6-Trihydroxy-3,-4′,7-trimethoxyflavone (4a) [3] was identified by comparison of its m.p., u.v., and alkali fragmentation products of the fully methylated and triethoxy derivatives with those described in the literature.[3] The ^{1}H n.m.r. spectrum is in Table 1.

5,6-Dihydroxy-3,3′,4′,7-tetramethoxyflavone (4b) was isolated as short yellow plates (21 mg), m.p. 211—213° (from acetone–ethanol), *m/e* 374 (M^+, 100%), 373 (53), 360 (5), 359 (8), 343 (21), 331 (14), 325 (9), 183 (7), 182 (5), 181 (4), 165 (7), and ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 343, 282, and 259 nm (ε 8 500, 7 600, and 9 450).

5,6-*Diacetoxy*-3,3′,4′,7-*tetramethoxyflavone* (4c) gave needles (61 mg), m.p. 206—208° (from benzene–ethyl acetate–acetone) (Found: C, 59.9; H, 4.6. $C_{23}H_{21}O_{10}$ requires C, 60.4; H, 4.6%); $\nu_{max.}$ ($CHCl_3$) 1 632 (CO stretching) and 1 775 cm^{-1} (acetyl); *m/e* 458 (M^+, 11%), 459 (3.5), 416 (8), 404 (5), 375 (21), and 374 (100); ^{1}H n.m.r. in Table 1. Alkaline hydrolysis of the 5,6-di-*O*-ethyl derivative gave 2′,3′-diethoxy-6′-hydroxy-2,4′-dimethoxyacetophenone,[3] m.p. 80°, and veratric acid.

Synthesis of 5,6-*dihydroxy*-3,3′,4′,7-*tetramethoxyflavone* (4b). A modified Allan–Robinson [20] method was used, followed by dealkylation at the 5-position of the intermediate flavone. A finely divided mixture of 3′,6′-dihydroxy-2,2′,4′-trimethoxyacetophenone [21] (1 g), veratric anhydride (3 g) prepared according to the method of Heap and Robinson,[22] and potassium 3,4-dimethoxybenzoate (1.5 g) was heated at 180° and 20 mmHg for 4 h. Aqueous KOH (3 ml; 1 : 1 w/w) and ethanol (30 ml) were added and the mixture refluxed for 30 min. The cooled mixture was filtered, acidified with 2M HCl, and extracted with ether (3 × 25 ml) which was then washed with $NaHCO_3$ solution and water. After removal of the ether under vacuum, yellow plates (120 mg), m.p. 185—190°, crystallized from ether–acetone–ethanol (Found: M^+, 388.114. $C_{20}H_{20}O_8$ requires *M*, 388.115). This compound was identified as 6-hydroxy-3,3′,4′,5,7-pentamethoxyflavone (4d), $\nu_{max.}$ ($CHCl_3$) 1 608 cm^{-1} (CO stretching); ^{1}H n.m.r. in Table 1; *m/e* 388 (M^+, 100%), 387 (55), 373 (6), 371 (5), 359 (6), 358 (21), 357 (78), 342 (9), 197 (4), 196 (3), 195 (3), 168 (5), and 167 (8).

A mixture of 6-hydroxy-3,3′,4′,5,7-pentamethoxyflavone (110 mg), nitrobenzene (3 ml), dry ether (15 ml), and $AlCl_3$ (0.3 g) [23] was stirred for 24 h at ambient temperatures, ice–water (10 ml) was added, and the mixture extracted with ether (3 × 20 ml). After removal of the solvent under vacuum the residue was separated by t.l.c. in benzene–acetone (8 : 2 v/v). The u.v. and ^{1}H n.m.r. spectral data and mixed m.p. of this compound (23 mg) (R_F 0.24) were identical with those of the natural 5,6-dihydroxy-3,3′,4′,7-tetramethoxyflavone (4b).

