Dimeric and Trimeric Flavonoids containing a Cyclopentane Ring: 6,7-Diaryl-6a,7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*][1]benzoxepins

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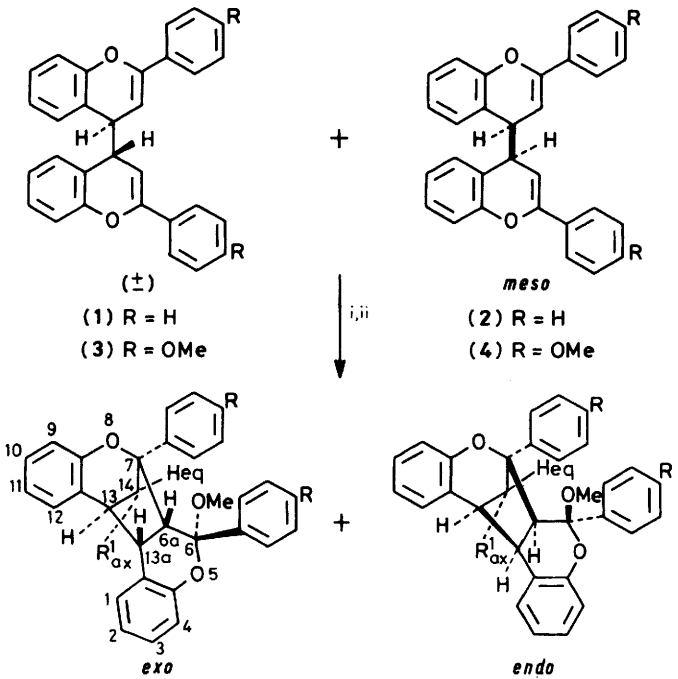
4,4'-Biflav-2-enes react with electrophiles in the presence of alcohols, yielding substituted 6,7-diaryl-6a,7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*][1]benzoxepins, *e.g.* (**6**)—(**15**). The structures and stereochemistries of these compounds have been deduced from their conversion into other analogues, *e.g.* (**18**)—(**21**), and from n.m.r. studies.

Trimeric flavonoids (**23**) and (**24**) containing the benzoxepin structure have been synthesised by the reaction of flavylium perchlorate with 4,4'-biflav-2-ene and alcohols. The structures of the trimers are not in any serious doubt but their stereochemistries are not fully known.

Having established that a flav-2-ene will react with alcohols and a variety of reagents to yield 2-alkoxyflavans,[1] we turned our attention to 4,4'-biflav-2-enes. We prepared 4,4'-biflav-2-ene by the general method of Reynolds *et al.*[2] but, unlike these authors who obtained stereochemically pure 4,4'-biflav-2-ene, we obtained a product which, as determined by examination of its n.m.r. spectrum, was an approximately 55:45 mixture of the racemic (**1**) and *meso* (**2**) isomers which we were not able to separate either by chromatography or by recrystallisation. We therefore used the mixture of stereoisomers in subsequent experiments and similarly we obtained a mixture of racemic (**3**) and *meso*-4,4'-dimethoxy-4,4'-biflav-2-ene (**4**) from 4'-methoxyflavylium perchlorate.



(±)
(1) R = H
(3) R = OMe

meso
(2) R = H
(4) R = OMe

(6) R = R¹ = H
(8) R = OMe, R¹ = H
(10) R = H, R¹ = Br
(12) R = H, R¹ = OH
(14) R = OMe, R¹ = OH

exo

(7) R = R¹ = H
(9) R = OMe, R¹ = H
(11) R = H, R¹ = Br
(13) R = H, R¹ = OH
(15) R = OMe, R¹ = OH

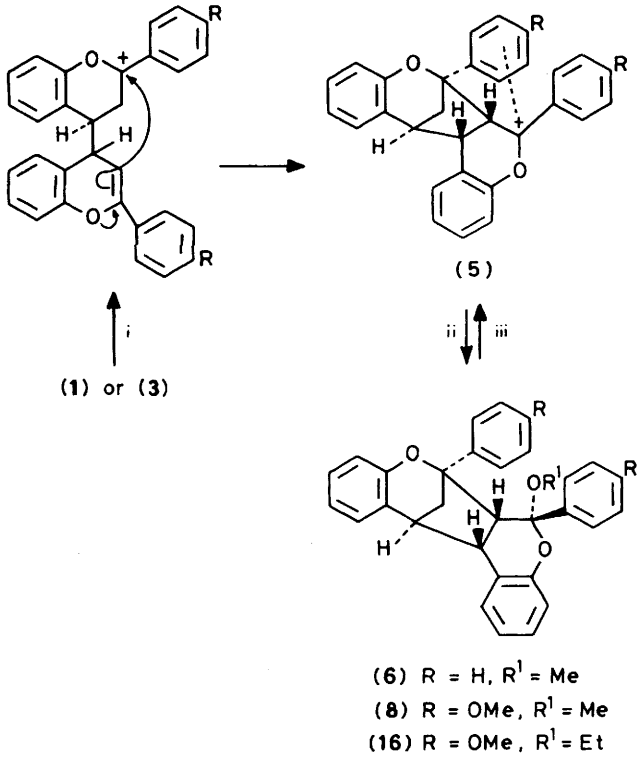
endo

All compounds are racemic. Relative stereochemistry is indicated.

Scheme 1. *Reagents:* i, $AlCl_3$ (R^1 = H) or *N*-bromosuccinimide (R^1 = Br) or *p*-$NO_2C_6H_4CO_3H$ (R^1 = OH); ii, MeOH

Treatment of a mixture of the stereoisomers of 4,4'-biflav-2-ene (**1**) and (**2**) with methanol and a small quantity of aluminium chloride (Scheme 1) gave by p.l.c. two crystalline solids each of which exhibited a molecular ion, *m/z* 446, in its mass spectrum, analysed for $C_{31}H_{26}O_3$, and had a ratio of 18:3 for the aromatic and methoxy protons in its n.m.r. spectrum, indicating the addition of only one molecule of methanol to the biflav-2-ene. The structure of the compounds was shown not to be that which would be formed simply by the addition of a molecule of methanol to one of the flavene units, as for the monomeric flav-2-enes,[1] by the fact that the n.m.r. spectrum of neither compound contained a doublet in the region τ 4—5 indicative of a vinylic proton at C-3 of a flavonoid, nor was a carbon–carbon double bond stretching frequency present at *ca.* 1 670 cm^{-1} in the i.r. spectra as is typical of flav-2-enes.[1] Structures which can be drawn for the products consistent with the physical data are (**6**) and (**7**) in which two bonds join the flavan units and a cyclopentane ring has been formed giving either the *exo*- or *endo*-6a,7,13,13a-tetrahydro-6,7-diphenyl-6*H*-7,13-methano[1]benzopyrano[3,4-*c*][1]benzoxepin skeleton, numbered as indicated.† The product of higher R_F corresponds to an *exo* stereoisomer since in the n.m.r. spectrum (see Table) no 13H, 13aH coupling is observed, consistent[3,4] with the dihedral bond angle of 90° found in a model of (**6**). In the product of lower R_F, 13a-H appears as a quartet and $J_{13,13a}$ is 6.0 Hz. A model of (**7**) shows that the dihedral bond angle between the hydrogen atoms at C-13 and C-13a in a product with the *endo* stereochemistry is approximately 30°, in agreement[3,4] with the coupling constant observed. In neither *exo* nor *endo* compound is there any observable coupling between the proton at C-13 and the axial proton at C-14. Spin decoupling experiments (reported in full in the Experimental section) support the assignments given to the signals in the n.m.r. spectrum of each compound. A plausible mechanism for the production of the *exo*-isomer (**6**) from the (±) stereoisomer of 4,4'-biflav-2-ene (**1**) is shown in Scheme 2. An analogous mechanism can be written for the transformation (**2**) ⟶ (**7**). It is proposed that initial protonation of a double bond occurs (methanol and aluminium chloride providing the proton), followed by cyclization to a stabilized carbonium ion (**5**). This intermediate then yields a ketal in the presence of methanol (compare reactions of monomeric flav-2-enes[1]). Since it has been shown[1] that 2-alkoxy groups in flavans are interchange-

† The term *exo* is used here to describe stereoisomers in which 13-H and 13a-H are *trans*; *endo* compounds are 13,13a-*cis*. The 6,6a assignment refers to the relationship of the 6-aryl group to the substituent, other than hydrogen, at position 6a. Where appropriate, the 7,14-stereochemistry is defined similarly.



