The Biosynthesis of Fungal Metabolites. Part V.[1] Structure of Variecoxanthones A, B, and C, Metabolites of *Aspergillus variecolor*; Conversion of Variecoxanthone A into (±)-De-*C*-prenylepishamixanthone

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Variecoxanthones A, B, and C, metabolites of a variant strain of *Aspergillus variecolor* are shown to be 8-hydroxy-1-hydroxymethyl-3-methyl-2-(3-methylbut-2-enyloxy)- (IV), 8-hydroxy-1-hydroxymethyl-3-methyl-5-(3-methylbut-2-enyl)-2-(3-methylbut-2-enyloxy)- (V), and 5-(2,3-epoxy-3-methylbutyl)-8-hydroxy-1-hydroxymethyl-2-(3-methylbut-2-enyloxy)-xanthone (VI), respectively. These structures were established by detailed spectroscopic comparisons with shamixanthone (I) and tajixanthone (II) and by hydrogenolysis of variecoxanthone A to 2,8-dihydroxy-1,3-dimethylxanthone (X). Acid-catalysed cyclisation of the variecoxanthone-A-derived compound, 1-formyl-8-hydroxy-3-methyl-2-(3-methylbut-2-enyloxy)xanthone (XI), gave 1,2-*cis*-2,3-dihydro-1,11-dihydroxy-2-isopropenyl-5-methylpyrano[3,2-*a*]xanthen-12(1*H*)-one (XIII). The *cis*-relationship of the 1- and 2-substituents in this compound and the corresponding *trans*-relationship in shamixanthone are confirmed by comparison of ^{1}H couplings in the hydrogenated derivatives (XIV) and (III), respectively with those in the synthetic 1,2-*cis*- and 1,2-*trans*-2,3-dihydro-1-hydroxy-2-isopropyl-7-methyl-1*H*-benzopyrans (XVI) and (XVII), respectively, prepared by reduction of the corresponding chromone (XVIII) with sodium borohydride. The relative stereochemistry of compounds (XVI) and (XVII) was determined by lanthanide-induced shift studies on their respective ^{13}C and ^{1}H n.m.r. spectra. The mechanistic and biogenetic implications of the acid-catalysed cyclisation of compound (XI) are discussed.

We have recently [1,2] established the structures of shamixanthone (I) and tajixanthone (II), metabolites of *Aspergillus variecolor* (IMI 112543), and have shown by ^{13}C-labelling studies that these compounds probably arise by oxidative fission of a polyketide-derived anthrone precursor with introduction of two prenyl residues from mevalonate. We have also suggested that these metabolites, together with arugosins A, B, and C,[3,4] constitute a biogenetically related group. As part of a search for related compounds we have investigated a number of variant strains of *A. variecolor* and from one, CBS 135·55, we have isolated three new compounds: variecoxanthones A ($C_{20}H_{20}O_5$), B ($C_{25}H_{28}O_5$), and C ($C_{25}H_{28}O_6$), together with shamixanthone (I), arugosins A and B, and sterigmatocystin.[5] We now report investigations leading to assignment of the structures (IV)—(VI), respectively, for the new compounds respectively.†

The spectroscopic properties of variecoxanthones A—C reveal their structural relationships to each other and to shamixanthone and tajixanthone. Thus, the presence of a *peri*-hydroxyxanthone chromophore is indicated by the closely similar u.v. spectra, *e.g.* (IV) has $\lambda_{max.}$ 374, 292, and 260 nm (ε 5500, 11,100, and 26,000), i.r. bands at 3500—3100 cm^{-1}, and an n.m.r. singlet at τ −2·6 to −2·9, showing exchange with D_2O. Furthermore all the compounds give typical iron(III) chelate colourations.