2′,3,4′,5′,5,7-*Substituted flavones.* 2′,3,4′,5′,5,7-Hexahydroxyflavone (2e) was isolated as the hexamethoxyflavone (2d) after methylation of the crude fraction (F_4).

2′,3,4′,5′,5,7-*Hexamethoxyflavone* (2d) was isolated as a fully *O*-methylated natural product and gave round yellow crystals (24 mg), m.p. 190—193° (from benzene–ethanol) (lit.,[3] 195—196°) (Found: M^+, 402.126. $C_{21}H_{22}O_8$ requires *M*, 402.130); $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1} (CO stretching), *m/e* 402 (M^+, 63%), ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 325, 293, and 246 nm (ε 9 500, 7 300, and 20 000). Alkali fragmentation gives 6′-hydroxy-2,2′,4′-trimethoxyaceto-

phenone,[3] m.p. 102—104°, and 2,4,5-trimethoxybenzoic acid,[3] m.p. 144°.

2′-*Hydroxy*-3,4′,5′,5,7-*pentamethoxyflavone* (2c) was obtained as yellow-orange nodular crystals (110 mg), m.p. 210—212° (from acetone–methanol) (Found: M^+, 388.119. $C_{20}H_{20}O_8$ requires M, 388.115), *m/e* 388 (M^+, 58%), 389 (12), 387 (38), 373 (12), 371 (16), 358 (23), 357 (100), 339 (13), 181 (34), 180 (22), 167 (7), 165 (7), and 151 (10); ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 329, 288, 254, and 232 nm (ε 4 800, 5 450, 8 800, and 12 150).

2′-Acetoxy-3,4′,5′,5,7-pentamethoxyflavone (2f) crystallized from acetone–methanol as orange-yellow flat crystals (210 mg), m.p. 78°, $\nu_{max.}$ ($CHCl_3$) 1 634 (CO stretching) and 1 765 cm^{-1} (acetyl), *m/e* 430 (M^+, 51%), 431 (15), 429 (14), 400 (21), 399 (77), 388 (34), 387 (100), 373 (23), 371 (29), 358 (20), 357 (75), 339 (19), and 181 (33); ^{1}H n.m.r. in Table 1.

5-Hydroxy-2′,3,4′,5′,7-pentamethoxyflavone (2a) gave yellow dendritic crystals (167 mg), m.p. 146—147° (lit.,[3] 149—150° (from acetone–methanol) (Found: C, 61.7; H, 5.2. Calc. for $C_{20}H_{20}O_8$: C, 61.8; H, 5.2%); $\nu_{max.}$ ($CHCl_3$) 1 655 cm^{-1} (CO stretching), *m/e* 388 (M^+, 100%), 387 (17), 374 (15), 373 (60), 358 (41), 357 (70), 345 (13), 315 (17), 195 (3), 181 (10), 180 (15), 167 (30), and 165 (8); ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 342, 303, 286, 267, and 234 nm (ε 16 900, 10 900, 10 900, 35 000, and 35 000).

5-Acetoxy-2′,3,4′,5′,7-pentamethoxyflavone (2g) crystallized as needles (43 mg), m.p. 190—193° (from benzene–ethanol), ^{1}H n.m.r. in Table 1.

Alkaline fragmentation of the 5-ethoxypentamethyl ether gives 2′-ethoxy-6′-hydroxy-2,4′-dimethoxyacetophenone,[3] m.p. 110°, and 2,4,5-trimethoxybenzoic acid, m.p. 144°.

2′,5-*Dihydroxy*-3,4′,5′,7-*tetramethoxyflavone* (2b) was obtained as branched yellow crystals (482 mg), m.p. 147—149 (from acetone–ethanol) (Found: C, 60.5; H, 4.8. $C_{19}H_{18}O_8$ requires C, 60.9; H, 4.8%), *m/e* 374 (M^+, 44%), 373 (20), 360 (8), 359 (6), 357 (4), 345 (5), 344 (15), 343 (43), 331 (6), 285 (23), 284 (94), 280 (30), 270 (12), 264 (22), 257 (23), 256 (100), 241 (18), 213 (26), 199 (11), 185 (28), 181 (9), 171 (19), 167 (23), 157 (15), and 129 (42); ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 364, 320, and 259 nm (ε 15 900, 12 300, and 33 800).