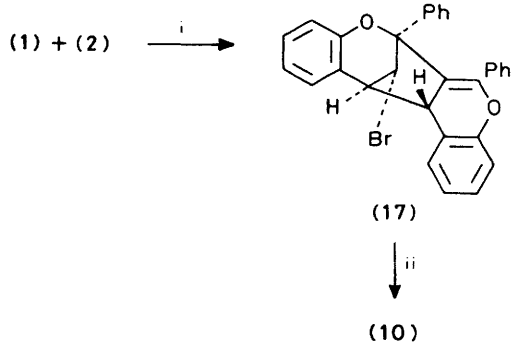
Scheme 2. *Reagents:* i, $AlCl_3$–R^1OH, ii, R^1OH, iii, $AlCl_3$

able in the presence of aluminium chloride (also, see later), it is to be expected that reaction of the ion (**5**) with methanol will be reversible and therefore the 6,6a-stereochemistry (*cis* or *trans*)* will be thermodynamically controlled. Formulation of both *exo* and *endo* products (**6**) and (**7**) as 6,6a-*trans*-compounds is mainly based on the shielding of the methoxy group (by 0.4—0.5 p.p.m.) observed in the n.m.r. spectra. Molecular models indicate that such shielding can be accounted for in (**6**) and (**7**) but not in the corresponding 6,6a-*cis*-isomers. Furthermore, the *exo*- and *endo*-6,6a-*trans*-stereoisomers (**6**) and (**7**) appear to be less internally hindered than the corresponding 6,6a-*cis*-stereoisomers and will, therefore, be thermodynamically more stable.

Treatment of a mixture of the (±)-(**3**) and *meso*-(**4**) stereoisomers of 4,4′-dimethoxy-4,4′-biflav-2-ene in dioxane with methanol and a catalytic amount of anhydrous aluminium chloride gave two substances, both with molecular weight 506. The n.m.r. spectra of these compounds, apart from the appearance of signals from the aromatic methoxy groups, were similar to those of the two products obtained by addition of methanol to 4,4′-biflav-2-ene. The products may, therefore, be assigned structures (**8**) and (**9**) with *exo*- and *endo*-6,6a-*trans*-stereochemistries. Treatment of the *exo*-6,6a-*trans*-6-methoxy compound (**8**) in dioxane with an excess of ethanol and a catalytic amount of anhydrous aluminium chloride (Scheme 2) gave the *exo*-6,6a-*trans*-6-ethoxy compound (**16**). The exchange of alkoxy groups indicates that a carbonium ion was generated at C-6 in this reaction, and this result provides evidence for the earlier suggestion that the formation of a ketal from the corresponding *exo* (or *endo*) carbonium ion in alcoholic solution is reversible in the presence of anhydrous aluminium chloride. No evidence was obtained to suggest that a mixture of *exo*-6,6a-*trans*- and *exo*-6,6a-*cis*-stereoisomers had been formed in this reaction. Examination of the n.m.r. spectrum of the crude *exo*-6-ethoxy compound (**16**) (recrystallisation might have caused just one stereoisomer to separate from a mixture of stereoisomers) revealed only one (highfield) triplet due to the methyl protons in an ethoxy group, and it may therefore be assumed that the configuration had been retained at C-6.

A mixture of the (±)- and *meso*-isomers of 4,4′-biflav-2-ene (**1**) and (**2**) in dioxane and methanol reacted rapidly with a 1.1 molar excess of *N*-bromosuccinimide (Scheme 1) yielding two major products the elemental analyses of which indicated that both products contained one bromine atom; the n.m.r. spectra were consistent with structures (**10**) and (**11**). As found for the *exo*- and *endo*-6-methoxy compounds (**6**) and (**7**) without a 14-substituent, the product of higher R_F corresponded to the *exo*-stereoisomer (**10**), since in this compound there was no appreciable 13,13a-coupling. The n.m.r. spectrum of this *exo*-stereoisomer also indicated that it had 7,14-*cis* stereochemistry (bromine atom at C-14 axial) since the proton remaining at C-14 was coupled to 13-H. The bromine atom therefore replaces the axial proton at C-14 in the analogous *exo*-compound (**6**), since in (**6**), 14_{ax}-H was not coupled to 13-H (see Table). The value of $J_{13,13a}$ (6.0 Hz) found in the product of lower R_F indicated that this compound was the *endo*-stereoisomer (**11**), and the existence of a 13,14 coupling showed that this stereoisomer, too, had 7,14-*cis*-stereochemistry. Since the methoxy group in both the *exo*-(**10**) and the *endo*-(**11**) products resonated at unusually highfield, it is likely that both compounds have the 6,6a-*trans*-stereochemistry. The mechanism of the reaction is probably similar to that suggested above for the formation of (**6**) and (**7**). Presumably, addition of positive bromine to one of the double bonds in (**1**) or (**2**) initially gives a bromonium ion which undergoes *trans* ring-opening on cyclization.

When the mixed isomers of 4,4′-biflav-2-ene were treated with bromine in acetic acid and acetic anhydride in the presence of anhydrous sodium acetate (Scheme 3), several products were detected by t.l.c. The major component of the mixture, and a small amount of starting material were isolated by p.l.c. The 4,4′-biflav-2-ene recovered was found by examination of its n.m.r. spectrum to be one stereoisomer, corresponding to that which predominated in the starting material, and that which was prepared in a pure condition by Reynolds *et al.*[2] It was possible to show that the recovered biflav-2-ene was the (±)- form (**1**) by causing it to react with *N*-bromosuccinimide in the presence of methanol when only the *exo*-14-bromo-6-methoxy compound (**10**), identified by t.l.c. comparison with an authentic sample, was produced. The elemental analysis and the n.m.r. spectrum of the major product were consistent with the unsaturated structure (**17**) having *exo*-7,14-*cis*-stereochemistry. It seems probable that elimination of acetic acid from the *exo*- and *endo*-



Scheme 3. *Reagents:* i, Br_2, AcOH–NaOAc; ii, MeOH–$AlCl_3$

* The term *exo* is used here to describe stereoisomers in which 13-H and 13a-H are *trans*; *endo* compounds are 13,13a-*cis*. The 6,6a assignment refers to the relationship of the 6-aryl group to the substituent, other than hydrogen, at position 6a. Where appropriate, the 7,14-stereochemistry is defined similarly.

Table. ^{1}H N.m.r. data for 6,7-diaryl-6a,7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*][1]benzoxepin derivatives [$\tau_H(CDCl_3)$, multiplicity, *J* in Hz]

Compound	6a-H	13-H	13a-H	14_{ax}-H	14_{eq}-H	6-subst.	$J_{6a,13a}$	$J_{13,13a}$	$J_{13,14_{ax}}$	$J_{13,14_{eq}}$	$J_{14_{ax},14_{eq}}$
(6)	6.37d	6.67d	5.87d	8.22d	7.50dd	7.51s	8	*ca.* 0	*ca.* 0	4	12
(7)	6.42d	6.70dd	5.85dd	7.83d	7.41dd	7.39s	12	6	*ca.* 0	4	12
(8)[a]	6.56d	6.79d	5.98d	8.32d	7.50dd	7.57s	8	*ca.* 0	*ca.* 0	4	12
(9)[a]	6.61d	6.80dd	5.99dd	7.90d	7.50dd	7.44s	12	6	*ca.* 0	3.5	12
(10)	6.25d	6.44d	5.82d		5.24d	7.54s	9	*ca.* 0		4	
(11)	6.35d	6.48dd	5.81dd		5.22d	7.40s	12.5	6		4	
(12)	6.36d	6.58d	6.02d		5.43dd[b]	7.51s	9	*ca.* 0		4	
(13)	6.43d	6.59m[c]	5.93dd		5.42dd[b]	7.40s	12	6		4.5	
(14)	6.46d	6.60br s[c]	6.08d		5.50dd[b]	7.52s	9	*ca.* 0		4	
(15)	6.46	6.68[c]	5.93dd		5.45dd[b]	7.39s	11.5	6		4.5	
(16)[a]	6.54d	6.80d	5.93d	8.32d	*ca.* 7.5m[d]	7.38m[d]	8	*ca.* 0	*ca.* 0	3.5	12
(17)		5.97d	5.97s		5.47d			*ca.* 0		4	
(18)		6.23t	5.66m[e]		5.66m[e]			3.5		3.5	
(19)	5.87d	6.23s	5.67d			7.42s	8.5	*ca.* 0			
(20)	6.08d	6.46s	5.74d	5.73d[f]		7.43s	8.5	*ca.* 0	*ca.* 0		
(21)	6.45d	6.88br s	6.27br dd	5.27br s			4.5	2	*ca.* 0		