Comparisons between the ^{1}H n.m.r. spectra of compounds (IV)—(VI) (Table 1) and those of shamixanthone (I) and tajixanthone (II) [*cf.* the following paper (Table 1)] enable structural assignments to be made as follows. (*a*) All compounds (IV)—(VI) show an aromatic methyl signal at τ *ca.* 7·6, coupled to an aromatic proton signal at τ *ca.* 2·8 (*J* 0·9 Hz) which has no further coupling. (*b*) The signals due to the dihydropyran residue in shamixanthone and tajixanthone are replaced in the three new compounds by signals due to an *O*-prenyl residue and a benzyl alcohol group in which the hydroxylic proton is coupled to the methylene protons (*J* 8 Hz). (*c*) Variecoxanthone B (V) has signals due to an aromatic prenyl substituent and variecoxanthone C (VI) shows signals for the corresponding epoxide, whereas variecoxanthone A (IV) lacks this C_5 residue [*cf.* 14-, 15-, 17-, and 18-protons in (V) and (VI)]. Furthermore, whereas the

Table 1

^{1}H Chemical shifts of principal metabolites and their transformation products (τ values for solutions in $CDCl_3$)

Compound	(IV)	(V)	(VI)	(X) †	(XIII)
1-OH *	−2·64	−2·86	−2·62	−3·06	−2·59
2-H	3·22	3·23	3·23	3·31	3·31
3-H	2·42	2·59	2·50	2·38	2·52
4-H	3·12			3·10	3·21
5-H	2·71	2·82	2·69	2·78	2·85
14-H		6·66	6·97		
15-H		4·71	6·97		
17-H's		8·26	8·56		
18-H's		8·26	8·67		
19-H's	5·58	5·60	5·58		5·55, 5·72
20-H	4·42	4·43	4·43		7·52
22-H's	8·20	8·20	8·20		5·25, 4·99
23-H's	8·29	8·29	8·29		8·03
24-H's	7·56	7·59	7·55	7·67	7·69
25-H	4·95	4·98	4·94	7·30	4·58
25-OH *	5·60	5·60	5·60		*ca.* 5·5
7-OH *				1·33	

* Exchangeable in D_2O. † In dimethyl sulphoxide.

† The numbering of the carbon atoms illustrated in structures (IV)—(VI) accords with the system used previously for shamixanthone,[3] tajixanthone,[2] and arugosin C.[4]

[1] Part IV, J. S. E. Holker, R. D. Lapper, and T. J. Simpson, *J.C.S. Perkin I*, 1974, 2135.

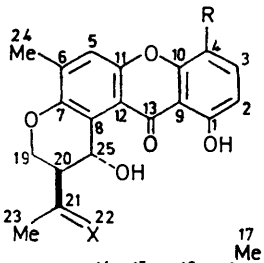
[2] K. K. Chexal, C. Fouweather, J. S. E. Holker, T. J. Simpson, and K. Young, *J.C.S. Perkin I*, 1974, 1584.

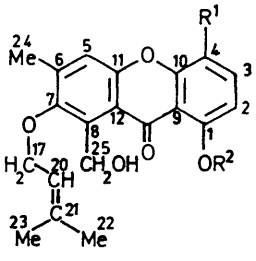
[3] J. A. Ballantine, D. J. Francis, C. H. Hassall, and J. L. C. Wright, *J. Chem. Soc.* (*C*), 1970, 1175.

[4] J. A. Ballantine, V. Ferrito, C. H. Hassall, and M. L. Jenkins, *J.C.S. Perkin I*, 1973, 1825.

[5] E. Bullock, J. C. Roberts, and J. G. Underwood, *J. Chem. Soc.*, 1962, 4179.

2- and 3-protons in (V) and (VI) are an *ortho*-coupled pair (J 9 Hz), the 2-proton in (IV) shows *ortho*- and *meta*-couplings (J 9 and 1 Hz), the 3-proton shows two *ortho*-couplings (J 9 and 9 Hz), and the additional 4-proton shows *ortho*- and *meta*-couplings (J 9 and 1 Hz).