2′,5-Diacetoxy-3,4′,5′,7-tetramethoxyflavone (2h) formed needles (63 mg), m.p. 196—197° (from ethyl acetate–ethanol); $\nu_{max.}$ ($CHCl_3$) 1 627 (CO stretching) and 1 765 cm^{-1} (acetyl), *m/e* 458 (M^+, 45%), ^{1}H n.m.r. in Table 1.

2′-*Acetoxy*-5-*hydroxy*-3,4′,5′,7-*tetramethoxyflavone* (2i) was obtained as needles (33 mg), m.p. 157—158° (from ethyl acetate–methanol), from incomplete acetylation of 2′,5-dihydroxy-3,4′,5′,7-tetramethoxyflavone (Found: C, 60.1; H, 5.1. $C_{21}H_{20}O_9$ requires C, 60.5; H, 4.8%), *m/e* 416 (M^+, 66%), 374 (70), and 343 (100), ^{1}H n.m.r. in Table 1.

Alkali fragmentation of 2′,5-diethoxy-3,4′,5′,7-tetramethoxyflavone gives 2′-ethoxy-6′-hydroxy-2,4′-dimethoxyacetophenone,[3] m.p. 110°, and 2-ethoxy-4,5-dimethoxybenzoic acid, m.p. 149°.

2′,6-*Dihydroxy*-3,4′,5′,5,7-*pentamethoxyflavone* (3a) was recovered as a brown amorphous solid (135 mg), m.p. 191—193° (Found: C, 59.4; H, 5.0. $C_{20}H_{20}O_9$ requires C, 59.4; H, 5.0%), *m/e* 404 (M^+ 85%), 403 (41), 390 (3), 389 (26), 387 (18), 386 (20), 385 (24), 374 (23), 373 (100), 355 (33), 197 (29), 195 (9), 181 (14), and 167 (16); ^{1}H n.m.r. in Table 1; $\lambda_{max.}$ (MeOH) 314, 254, and 238 nm (ε 22 300, 23 800, and 27 100).

2′-6-Diacetoxy-3,4′,5′,5,7-pentamethoxyflavone (3c) gave needles (224 mg), m.p. 208—210° (from acetone–ethyl acetate–methanol); $\nu_{max.}$ ($CHCl_3$) 1 630 (CO stretching) and 1 765 cm^{-1} (acetyl), *m/e* 488 (M^+, 67%), 457 (48), 446 (40), 445 (100), 415 (47), and 403 (50).

Alkali fragmentation of 2′,6-diethoxypentamethoxyflavone, m.p. 136—137°, gives 3′-ethoxy-6′-hydroxy-2,2′,4′-trimethoxyacetophenone,[3] m.p. 78°, and 2-ethoxy-4,5-dimethoxybenzoic acid,[24] m.p. 149°.

2′,3′,3,4′,5,6,7-Heptahydroxyflavone (3d) was isolated as the heptamethyl ether (3b) as needles (52 mg), m.p. 190—192° (from benzene–methanol) (lit.,[5] 186—188° (Found: C, 60.9; H, 5.7. Calc. for $C_{22}H_{24}O_9$: C, 61.1; H, 5.6%), *m/e* 432 (M^+, 52%), 433 (13.5), 431 (16), 419 (26), 418 (100), 402 (8), 401 (16), 400 (56), 389 (4), 371 (10), 211 (15), 202 (21), and 195 (15); $\lambda_{max.}$ (MeOH) 305, 256, and 238 nm (ε 16 500, 20 000, and 28 000).