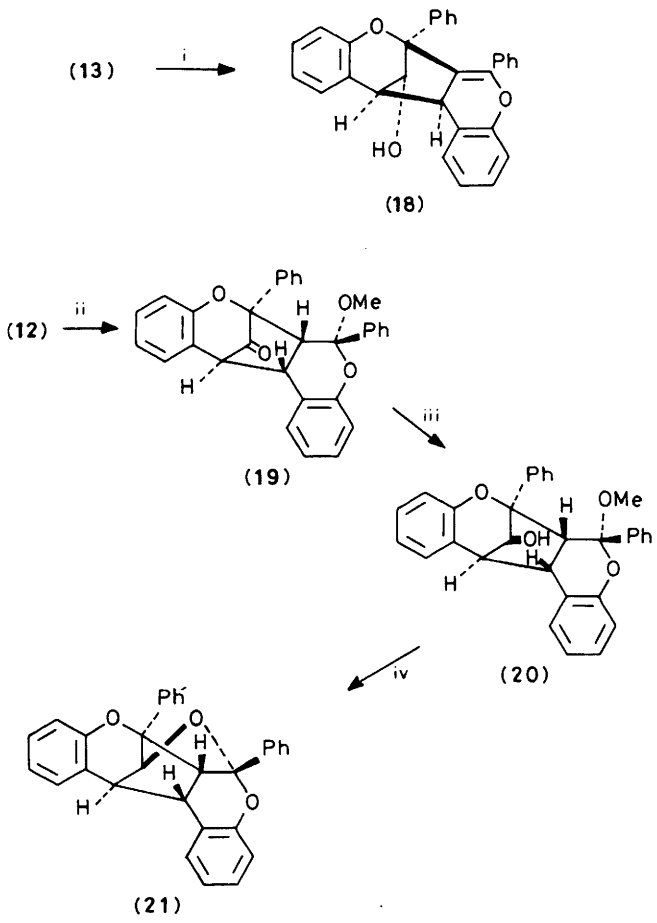
[a] Spectrum obtained in CCl_4. [b] Doublet after addition of D_2O. [c] Obscured by MeOH of crystallization. [d] Position of OCH_2CH_3: obscures 14_{eq}-H. [e] Superimposed signals. [f] Singlet after addition of D_2O.

7,14-*cis*-6,6a-*trans*-6-acetoxy-14-bromo compounds which were expected to be the major products of the reaction, occurred spontaneously. The major product (**17**) was obtained in only 29% yield; by-products are presumably formed by addition of bromine to this compound and, particularly, to the *endo*-analogue. When treated with methanol and anhydrous aluminium chloride (Scheme 3), the unsaturated compound (**17**) was slowly converted, in 75% yield, into the *exo*-7,14-*cis*-6,6a-*trans*-14-bromo-**6**-methoxy ketal (**10**).

The route shown in Scheme 1 was also used to obtain *exo*- and *endo*-14-hydroxy compounds (**12**), (**13**), (**14**), and (**15**). Here it may be postulated that it is an intermediate epoxide, formed by reaction of *p*-nitroperbenzoic acid with one double bond in each stereoisomer of the starting biflav-2-ene, that undergoes *trans*-ring opening on cyclization, yielding 7,14-*cis*-products. All the alcohols prepared formed crystalline tosylates. Treatment of the tosylates of the alcohols (**12**) and (**13**) with lithium aluminium hydride regenerated the original alcohols, and did not displace the tosylate anion, a result which is not surprising, since the approach of the aluminohydride ion to C-14 from the side opposite to the toluene-*p*-sulphonyl group is sterically hindered.

It has already been suggested that when ketals based on the 6a,7,13,13a-tetrahydro-6,7-diphenyl-6*H*-7,13-methano[1]-benzopyrano[3,4-*c*][1]benzoxepin skeleton are treated with anhydrous aluminium chloride a carbonium ion, *e.g.* (**5**), is generated and it was of interest to determine what would happen to such a carbonium ion in the absence of an added nucleophile. When a small amount of anhydrous aluminium chloride was added to the *endo*-14-hydroxy-6-methoxy compound (**13**) in dry benzene (Scheme 4) a highly coloured solution was produced from which a substance, m.p. 189—192 °C, was isolated in 44% yield. Elemental analysis, and i.r., n.m.r., and mass spectral data suggested that this compound had the unsaturated structure (**18**) with the *endo*-7,14-*cis*-stereochemistry. Clearly in the absence of a nucleophile, loss of a proton occurs; in the alcohol (**18**) the axial 14-hydroxy group is not well positioned for intramolecular nucleophilic attack.

Oxidation of the *exo*-14-hydroxy-6-methoxy compound (**12**) with the chromium trioxide–pyridine complex[5] (Scheme 4) occurred very slowly, and after the reaction mixture had been left for about 1 month at room temperature the major product was isolated in 71% yield as a colourless, amorphous solid with no distinct m.p. The elemental analysis, and the n.m.r. and mass

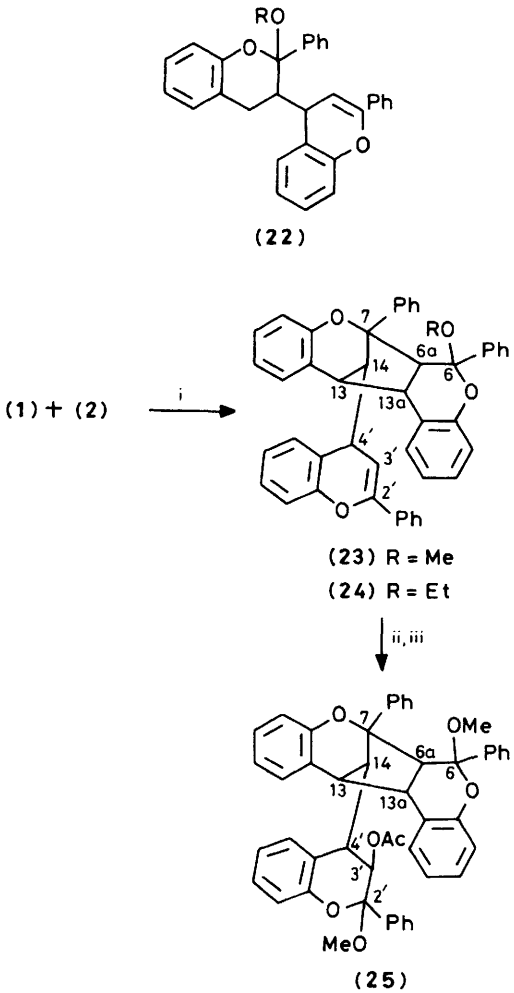


Scheme 4. *Reagents:* i, $AlCl_3$–benzene; ii, CrO_3–pyridine; iii, $LiAlH_4$; iv, aq. HCl

spectra of this substance were consistent with structure (**19**) with *exo*-6,6a-*trans*-stereochemistry. A crystalline oxime, m.p. 233—236 °C, was prepared. The high frequency i.r. absorption found in the ketone [$\nu_{CO}(CHCl_3)$: 1 777 cm^{-1}] is strong evidence that the carbonyl group is present in a strained ring. Treatment of the *exo*-ketone (**19**) with lithium aluminium

hydride (Scheme 4) gave the *exo*-7,14-*cis*-14-ol (**12**) in only 5—6% yield. The major product was instead the epimeric *exo*-7,14-*trans*-alcohol (**20**). The structure of this compound was readily deduced from its n.m.r. spectrum since, in contrast to the *exo*-7,14-*cis*-stereoisomer (**12**), no appreciable 13,14-coupling was observed (see Table). This was predicted for a compound in which the 14-substituent occupies the equatorial position. The 7,14-*trans*-alcohol (**20**) is undoubtedly the major product of the reduction because approach of aluminohydride ion to the carbonyl group in the ketone (**19**) is hindered from one direction by the rigid condensed ring system.