(I) $R = CH_2{:}CH{=}C(Me)Me$, $X = CH_2$

(II) $R = CH_2{:}CH{-}C(Me)Me$ (epoxide), $X = CH_2$

(III) $R = CH_2{:}CH_2{:}CHMe_2$, $X = H, Me$

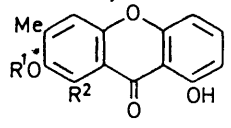
(IV) $R^1 = R^2 = H$

(V) $R^1 = CH_2{:}CH{=}C(Me)Me$, $R^2 = H$

(VI) $R^1 = CH_2{:}CH{-}C(Me)Me$ (epoxide), $R^2 = H$

(VII) $R^1 = CH_2{\cdot}CH{=}CMe_2$, $R^2 = Me$

(VIII) $R^1 = CH_2{\cdot}CH{-}CMe_2$ (epoxide), $R^2 = Me$

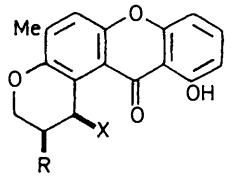


(IX) $R^1 = CH_2{:}CH_2{\cdot}CHMe_2$, $R^2 = Me$

(X) $R^1 = H$, $R^2 = Me$

(XI) $R^1 = CH_2{:}CH{=}CMe_2$, $R^2 = CHO$

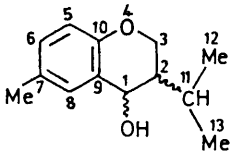
(XII) $R^1 = CH_2{\cdot}CH{=}CMe_2$, $R^2 = H$



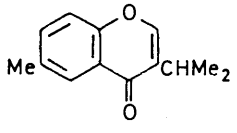
(XIII) $R = CMe{=}CH_2$, $X = OH$

(XIV) $R = CHMe_2$, $X = OH$

(XV) $R = CHMe_2$, $X = H$



(XVI) *cis* (XVII) *trans*



(XVIII)

Hydrogenolysis of variecoxanthone A (IV) over palladium–carbon in ethyl acetate gave the dihydro-deoxy-derivative (IX) and the de-*O*-prenyl-deoxy-derivative (X). The structure of compound (X) was confirmed by comparison with 2,8-dihydroxy-1,3-dimethylxanthone prepared by condensation of 2,6-dihydroxybenzoic acid and 2,6-dimethylhydroquinone with phosphoric trichloride and zinc chloride.[6] The formation of compound (X) establishes the structure of variecoxanthone A apart from the positions of the hydroxymethyl and *O*-prenyl groups, both of which are removed in the transformation. However, since variecoxanthone A has been shown to be a *peri*-hydroxyxanthone, the *O*-prenyl group must be located as shown in structure (IV).

Oxidation of variecoxanthone A with either Jones [7] or Collins [8] reagent gave the aldehyde (XI) [τ −0·69 (CHO)], which was decarbonylated with chlorotristriphenylphosphinerhodium(I) in benzene [9] to give compound (XII). The introduced aromatic proton (τ 2·78) in this compound shows no coupling greater than *ca.* 0·3 Hz, which represents the spectral resolution obtained. The absence of an *ortho*-coupling is consistent with structure (XII) and hence the hydroxymethyl substituent in variecoxanthone A must be located as shown in structure (IV).

The positions of the *C*-prenyl residue in variecoxanthone B (V) and the corresponding epoxide in variecoxanthone C (VI) have been confirmed by the methods previously described for shamixanthone (I) and tajixanthone (II), respectively.[2] Thus, the absence of an $M^+ - 56$ ion in the mass spectrum of the metabolite (V) and the chemical shift differences of the methoxy protons in the derived methyl ethers (VII) and (VIII) for solutions in C_6D_6 and $CDCl_3$ [$\tau(C_6D_6) - \tau(CDCl_3)$ 0·45 and 0·49 p.p.m., respectively] are consistent with the structures.