Alkaline degradation of the heptamethyl ether gives 6′-hydroxy-2,2′,3′,4′-tetramethoxyacetophenone, m.p. 75—76°, and 2,3,4-trimethoxybenzoic acid,[25] m.p. 99°.

3,4,8,10-Tetrahydroxy-9-methoxy-5,7-dioxo[2]benzopyrano[4,3-*b*][1]benzopyran, distemonanthin[3] (5a) was isolated as the tetra-acetyl derivative (5b) as needles (512 mg), m.p. 222—223° (from ethyl acetate–methanol) (lit.,[3] 225—227°); *m/e* 526 (M^+, 5%), 485 (6), 484 (25), 443 (8), 442 (31), 401 (9), 400 (42), 370 (8), 359 (18), and 358 (100), ^{1}H n.m.r. in Table 2.

Distemonanthin (5a) was obtained from acid hydrolysis of (5b) as yellow needles, m.p. 340° (decomp.) (from benzene–pyridine) (lit.,[3] 351° in vacuum); *m/e* 358 (M^+, 100%), 359 (18), 357 (10), 344 (12), 343 (63), 341 (25), 340 (65), 329 (15), 328 (32), 315 (75), 312 (10), 302 (9), 272 (4), 258 (5), 189 (4), 187 (4), and 165 (6).

3,5,6,7,3′,4′-Hexamethoxyflavone-2′-carboxylic acid and its flavone ester were both obtained from distemonanthin tetra-*O*-methyl ether (6c). Their physical constants were in agreement with those in the literature.[3]

3,4,8,10-Tetrahydroxy-9-methoxy-7-oxo[2]benzopyrano-[4,3-*b*][1]benzopyran, benthamianin (6a) was isolated as the tetra-acetate (6b). *Benthamianin tetra-acetate* was recovered as a non-crystalline yellow solid (920 mg), m.p. 105—106° (Found: C, 58.5; H, 4.1. $C_{25}H_{20}O_{12}$ requires C, 58.6; H, 3.9%); $\nu_{max.}$ ($CHCl_3$) 1 636 (CO stretching) and 1 779 cm^{-1} (acetyl); *m/e* 512 (M^+ 5%), 485 (2), 484 (4), 471 (4), 470 (15), 443 (14), 442 (56), 429 (22), 428 (100), 402 (13), 400 (30), 387 (17), 386 (83), 385 (25), 370 (9), 359 (11), 358 (16), 357 (12), 344 (33), 343 (37), 329 (19), 328 (19), 315 (17), 301 (8), 252 (18), 244 (7), and 219 (7); ^{1}H n.m.r. in Table 2.

Acid hydrolysis of the tetra-acetate yielded benthamianin (6a) as a yellow non-crystalline solid (110 mg), m.p. 230—235° (decomp.); *m/e* 344 (M^+ 100%), 345 (23), 343 (31), 330 (11), 329 (67), 327 (7), 326 (38), 315 (12), 314 (28), 301 (32), 285 (14), 252 (11), 244 (11), 209 (7), 197 (13), 195 (16), 192 (7), 183 (5), 182 (6), and 181 (10); ^{1}H n.m.r. in Table 2; $\lambda_{max.}$ (MeOH) 381, 280, 262, and 231 (ε 59 400, 74 000, 58 400, and 58 400); $\lambda_{max.}$ (MeOH–NaOAc–H_3BO_3) 405 and 268 nm.

Benthamianin tetra-*O*-methyl ether (6c) was prepared by methylation of benthamianin with $(CH_3)_2SO_4$ in acetone over anhydrous K_2CO_3. The *tetra-O-methyl ether* was recovered as a non-crystalline brown solid (40 mg), m.p. 59—60° (Found: C, 62.8; H, 5.1. $C_{21}H_{20}O_8$ requires C, 62.9; H, 5.0%), $\nu_{max.}$ ($CHCl_3$) 1 634 cm^{-1} (CO stretching), *m/e* 400 (M^+, 23%), 399 (3), 386 (22), 385 (100), 372 (5),

371 (6), 357 (9), 341 (6), 211 (6), 210 (9), 195 (9), and 167 (11), ^{1}H n.m.r. in Table 2.