The *exo*-7,14-*trans*-alcohol (**20**) which is also a ketal, was found to be extremely sensitive to acid. Treatment of it with aqueous hydrochloric acid in dioxane gave a compound, m.p. 272—273 °C in 76% yield. The elemental analysis, and n.m.r., i.r., and mass spectra of this material were consistent with structure (**21**). Even recrystallisation from methanol which had not first been distilled from anhydrous potassium carbonate caused partial conversion of the *exo*-7,14-*trans*-alcohol (**20**) into the *exo*-6,14-epoxy compound (**21**), and some of this product was also isolated during an abortive attempt to prepare the tosylate of the alcohol (**20**). The ready formation of the epoxy compound (**21**) presumably involves the action of acid on the ketal (**20**) generating a carbonium ion at C-6 which can readily be attacked, intramolecularly, by the equatorial hydroxy group at C-14. With the aid of a model of the *exo*-6,14-epoxy compound (**21**) it can be seen that the molecule necessarily has a



Scheme 5. *Reagents:* i, flavylium perchlorate, ROH; ii, *p*-$O_2NC_6H_4CO_3H$, MeOH; iii, Ac_2O–pyridine

6,6a-*trans*- and a 7,14-*trans*-stereochemistry, and the prefix '*exo*' is superfluous, since no analogous *endo*-compound could be formed.

Flav-2-enes react with flavylium salts in alcohols to yield dimers (**22**).[6] Therefore as a possible route to trimers containing a cyclopentane ring, we investigated the reaction of the mixed isomers of 4,4'-biflav-2-ene with flavylium perchlorate in methanol (Scheme 5) which gave a crystalline solid (20%). Elemental analysis was consistent with the formula $C_{46}H_{36}O_4$ and a molecular ion, *m/z* 652, indicated that the substance was trimeric. The n.m.r. spectrum of the compound could not be fully interpreted, but a number of important features were observed; (1) a singlet at τ 7.49 attributable to a shielded methoxy group, the appearance of which is a strong indication that the trimer is a ketal and contains a cyclopentane ring, as in structure (**23**). (2) A doublet split by 6.5 Hz at τ 5.41 which may be assigned to the vinylic proton at C-3' in a compound of structure (**23**) [the analogous proton in the unsaturated dimer (**22**) resonates at τ 5.34 (*J* 6.2 Hz)]. (3) A doublet with line separation *ca.* 12 Hz at τ 6.38; this signal is similar to that of 6a-H in compounds previously obtained with *endo* stereochemistry. (4) A double doublet at τ 6.12, which could be assigned to 13a-H in a compound of structure (**23**) with *endo* stereochemistry. These data indicate that it is a stereoisomer of an *endo*-compound with structure (**23**) and an analogous compound (**24**) was obtained when the reaction was carried out in ethanol. No *exo*-trimers were isolated from these reactions but the *exo*-6,6a-*trans*-6-methoxyflavonoid dimer (**6**) (23%), previously obtained, was produced instead.

The double bond in the trimer (**23**) reacted with *p*-nitroperbenzoic acid and methanol to give, as expected, two isomeric 2',3'-*cis*-alcohols with different 3',4'-stereochemistries. Acetylation of the mixture of alcohols and separation by p.l.c. gave crystalline acetates. The elemental analysis, the mass spectrum (*m/z* 742), and the n.m.r. spectra (see Experimental section) were consistent with a trimeric *endo*-structure (**25**) for both acetates.

Experimental

N.m.r. spectra were recorded on a Perkin Elmer R14 100 MHz instrument, in deuteriochloroform unless otherwise stated; coupling constants are quoted in Hz. Relevant signals for compounds (**6**)—(**21**) are collected in the Table. Mass spectra were recorded on a Varian MAT CH7 or an AE1 MS9 instrument. Direct insertion was used and the probe temperature is recorded. Figures in brackets indicate the intensity of signals relative to the base peak (100%). I.r. spectra in CCl_4 were recorded on a Unicam SP 1000 or on a Perkin-Elmer 257 instrument. Alumina for columns was Camag neutral 5% deactivated with water. T.l.c. plates were coated with Merck Kieselgel HF_{254} silica. P.l.c. plates (100 × 20 cm or 20 × 20 cm) were coated with a 1 mm layer of Merck Kieselgel PF_{254} silica. Petroleum refers to redistilled light petroleum, b.p. 60—80 °C and ether refers to diethyl ether.

4,4'-Biflav-2-ene (**1**) *and* (**2**)[2].—Flavylium perchlorate (25.0 g) was dissolved in dry acetonitrile (700 ml), and nitrogen was passed through the solution for 1 h, before zinc dust (40 g) was added. The mixture was stirred under nitrogen for 3 h, and then heated to boiling as quickly as possible. The hot solution was filtered through a pad of Celite which was washed with more acetonitrile, and the filtrate was evaporated to *ca.* 300 ml. After 2 days, a pale yellow solid (11.0 g) was collected. Recrystallisation of the crude product from acetonitrile (400 ml) gave 4,4'-biflav-2-ene as needles (8.2 g), m.p. 157—161 °C (decomp.) (lit.,[2] m.p. 161—166 °C for a 60:40 mixture of stereoisomers). The product was shown to be approximately a

55:45 mixture of stereoisomers (**1**) and (**2**) by n.m.r.: τ 2.34—3.30 (36 H, m, aromatics in both stereoisomers), 4.48, 6.16 [each *ca.* 1.8 H, each a 'doublet' (actually a multiplet is seen on expansion), *J* 4.5, both C-3 and C-4 protons respectively in one stereoisomer], 4.94, 6.01 (each *ca.* 2.2 H, each a 'doublet' *J* 4.0, both C-3 and both C-4 protons respectively in the other stereoisomer). This material was used in the experiments described below unless stated to the contrary.

4,4′-*Dimethoxy*-4,4′-*biflav*-2-*ene* (**3**) *and* (**4**).—Nitrogen was passed for 1 h through a solution of 4′-methoxyflavylium perchlorate (25.0 g) in dry acetonitrile (700 ml) before zinc dust (40 g) was added. The mixture was stirred under nitrogen for 3.75 h, then quickly heated to boiling, filtered through Celite, and the filtrate was evaporated to *ca.* 300 ml. After 15 h, a yellow solid (3.03 g) was collected. Recrystallisation of the crude product from acetonitrile gave 4,4′-*dimethoxy*-4,4′-*biflav*-2-*ene* as needles (1.36 g), m.p. 185—196 °C after initial decomposition from *ca.* 175 °C (Found: C, 80.8; H, 5.5. $C_{32}H_{26}O_4$ requires C, 81.0; H, 5.5%); τ (satd. pyridine) 4.75 (2 H, 'doublet', 3-H), 5.83 (2 H, 'doublet', 4-H), 6.41 (6 H, s, Ar-OCH_3 × 2). Also 6.31 (*ca.* 0.2 H, s, ArOCH_3 in the other, less soluble, stereoisomer).

Reaction of 4,4′-*Biflav*-2-*ene with Methanol in the Presence of Anhydrous Aluminium Trichloride.*—A stirred mixture of 4,4′-biflav-2-ene (500 mg), dioxane (40 ml), methanol (40 ml), and powdered anhydrous aluminium trichloride (*ca.* 100 mg) was kept at room temperature for 24 h when t.l.c. indicated that no starting material remained, and that two major products had formed. Ether (200 ml) was added, and the solution washed with 10% aqueous sodium hydroxide (2 × 100 ml) and water (100 ml), and dried. After removal of the solvent, the products were separated by p.l.c. [2 × 100 cm plates eluted (× 4) with benzene–petroleum, 25:75 v/v]. The higher running band gave a solid which separated from methanol yielding exo-6,6a-trans-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**6**) as prisms (220 mg), m.p. 187.5—189.5 °C (Found: C, 83.5; H, 6.0. $C_{31}H_{26}O_3$ requires C, 83.4; H, 5.9%); *m/z* (110 °C) 446 (M^+, 6.5), 207 (100), 414 (99), 105 (55), 121 (45), and 415 (40); $\nu_{max.}$ 1 485, 1 055, 700, and 1 035 cm^{-1}. Spin decoupling (90 MHz instrument) gave the following results.

Irradiation at τ 5.87 (13a-H resonance) causes: (*a*) collapse of doublet at τ 6.37 into a broad singlet with shoulder (removal of $J_{6a,13a}$); (*b*) slight sharpening of the doublet at τ 6.67 (removal of $J_{13,13a}$); (*c*) sharpening of the doublet at τ 8.22 (removal of $J_{14,13a}$).

Irradiation at τ 6.67 (13-H resonance) causes: (*a*) slight sharpening of the doublet at τ 5.87 (removal of $J_{13,13a}$); (*b*) no measurable narrowing of the doublet at τ 6.37 ($J_{6a,13} = 0$); (*c*) collapse of the quartet at τ 7.51 into a doublet, *J* 12.0 (removal of $J_{13,14}$).