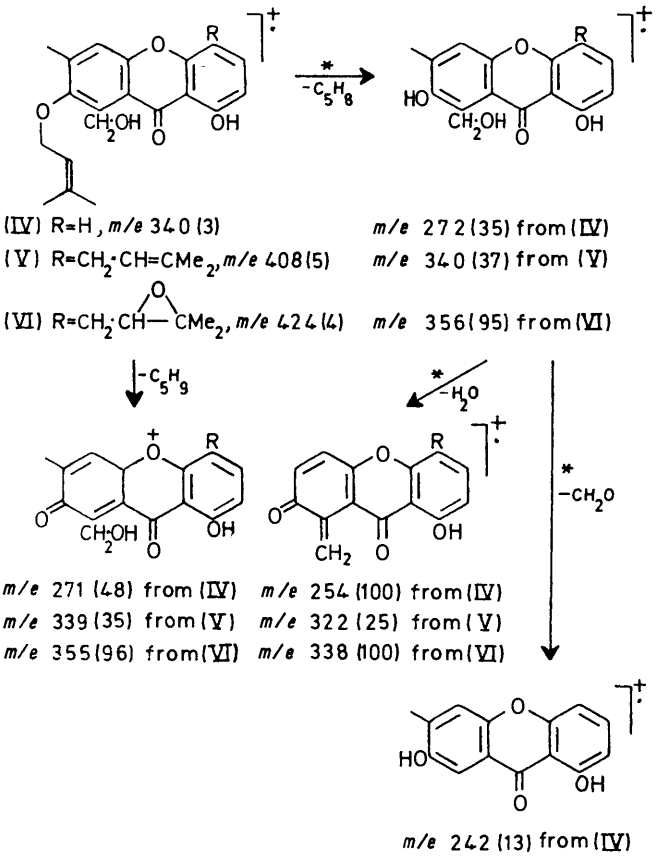
The principal mass spectral fragmentation patterns of the variecoxanthones, summarised in the Scheme, accord with the proposed structures. In each case the initial loss of C_5H_8 from the *O*-prenyl residue is followed by loss of water. In variecoxanthone A there is also a competitive loss of CH_2O from the initial fragment. In variecoxanthones B and C subsequent fragmentations of the ions *m/e* 322 and 338, respectively, parallel those previously described for shamixanthone and tajixanthone, respectively.[2]

Variecoxanthone C is chiral, having an asymmetric centre at C-15, whereas variecoxanthones A and B are achiral. Unfortunately, the small amounts of variecoxanthone C available for investigation have precluded determination of the specific rotation and the absolute configuration at C-15.

A reaction of the aldehyde (XI) was of particular interest. Under very mild acidic conditions (0·002M-HCl in $CHCl_3$) it was isomerised at room temperature to (±)-de-*C*-prenylepishamixanthone (XIII). The presence of a substituted dihydrobenzopyran ring in this compound was indicated by its ^1H n.m.r. spectrum, which showed chemical shifts closely similar to those of the corresponding ring in shamixanthone, *cf.* protons 19—23 and 25 and 25-OH for compounds (XIII) and (I) in Table 1. Furthermore, compound (XIII) did not show signals corresponding to those of the *O*-prenyl and aldehyde groups in the precursor (XI). Hydrogenation of compound (XIII) over palladium–carbon in ethyl acetate gave a mixture of the dihydro-derivative (XIV) and the dihydro-deoxy-derivative (XV). This closely parallels the hydrogenation of shamixanthone [2] and pro-

[6] J. Stöckigt, Ph.D. Thesis, Munster, 1971.
[7] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2555.
[8] J. C. Collins, *Tetrahedron Letters*, 1968, 3363.
[9] Y. Shimizu, H. Mistuhashi, and E. Caspi, *Tetrahedron Letters*, 1966, 4113.

vides confirmation for the similar residue in both compounds. However, despite similar chemical shift values, significant differences in *vic*-couplings are apparent in the



SCHEME Principal mass spectral fragmentations of variecoxanthones A—C [(IV)—(VI)]; relative abundances in parentheses. Metastable ions are indicated by asterisks.