Synthesis of Benthamianin Tetramethyl Ether (6c) *and the 5,6-Dimethoxy Derivative of Peltogynin Trimethyl Ether* (6d) *from Oxyayanin B Tri-O-methyl Ether* (4a).—Oxyayanin B tri-O-methyl ether (160 mg) in methanol (100 ml) was irradiated for 7 h at 350 nm (Rayonet photochemical reactor, New England Ultra-Violet Co.) in a quartz vessel while nitrogen was passed through for 5 min at half-hourly intervals. After removal of the solvent the product was separated by t.l.c. in benzene–acetone (7 : 2 v/v) into three bands, R_F 0.43, 0.26, and 0.12. The compound with the highest R_F value proved to be the starting material, while benthamianin tetra-*O*-methyl ether (45 mg) was isolated from the R_F 0.26 band.

5,6-Dimethoxypeltogynin trimethyl ether (6d) was obtained from the lowest R_F band (0.12) as short crystals (59 mg), m.p. 186—188° (from acetone–methanol) (Found: C, 62.8; H, 5.1. $C_{21}H_{20}O_8$ requires C, 62.9; H, 5.0%), $\nu_{max.}$ ($CHCl_3$) 1 634 cm^{-1} (CO stretching), *m/e* 400 (M^+, 55%) and 385 (100), ^{1}H n.m.r. in Table 2.

Conversion of benthamianin tetra-acetate (6c) into distemonanthin tetra-acetate (5b) was achieved by stirring a mixture of (6c) (160 mg), activated MnO_2,[26] and chloroform (15 ml) for 48 h at ambient temperatures. Solids were removed by filtration and the solvent evaporated. Separation of the residue yielded distemonanthin tetra-acetate (23 mg, 14%), as confirmed by its m.p. and ^{1}H n.m.r. spectrum. Benthamianin tetra-acetate in acetone undergoes autoxidation to distemonanthin tetra-acetate over ten days.

Synthesis of Benthamianin (6a) *by Reduction of Distemonanthin* (5a).—Two separate mixtures, one consisting of distemonanthin (150 mg), diglyme (2 ml), pyridine–dioxan (4 ml, 1 : 1, v/v), and anhydrous ether (5 ml) and the other of BF_3 [11] (900 mg), diglyme (1 ml), and anhydrous ether (5 ml) were simultaneously and slowly added with stirring to a mixture of $NaBH_4$ (200 mg) and diglyme (1 ml) in anhydrous ether (5 ml), kept in an ice-bath during the mixing process. After 30 min additional $NaBH_4$ (100 mg) was added and left for 20 min. The reaction mixture was then refluxed at 60° for 1 h, cooled, and carefully acidified with diluted HCl (1 : 30). After separation, the ether solution was consecutively washed with diluted HCl, sodium hydrogencarbonate solution, and water (5 ml). The solution was dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was acetylated with acetic anhydride in pyridine and the product obtained was analysed. The m.p. (mixed) and ^{1}H n.m.r. spectrum confirmed the product as benthamianin tetra-acetate (6b).

Oxidation of Benthamianin Tetramethyl Ether (6c) *to Distemonanthin Tetramethyl Ether* (5c).—Benthamianin tetramethyl ether (150 mg), acetic acid (0.2 ml), and potassium permanganate (0.5 g) in acetone (100 ml) were stirred for 1 h at room temperature. Water (20 ml) was added to the mixture and sulphur dioxide passed through until the solution was clear. After removal of the solvent and water under vacuum, the residue was separated by t.l.c. in a mixture of benzene–acetone (8 : 2 v/v). The band with R_F 0.42 gave plates (22 mg, 15%), which proved to be identical to the methylated product of distemonanthin (5c) with respect to m.p.[3] (mixed) and ^{1}H n.m.r.

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