Irradiation at τ 8.22 (14-H resonance) causes: (*a*) sharpening of the doublet at τ 5.87 (removal of $J_{14,13a}$); (*b*) sharpening of the doublet at τ 6.37 (removal of $J_{14,6a}$); (*c*) a minute narrowing of the doublet at τ 6.67 (removal of $J_{13,14}$); (*d*) collapse of the quartet at τ 7.51 owing to removal of $J_{14,14}$ (the resulting doublet is completely obscured by the OCH_3 singlet).

Maximum *J* values estimated from narrowing of signals at half height are: $J_{14,6a}$ *ca.* 1.3, $J_{13,14}$ *ca.* 0, $J_{14,13a}$ *ca.* 1.5, $J_{6a,13}$ *ca.* 0, $J_{13,13a}$ *ca.* 0.7. The band of lower R_F gave a solid which separated from methanol yielding endo-6,6a-trans-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**7**) as needles (137 mg), m.p. 192.5—196 °C (Found: C, 83.2; H, 5.8. $C_{31}H_{26}O_3$ requires C, 83.4; H, 5.9%); *m/z* (125 °C) 446 (M^+, 22), 207 (100), 414 (37.5), 208 (25), 239 (24), and 77 (23); $\nu_{max.}$ 1 141, 705, 1 490, and 1 031 cm^{-1}. Strong bands at 1 075 and 1 091 cm^{-1} were also observed; these are not present in the i.r. spectrum of the *exo*-stereoisomer (**6**). Spin decoupling (90 MHz instrument) gave the following results.

Irradiation at τ 6.70 (13-H resonance) causes: (*a*) collapse of the quartet at τ 5.85 into a doublet, *J* 12.0 (removal of $J_{13,13a}$); (*b*) collapse of the quartet centred at τ 7.41 to a doublet, *J* 12.5 (removal of $J_{13,14}$); (*c*) slight narrowing of the doublet at τ 7.83 (removal of $J_{13,14}$ *ca.* 0.6).

The *endo* stereoisomer (**7**) is dimorphic. A second recrystallisation from methanol gave the product as well formed crystals, some of which were needles, m.p. 195—196 °C, and some of which were cubes, m.p. 193—196.5 °C. The two forms were separated by hand picking, and found to have identical n.m.r. spectra.

Reaction of 4,4′-*Dimethoxy*-4,4′-*biflav*-2-*ene with Methanol in the Presence of Anhydrous Aluminium Trichloride.*—To a suspension of 4,4′-dimethoxy-4,4′-biflav-2-ene (572 mg) in dioxane (50 ml) and methanol (50 ml) was added powdered anhydrous aluminium trichloride (*ca.* 50 mg). The mixture was stirred until the solid dissolved (2.25 h), when t.l.c. indicated that no starting material remained, and that two products had been formed. The mixture was diluted with ether (400 ml), washed with 10% aqueous sodium hydroxide (2 × 200 ml) followed by water (4 × 200 ml), and then dried. After removal of the solvent, the products were separated by p.l.c. [2 × 100 cm. plates eluted (× 3) with benzene–petroleum, 20:80 v/v]. The band of higher R_F gave a solid which was recrystallised from methanol yielding exo-6,6a-trans-6-*methoxy*-6,7-*bis*(p-*methoxyphenyl*)-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**8**) as prisms (266 mg), m.p. 164—172 °C (decomp.) (Found: C, 78.0; H, 5.7. $C_{33}H_{30}O_5$ requires C, 78.2; H, 6.0%); *m/z* (140 °C) 506 (M^+, 14), 474 (100), 237 (79), 135 (65), 475 (40), and 238 (24); $\nu_{max.}$ (Nujol); 763, 1 239, 831, and 1 251 cm^{-1}.

The band of lower R_F gave a solid which was recrystallised from methanol yielding endo-6,6a-trans-6-*methoxy*-6,7-*bis*(p-*methoxyphenyl*)-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]-*benzopyrano*[3,4-c][1]*benzoxepin* (**9**) as needles (141 mg), m.p. 178—185 °C (decomp.) (Found: C, 78.4; H, 6.0%); *m/z* (140 °C) 506 (M^+, 7), 474 (100), 237 (70), 475 (39), 238 (34), and 194 (18); $\nu_{max.}$ (Nujol) 1 248, 1 258, 830, and 759 cm^{-1}.

exo-6,6a-trans-6-*Ethoxy*-6,7-*bis*(p-*methoxyphenyl*)-6a,7,13,-13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**16**).—*exo*-6,6a-*trans*-6-Methoxy-6,7-bis(*p*-methoxyphenyl)-6a,7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*]benzoxepin (**8**) (150 mg) in dioxane (13 ml) and ethanol (13 ml) was treated with anhydrous aluminium trichloride (*ca.* 20 mg). After 2.25 h the mixture was diluted with ether (200 ml), and washed with 10% aqueous sodium hydroxide (× 2), and water (× 5), and then dried. Removal of the solvent gave crystals which separated from ethanol (2 crops) yielding the 6-*ethoxy ketal* (**16**) as needles (78 mg), m.p. 134—136 °C (Found: C, 78.5; H, 6.3. $C_{34}H_{32}O_5$ requires C, 78.4; H, 6.2%); *m/z* (80 °C) 520 (M^+, 3), 135 (100), 474 (62.5), 237 (54), 475 (27), and 238 (20.5); $\nu_{max.}$ (Nujol): 1 235, 756, 830, and 1 038 cm^{-1}.

Reaction of 4,4′-*Biflav*-2-*ene with* N-*Bromosuccinimide in the Presence of Methanol.*—To a stirred solution of 4,4′-biflav-2-ene (500 mg) in dioxane (25 ml) and methanol (12.5 ml) was added *N*-bromosuccinimide (245 mg) in methanol (18 ml) during 3 min. After 20 min cyclohexene (0.5 ml) was added when t.l.c. indicated that no starting material remained and that two products had been formed. The solvent was evaporated and a solution of the residue in ether (250 ml) was washed with water (3 × 150 ml) and dried. After removal of the solvent, the

residue was transferred to a column of neutral alumina (170 g) made up in benzene–petroleum, 50:50 (v/v). Elution with benzene–petroleum mixtures of gradually increasing polarity (ultimately 70:30) afforded a complete separation of the two products. Evaporation of fractions containing the faster running compound gave a solid which on recrystallisation from methanol (2 crops) yielded exo-7,14-cis-6,6a-trans-14-*bromo*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*-[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**10**) as prisms (333 mg), m.p. 137—138 °C (decomp.) (Found: 70.8; H, 5.1; Br, 15.25. $C_{31}H_{25}BrO_3$ requires C, 70.8; H, 4.8; Br, 15.2%); *m/z* (140 °C) M^+ not observed, 412 (100), 413 (34), 411 (13), 414 (7), 77 (8.5), and 305 (6); $\nu_{max.}$ 1 491, 705, 1 065, and 1 458 cm^{-1}.

Evaporation of fractions containing the other product gave a solid which was recrystallised from methanol yielding endo-7,14-cis-6,6a-trans-14-*bromo*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,-13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**11**) as plates (235 mg), m.p. 143—163 °C (decomp.) (Found: C, 70.6; H, 4.7; Br, 15.25%); *m/z* (130 °C) 525 (M^+, 1), 207 (100), 413 (80), 414 (28), 208 (19), and 77 (10); $\nu_{max.}$ 709, 1 044, 1 408, and 1 467 cm^{-1}.

Reaction of 4,4′-*Biflav*-2-*ene with Bromine in Acetic Acid.*—To a stirred suspension of 4,4′-biflav-2-ene (414 mg) in acetic acid–acetic anhydride (9:1 v/v, 20 ml) containing anhydrous sodium acetate (1.33 g) was added bromine (168 mg) in acetic acid–acetic anhydride (10 ml) at 10—15 °C during 1 h. The mixture was stirred for 6.5 h, cyclohexene (0.2 ml) was added, and the reaction mixture kept at 0 °C overnight. The solvent was removed, the residue was taken up in ether, and the solution washed with saturated aqueous sodium hydrogen carbonate, and then dried. Evaporation gave a yellow oil which was separated by p.l.c. [2 × 100 cm plates eluted (×4) with benzene–petroleum 10:90 v/v and (×2) 20:80 v/v]. Removal of the major product in ether gave a solid which was recrystallised from methanol yielding exo-7,14-cis-14-*bromo*-6,7-*diphenyl*-13,13a-*dihydro*-7H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**17**) as prisms (141 mg), m.p. 135—145 °C (decomp.) (Found: C, 72.7; H, 4.2; Br, 16.5. $C_{30}H_{21}BrO_2$ requires C, 73.0; H, 4.3; Br, 16.2%); *m/z* (90 °C) 492/490 ($M^+ - 2$, 6.5), 412 (100), 413 (47), 411 (23), 414 (18.5); $\nu_{max.}$ 1 657 (C=C), 1 485, 1 225, and 699 cm^{-1}.