n.m.r. spectra of the dihydro-derivative (XIV) and tetrahydroshamixanthone (III) (Table 2). These must

TABLE 2

Chemical shifts and couplings of the dihydropyran residues in tetrahydroshamixanthone (III), *trans*-4-hydroxy-3-isopropylchroman (XVII), (±)-dihydrodeprenylepishamixanthone (XIV), and *cis*-4-hydroxy-3-isopropylchroman (XVI) (solutions in $CDCl_3$) (proton labelling as in Figure 1)

Compound:		(III)	(XVII)	(XIV)	(XVI)
τ Values	a	*ca.* 8·5	*ca.* 8·5	*ca.* 8·5	8·51
	b	*ca.* 8·5	*ca.* 8·5	*ca.* 8·0	8·22
	c	5·73	5·82	6·03	6·11
	d	5·61	5·92	5·63	5·83
	e	4·74	5·45	4·67	5·40
J/Hz	ab	?	?	?	9·7
	ac	2·1	2·4	11·9	11·9
	ad	3·0	4·6	3·5	3·5
	ae	2·8	3·9	3·5	2·6
	cd	11·0	11·3	10·4	10·8
	ce	1·0	0·9	1·4	1·4

be due to different relative configurations of the isopropyl and hydroxy-substituents in the two compounds, and since these have been assigned a *trans*-diaxial relationship in tetrahydroshamixanthone, they must be *cis*-related in (±)-dihydrodeprenylepishamixanthone (XIV).

In view of the structural and probable biogenetic significance of these stereochemical assignments it was decided to provide independent proof. Accordingly, the model compounds *cis*- and *trans*-3-isopropyl-6-methylchroman-4-ol, (XVI) and (XVII) respectively, were synthesised by reduction of the corresponding chromone (XVIII) with sodium borohydride, and separated by t.l.c. It is interesting that the proportions of the two isomers depended on the reduction conditions. Thus, in propan-2-ol at room temperature, the lower melting, less polar *cis*-isomer was formed as the principal product (*cis* : *trans*, 10 : 1), whereas in refluxing ethanol relatively more of the *trans*-isomer was formed (*cis* : *trans*, 9 : 4). Presumably this reflects the greater bulk of the propan-2-ol-solvated borohydride complex compared with the ethanol solvate, and the greater stereoselectivity of the former. The formation of the *cis*-isomer is then determined by approach of the reducing agent to the carbonyl group from the opposite side of the ring to the isopropyl group.

Studies of ^1H couplings (Table 2) and lanthanide-induced shifts (LIS) in the ^{13}C and ^1H n.m.r. spectra (Tables 3 and 4) confirmed the relative stereochemistry

TABLE 3

^{13}C Chemical shifts and LIS produced by $Eu(fod)_3$ [positive LIS are downfield; values quoted are the sum from three experiments with 1 : 20, 1 : 10, and 3 : 20 ratios of $Eu(fod)_3$ to compound]

	cis-Isomer (XVI)		*trans*-Isomer (XVII)	
Assignment	δ	LIS (p.p.m.)	δ	LIS (p.p.m.)
1	64·3	11·2	66·1	16·3
2	44·8	3·4	46·0	5·5
3	63·8	3·2	63·5	3·9
5	116·1	1·7	116·0	2·3
6	130·1	0·9	129·7	1·7
7 or 9	129·0	1·5	129·3	2·5
8	130·1	2·9	129·7	4·5
9 or 7	123·6	3·8	123·2	2·1
10	151·5	2·8	151·9	3·5
11	24·9	3·2	25·4	2·7
12 or 13	20·8	1·2	20·9	1·4
13 or 12	21·6	2·1	19·7	1·4
14	20·5	−0·7	20·3	0·5