Unchanged 4,4′-biflav-2-ene was recovered by p.l.c. and obtained as a solid (22 mg). The n.m.r. spectrum of this material indicated that it consisted of only one stereoisomer (that responsible for the 'doublets' at τ 4.94 and 6.01). Recrystallisation from methanol gave needles (12 mg), m.p. 162—164 °C (decomp.) [lit.,[2] m.p. 167—168 °C (decomp.) for the pure stereoisomer]. A sample (5 mg) of the pure stereoisomer in dioxane (1 ml) and methanol (0.5 ml) was treated with *N*-bromosuccinimide (3 mg) in methanol (1 ml). After 10 min t.l.c. indicated that only one product had been formed with R_F identical with that of *exo*-7,14-*cis*-6,6a-*trans*-14-bromo-6-methoxy-6,7-diphenyl-6a,7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*][1]benzoxepin (**10**).

Reaction of exo-7,14-cis-14-*Bromo*-6,7-*diphenyl*-13,13a-*dihydro*-7H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**17**) *with Methanol in the Presence of Anhydrous Aluminium Trichloride.*—The unsaturated *exo*-14-bromo compound (**17**) (99 mg), dioxane (2 ml), methanol (2 ml), and powdered anhydrous aluminium chloride (*ca.* 100 mg) were kept at 20 °C for 16 days. The mixture was diluted with ether (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 × 30 ml) water, (3 × 30 ml), and then dried. The solvent was removed and the residue was purified by elution with benzene from a column of neutral alumina (50 g). Evaporation of solvent from the fractions containing the major product, followed by recrystallisation of the residue from methanol gave *exo*-7,14-*cis*-6,6a-*trans*-14-bromo-6-methoxy-6,7-diphenyl-6a,-7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*]-[1]benzoxepin (**10**) as needles (80 mg), m.p. 125—129 °C (decomp.). The n.m.r. spectrum of the product was identical with that of the *exo*-14-bromo compound (**10**) obtained previously.

Reaction of 4,4′-*Biflav*-2-*ene with* p-*Nitroperbenzoic Acid in the Presence of Methanol.*—*p*-Nitroperbenzoic acid (2.43 g) in dichloromethane (115 ml) was added during 35 min to a stirred solution of 4,4′-biflav-2-ene (2.0 g) in dichloromethane (35 ml) and methanol (75 ml). T.l.c. indicated that no starting material remained and that a mixture of three products had been formed. The solvent was evaporated, and a solution of the residue in chloroform (200 ml) was washed with saturated aqueous sodium hydrogen carbonate (3 × 150 ml) and then dried. The solvent was evaporated and the residue transferred to a column of neutral alumina (320 g) made up in benzene. Elution with benzene containing progressively more ethyl acetate (up to 15%) separated the two major products, but neither (particularly that of higher R_F) was freed from the minor component.

Evaporation of fractions containing the faster-running product yielded a solid which on recrystallisation from methanol afforded exo-7,14-cis-6,6a-trans-14-*hydroxy*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c]*benzoxepin* (**12**) as prisms (1.13 g), m.p. 176.5—178.5 °C [Found (on material dried *in vacuo* at 23 °C): C, 79.25, 79.4; H, 5.7, 6.1. $C_{31}H_{26}O_4 \cdot 0.5CH_3OH$ requires C, 79.05; H, 5.9%; Found (on material crushed, and dried *in vacuo* at 68 °C for 36 h); C, 80.8; H, 5.9. $C_{31}H_{26}O_4$ requires C, 80.5; H, 5.7%]; *m/z* (120 °C) 462 (M^+, 100), 430 (99), 207 (75), 431 (52), 223 (51), and 105 (42); $\nu_{max.}$ 3 590 (OH) 1 050, 1 483, and 700 cm^{-1}.

Evaporation of fractions containing the slower-running component gave a gum which was recrystallised from methanol (2 crops) yielding endo-7,14-cis-6,6a-trans-14-*hydroxy*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**13**) as needles (480 mg), m.p. 109.5—112 °C [Found (on material dried *in vacuo* at room temperature for 2 days): C, 78.95; H, 5.7. $C_{31}H_{26}O_4 \cdot 0.5CH_3OH$ requires C, 79.05; H, 5.9%; Found (on material crushed, and dried *in vacuo* at 45—50 °C for 24 h, m.p. 109.5—112 °C): C, 79.1; H, 6.2%; Found (on material dried in air for 2.7 years, m.p. 180—181 °C): C, 80.25; H, 5.9. $C_{31}H_{26}O_4$ requires C, 80.5; H, 5.7%], *m/z* (125 °C) 462 (M^+, 60), 207 (100), 223 (50), 239 (37), 105 (35), and 311 (18); $\nu_{max.}$ 3 580 (OH), 1 140, 701, and 1 111 cm^{-1}.

Tosylates of exo- *and* endo-7,14-cis-6,6a-trans-14-*Hydroxy*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*-[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**12**) *and* (**13**) *and Their Reaction with Lithium Aluminium Hydride.*—Treatment of a sample of the *exo*-7,14-*cis*-alcohol (231 mg) with toluene-*p*-sulphonyl chloride (381 mg) in dry pyridine (12 ml) for 48 h, followed by recrystallisation of the crude product from methanol, gave the exo-*tosylate* as prisms (251 mg), m.p. 109.5—119 °C (decomp.) (Found: C, 73.9; H, 5.2; S, 5.4. $C_{38}H_{32}O_6S$ requires C, 74.0; H, 5.2, S, 5.2%).

A sample of the tosylate (162 mg) was caused to react with lithium aluminium hydride (250 mg) in dry ether (25 ml). After 6 h, excess of lithium aluminium hydride was decomposed with wet ether and water and the products were extracted into ether. Removal of the solvent, followed by recrystallisation of the residue from methanol, gave back the *exo*-7,14-*cis*-alcohol (**12**) as prisms (56 mg), m.p. 170.5—177 °C. The n.m.r. spectrum of this material was identical with that of the *exo*-7,14-*cis*-alcohol (**12**) obtained previously. A further recrystallisation gave

prisms, m.p. 175—178 °C; mixed m.p. with an authentic sample of the *exo*-7,14-*cis*-alcohol 176—178.5 °C.

Treatment of a sample of the *endo*-7,14-*cis*-alcohol (226 mg) with toluene-*p*-sulphonyl chloride (380 mg) in dry pyridine (10 ml) for 5 days, followed by recrystallisation of the crude product from ethanol, afforded the endo-*tosylate* as prisms (217 mg), m.p. 149—152 °C (decomp.) (Found: C, 73.9; H, 5.2; S, 5.2. $C_{38}H_{32}O_6S$ requires C, 74.0; H, 5.2; S, 5.2%).

Treatment of the tosylate (157 mg) with lithium aluminium hydride (250 mg) in dry ether (20 ml) regenerated the *endo*-7,14-*cis*-alcohol (**13**) as needles (30 mg) (from methanol), m.p. 109.5—111.5 °C. A mixed m.p. with a sample of the *endo*-7,14-*cis*-alcohol previously obtained was 109—111 °C, and the i.r. spectra of the two samples were identical.

Reaction of 4,4′-*Dimethoxy*-4,4′-*biflav*-2-*ene with* p-*Nitroperbenzoic Acid in the Presence of Methanol.*—To a stirred suspension of 4,4′-dimethoxy-4,4′-biflav-2-ene (500 mg) in dichloromethane (35 ml) and methanol (75 ml) was added a solution of *p*-nitroperbenzoic acid (528 mg) in dichloromethane (115 ml) dropwise during 30 min. The solid dissolved during the addition, after which t.l.c. indicated that no starting material remained, and that two major products had been formed. The reaction mixture was worked up in the usual way, and the products were separated by p.l.c. [2 × 100 cm plates eluted (×4) with benzene–ethyl acetate 92:8 v/v]. Work-up (with ether) of the band of higher R_F gave a solid (294 mg) which was recrystallised from methanol yielding exo-7,14-cis-6,6a-trans-14-*hydroxy*-6-*methoxy*-6,7-*bis*(p-*methoxyphenyl*)-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**14**) as needles (181 mg), m.p. 115—125 °C (Found: C, 73.8; H, 6.2. $C_{33}H_{30}O_6 \cdot CH_3OH$ requires C, 73.6; H, 6.2%); *m/z* (130 °C) 522 (M^+, 36), 135 (100), 237 (81), 151 (41), 252 (25), and 194 (22); $\nu_{max.}$ 3 595 (OH) 1 180, 1 056, 1 115, and 1 488.

Work-up (with ether) of the band of lower R_F gave a solid (173 mg) which was recrystallised from methanol yielding endo-7,14-cis-6,6a-trans-14-*hydroxy*-6-*methoxy*-6,7-*di*(p-*methoxyphenyl*)-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**15**) as cubes (90 mg), m.p. 112—114 °C, which slowly became efflorescent [Found (on material dried *in vacuo* at 23 °C, and left in air for several days): C, 75.6; H, 5.7. $C_{33}H_{30}O_6$ requires C, 75.8; H, 5.8%]; *m/z* (130 °C) 522 (M^+, 40), 237 (100), 135 (45), 253 (35), 151 (26), and 269 (25); $\nu_{max.}$ 3 590 (OH), 1 181, 1 142, 1 464 cm^{-1}.

Treatment of a sample of the *exo*-alcohol (**14**) with toluene-*p*-sulphonyl chloride in pyridine for 3 days gave the exo-*tosylate* as prisms (from methanol) m.p. 88—92 °C with decomposition from 83 °C (Found: C, 71.1; H, 5.4; S, 4.4. $C_{40}H_{36}O_8S$ requires C, 71.0; H, 5.4; S, 4.7%).

Treatment of a sample of the *endo*-alcohol (**15**) with toluene-*p*-sulphonyl chloride in pyridine gave the endo-*tosylate* (after two recrystallisations from methanol) as needles, m.p. 163—174 °C (decomp.) (Found: C, 71.2; H, 5.3; S, 4.9%).

Reaction of endo-7,14-cis-6,6a-trans-14-*Hydroxy*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c]*benzoxepin* (**13**) *with Anhydrous Aluminium Chloride in Benzene.*—A solution of the *endo*-7,14-*cis*-alcohol (**13**) (200 mg) in AnalaR benzene (10 ml) was refluxed for 10.5 h when t.l.c. indicated that no reaction had occurred. After the solution had been cooled, a small quantity of powdered anhydrous aluminium chloride (*ca.* 30 mg) was added to it; the solution was then boiled for 10 min when t.l.c. indicated that only a trace of starting material remained and that a major product had been formed. Ether (200 ml) was added, and the solution was washed with 10% aqueous sodium hydroxide (3 × 150 ml) and water (150 ml) and then dried.

Removal of the solvent gave a gum which was dissolved in dichloromethane (5 ml) and decolourised by the addition of a small quantity of neutral alumina (*ca.* 100—200 mg). The solution was filtered, the solvent was evaporated, and the residue was recrystallised from methanol (2 crops) yielding endo-7,14-cis-6,7-*diphenyl*-14-*hydroxy*-13,13a-*dihydro*-7H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**18**) as prisms (82 mg), m.p. 189—192 °C (Found: C, 83.5; H, 5.0. $C_{30}H_{22}O_3$ requires C, 83.7; H, 5.15%); *m/z* (140 °C) 430 (M^+, 100), 412 (53), 295 (49), 323 (41), 77 (40), and 296 (31); $\nu_{max.}$(Nujol) 3 555 (OH), 1 678 (C=C), 758 and 696 cm^{-1}.

exo-6,6a-trans-6-*Methoxy*-14-*oxo*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**19**).—To a stirred suspension of the chromium trioxide–pyridine complex[5] from chromium trioxide (4.0 g) in pyridine (40 ml) was added powdered *exo*-7,14-*cis*-6,6a-*trans*-14-hydroxy-6-methoxy-6a,7,13,13a-tetrahydro-6*H*-7,13-methano-[1]benzopyrano[3,4-*c*][1]benzoxepin (**12**) (1.0 g) at 22 °C. The mixture was stirred for 1 h and kept for 1 month when t.l.c. indicated that no starting material remained. The mixture was added dropwise to water (1 l) and then extracted with ether (3 × 700 ml). The combined extracts were dried and evaporated and the product was purified on a column of neutral alumina (15 g, 10% deactivated) eluted with benzene. Recrystallisation from methanol yielded the exo-*ketone* (**19**) as an amorphous solid (970 mg) without a distinct m.p. (*ca.* 168—178 °C) (Found: C, 80.7; H, 5.2. $C_{31}H_{24}O_4$ requires C, 80.85; H, 5.25%); *m/z* (120 °C) 460 (M^+, 45), 207 (100), 105 (85), 194 (65), 428 (47), and 221 (38); $\nu_{max.}(CHCl_3)$ 1 777 (CO), 1 215br, 1 013, and 702 cm^{-1}.

The *exo*-ketone (105 mg) with hydroxylamine hydrochloride (80 mg) in dry pyridine (2 ml) and ethanol (2 ml) for 5 weeks gave the *oxime* (78 mg), as cubes (from methanol), m.p. 233—236 °C (decomp.) (Found: C, 78.6; H, 5.5; N, 3.1. $C_{31}H_{25}NO_4$ requires C, 78.3; H, 5.3; N, 2.95%); *m/z* (95 °C) 475 (M^+, 17) and 105 (100).

Reduction of exo-6,6a-trans-6-*Methoxy*-14-*oxo*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**19**) *with Lithium Aluminium Hydride.*—To a stirred solution of lithium aluminium hydride (52 mg) in dry ether (10 ml) was added the solid *exo*-ketone (**19**) (123 mg) at 0 °C. After 1.75 h, t.l.c. indicated that no starting material remained, and that a major product had been formed. Excess of lithium aluminium hydride was decomposed avoiding the use of acid, and the products were extracted into ether. Evaporation of the solvent gave a solid which was purified by p.l.c. [1 × 100 cm plate eluted (×2) with benzene–ethyl acetate, 95:5 v/v]. Work-up gave the major product as a gum (98 mg) which was recrystallised from redistilled, acid-free methanol yielding exo-7,14-trans-6,6a-trans-14-*hydroxy*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin*(**20**) as cubes (73 mg), m.p. 178.5—180.5 °C (Found: C, 80.5; H, 5.5. $C_{31}H_{26}O_4$ requires C, 80.5; H, 5.7%); *m/z* (50 °C) 462 (M^+, 7), 413 (100), 412 (70), 414 (40), 207 (24), and 105 (22); $\nu_{max.}$ 3 570 (OH), 1 478, 1 139, 1 042, and 696 cm^{-1}.

In another experiment, the product (**20**) partially cyclised to the epoxy compound (**21**) (see below) when recrystallised from technical methanol which had not been distilled from anhydrous potassium carbonate.

Cyclisation of exo-7,14-trans-6,6a-trans-14-*Hydroxy*-6-*methoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]-*benzopyrano*[3,4-c][1]*benzoxepin* (**20**).—0.2M-Hydrochloric acid (0.5 ml) was added to a solution of the *exo*-7,14-*trans*-alcohol (**20**) (61 mg) in dioxane (5 ml), and the solution was allowed to stand for 14 h when t.l.c. indicated that no starting

material remained and that a major product had been formed. The mixture was diluted with ether (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 × 30 ml) and then dried. Removal of the solvent gave a solid which was recrystallised from methanol affording 6,14-*epoxy*-6,7-*diphenyl*-6a,7,13,13a-*tetrahydro*-6H-7,13-*methano*[1]*benzopyrano*[3,4-c][1]*benzoxepin* (**21**) as needles (43 mg), m.p. 272—273 °C (Found: C, 83.8; H, 4.95. $C_{30}H_{22}O_3$ requires C, 83.7; H, 5.15%); *m/z* (120 °C) 430 (M^+, 20), 207 (100), 105, (43), 208 (20), 194 (15), and 77 (15); $\nu_{max.}$(Nujol) 1 262, 1 237, 961, and 760 (doublet) cm^{-1}.

Trimers from the Reaction of Flavylium Perchlorate with 4,4′-Biflav-2-ene in the Presence of Alcohols.—The 'methoxy-trimer', probable gross structure (**23**). To a stirred solution of flavylium perchlorate (413 mg) in acetonitrile (12.5 ml) and methanol (12.5 ml) was added a solution of 4,4′-*biflav*-2-*ene* (500 mg consisting, approximately, of a 50:50 mixture of stereoisomers) in dioxane (25 ml) during 4 min. Shortly after the end of the addition a solid separated. After 1 h, anhydrous sodium acetate (440 mg) in methanol (25 ml) was added dropwise during 5 min causing the reaction mixture to become colourless, and more precipitate to be formed. The mixture was stirred for a further 12 h and allowed to stand for 18 h, before the product was collected, washed with methanol, and dried *in vacuo*, yielding the crude '*methoxy-trimer*' (156 mg) as a powder, m.p. 247—248.5 °C (decomp.). A sample was recrystallised from chloroform–methanol yielding very small needles, m.p. 247—251 °C (decomp.) (Found: C, 84.4; H, 5.4. $C_{46}H_{36}O_4$ requires C, 84.65; H, 5.6%); τ (sat. $CDCl_3$) 2.83—3.87 (*ca.* 27 H, m, aromatics), 5.41 (1 H, d, 3′-H), 6.12 (1 H, dd, 13a-H), 6.38 (1 H, d, 6a-H), 6.60 (1 H, poorly defined q, 4′-H?), 7.02—7.17 (2 H, complex, 13-H and 14-H?), 7.49 (3 H, s, OCH_3), $J_{6a,13a}$ 12.0, $J_{13,13a}$ 5.0, and $J_{3',4'}$ 6.5; *m/z* (180 °C) 652 (M^+, 1.5), 207 (100), 208 (20), 178 (7), 105 (5), and 121 (4); $\nu_{max.}$(Nujol) 1 245, 765, 750, and 698 cm^{-1}.

Examination of the reaction mixture by t.l.c. after crude trimer had been filtered off, showed that at least six other products had been formed. The solvent was evaporated, and sodium acetate was removed by washing a suspension of the residue in ether with water. The organic layer was dried and evaporated to yield a gum. Three major components were separated by p.l.c. [2 × 100 cm plates eluted (×4) with benzene–petroleum, 40:60 v/v]. Work-up (with ether) of the fastest running band gave a solid (124 mg), the n.m.r. spectrum of which indicated that a high proportion of *exo*-6,6a-*trans*-6-methoxy-6,7-diphenyl-6a,7,13,13a-tetrahydro-6*H*-7,13-methano[1]benzopyrano[3,4-*c*][1]benzoxepin (**6**) was present. Two recrystallisations from methanol gave the product as needles (37 mg), m.p. and mixed m.p. with (**6**) 187.5—190 °C. No further pure, crystalline products were isolated from this reaction.

The 'ethoxy-trimer', probable gross structure (**24**). To a stirred solution of flavylium perchlorate (413 mg) in acetonitrile (12.5 ml) and ethanol (12.5 ml) was added a solution of 4,4′-biflav-2-ene (500 mg consisting of an approximately 50:50 mixture of stereoisomers) in dioxane (25 ml) during 5 min and, after *ca.* 1 h a solid began to separate. After 27 h, the crude product was collected, washed with ethanol, and dried *in vacuo* yielding a powder (76 mg), m.p. 254—257 °C (decomp.). A sample of the crude product was recrystallised from chloroform–methanol giving the '*ethoxy-trimer*' as fluffy needles, m.p. 251.5—255.5 °C after decomposition from *ca.* 240 °C (Found: C, 84.45; H, 5.9. $C_{47}H_{38}O_4$ requires C, 84.7; H, 5.7%); τ (sat. $CDCl_3$) 2.20—3.86 (*ca.* 27 H, m, aromatics), 5.40 (1 H, d, 3′-H), 6.10 (1 H, dd, 13a-H), 6.38 (*ca.* 1 H, d, 6a-H), 6.60 (1 H, dd, 4′-H), 7.08—7.30 (4 H, 14-H and 13-H?, plus OCH_2CH_3), 9.45 (3 H, t, *J* 7. OCH_2CH_3), $J_{6a,13a}$ 12.0, $J_{13,13a}$ 4.0, $J_{3',4'}$ 6.5; *m/z* (500 °C MS9) 666 (M^+, 16), 207 (100), 208 (20), 413 (14), 414 (5), and 105 (5); $\nu_{max.}$(Nujol) 1 662 (C=C), 1 251, 768, and 762 cm^{-1}.

Reaction of the 'methoxy-trimer' with p-*nitroperbenzoic acid in the presence of methanol.* To a stirred suspension of the crude 'methoxy-trimer' (250 mg) in dichloromethane (15 ml), and methanol (35 ml) was added *p*-nitroperbenzoic acid (132 mg) in dichloromethane (55 ml) dropwise during 15 min. After 40 min all the solid had dissolved. The mixture was kept for 20 h when t.l.c. indicated that no starting material remained; multiple elution revealed two products.

The solvents were evaporated, the residue was dissolved in dichloromethane (200 ml), and the solution was washed with saturated aqueous sodium hydrogen carbonate (4 × 150 ml) and dried. Evaporation gave a solid (244 mg), the complex n.m.r. spectrum of which contained four three-proton singlets at τ 7.49, 7.46 (OCH_3 at C-6 in each diastereoisomer), 6.96 and 6.90 (OCH_3 at C-2′ in each diastereoisomer), and two 1 H doublets at τ 4.36 and 4.44 (C-3′ in each diastereoisomer).

Treatment of the above mixture (175 mg) with acetic anhydride (2 ml) in pyridine (4.5 ml) for 4 days gave, after work-up, a solid (161 mg) which was found by t.l.c. with multiple elution to consist of two components which were separated by p.l.c. [2 × 20 cm plates eluted (×4) with ether–light petroleum b.p. 40—60 °C 3:97 v/v, (×5) with 5:95 v/v, and (×3) with 10:90 v/v]. The band of higher R_F gave a gum (61 mg) which was recrystallised from methanol (2 crops) yielding a *trimeric acetoxy-dimethoxyflavan*, probable gross structure (**25**) as efflorescent prisms (42 mg), m.p. 222—224.5 °C (Found: C, 79.2; H, 5.85. $C_{49}H_{42}O_7$ requires C, 79.2; H, 5.7%); τ 2.61—3.90 (*ca.* 27 H, m, aromatics), 5.27 (1 H, d, 3′-H), 5.95—6.14 (2 H, m, 13-H and 13a-H), 6.26 (1 H, d, 6a-H), 6.77—6.90 (4 H, s at 6.90, OCH_3 at C-2′, partially obscuring a multiplet, 14-H), 7.06 and 7.18 (1 H together, 2 doublets, 4′-H), 7.48 (3 H, s, OCH_3 at C-6), 8.83 (3 H, s, $OCOCH_3$), $J_{13,14}$ 4.0, $J_{6a,13a}$ 12.0, $J_{3',4'}$ 2.0, $J_{14,4'}$ and $J_{13,13a}$ cannot be obtained; *m/z* (325 °C, MS9) 742 (M^+, 3.5), 413 (100), 207 (68), 680 (50), 411 (37), and 414 (35); $\nu_{max.}$($CHCl_3$) 1 741 (CO), 1 489, 1 242, and 1 035 cm^{-1}.

The band of lower R_F gave a gum (79 mg) which was recrystallised from methanol yielding a *trimeric acetoxy-dimethoxyflavan*, probable gross structure (**25**) as prisms (72 mg), m.p. 149—152 °C (Found: C, 78.9; H, 5.7. $C_{49}H_{42}O_7$ requires C, 79.2; H, 5.7%); τ 2.21—4.40 (*ca.* 27 H, m, aromatics), 5.54 (1 H, d, 3′-H), 6.26 (1 H, dd, 13a-H), 6.68 (1 H, d, 6a-H), 7.00—7.10 (4 H, s, at 7.10, OCH_3 at C-6, superimposed on 14-H and part of 4′-H), 8.40 (3 H, s, $OCOCH_3$), $J_{13,14}$ 4.0, $J_{6a,13a}$ 12.0, $J_{13,13a}$ 6.0, $J_{3',4'}$ 2.5, $J_{14,4'}$ not obtainable; *m/z* (110 °C, MS9) 742 (M^+, 25), 207 (100), 413 (37.5), 651 (24), 105 (17.5) 120 (14), 414 (13), $\nu_{max.}$($CHCl_3$) 1 739 (CO), 1 489, 1 240, 1 012 cm^{-1}.

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