and conformations of the two isomers (XVI) and (XVII) as shown in Figure 1. The small vicinal couplings, J_{ac}, J_{ad}, and J_{ae} in the *trans*-isomer are consistent with gauche conformations of the individual protons and hence a pseudodiaxial relationship of the isopropyl and hydroxy-substituents. In the *cis*-isomer the large vicinal couplings J_{ac} and small gauche coupling J_{ae} indicate anti- and gauche-conformations of the respective hydrogen atoms and hence a pseudoequatorial conformation of the isopropyl group. From the LIS studies it is clear that in both isomers the co-ordination site for the shift reagent, $Eu(fod)_3$, is the C-1 hydroxy-group, *i.e.* the largest shifts are observed at C-1 and H-1. The larger shifts in the atoms of the isopropyl group, *i.e.* 11, 12, and 13 of the *cis*-isomer, as compared with the *trans*-isomer, confirm the

gauche relationship of this group with the hydroxy-group in the former compound and the diaxial relationship in

TABLE 4

^{1}H Chemical shifts and LIS produced by Eu(fod)$_3$ [positive LIS are downfield; values quoted are the sum from three experiments containing 1 : 20, 1 : 10, and 1 : 5 ratios of Eu(fod)$_3$ to compound; assignments in parentheses refer to Figure 1]

	cis-Isomer (XVI)		*trans*-Isomer (XVII)	
Assignment	τ	LIS (p.p.m.)	τ	LIS (p.p.m.)
1(H_c)	5·40	3·31 *	5·45	4·68 *
2(H_a)	8·51	2·81	*ca.* 8·5	6·91
3(H_c)	6·11	4·14	5·82	6·03
3(H_d)	5·83	2·08	5·92	3·05
5	3·31	1·07	3·33	1·87
6	3·06	0·67	3·04	1·34
8	3·01	2·36	2·90	5·06
11(H_b)	8·22	4·22	*ca.* 8·5	3·34
12	8·99	1·71	{9·01	{1·09
13	8·89	1·27		
14	7·75	−0·22	7·74	0·42

* For 1 : 20 and 1 : 10 ratios only.

the latter. In further agreement, all the other atoms in the *cis*-isomer show smaller shifts than the corresponding ones in the *trans*-isomer owing to the greater steric hindrance of the hydroxy-group co-ordination site by the isopropyl group in the former compound.

The close correspondence in ^{1}H couplings between the *cis*-compound (XVI) and dihydrode-*C*-prenylepishamixanthone (XIV) and between the *trans*-compound (XVII) and tetrahydroshamixanthone (III) provides clear evidence for the stereochemical assignments and conformations of the compounds derived from the natural products.

The formation of the *cis*-product (XIII) from the *O*-prenyloxy-aldehyde (XI) under very mild acid-catalysed conditions could formally be regarded either as an electrophilic addition of the protonated aldehyde species

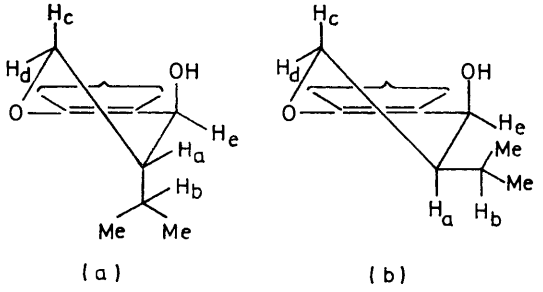


FIGURE 1 Conformations of the dihydrobenzopyran ring substituents in: (a) tetrahydroshamixanthone (III) and *trans*-4-hydroxy-3-isopropylchroman (XVII), and (b) (±)-dihydrodeprenylepishamixanthone (XIV) and *cis*-4-hydroxy-3-isopropylchroman (XVI)

or an acid-catalysed ' ene-reaction.' [10] Although analogous reactions betwene alkenes and carbonyl compounds are relatively well known [11-13] the detailed mechanisms do not appear to be clearly understood. However, in the present case the stereospecific formation of the *cis*-product (XIII) is difficult to rationalise on the basis of a mechanism involving electrophilic addition. It is far more likely that this is a synchronous ' ene-reaction ' involving a transition state of the type shown in Figure 2(A). The alternative transition state [Figure 2(B)],

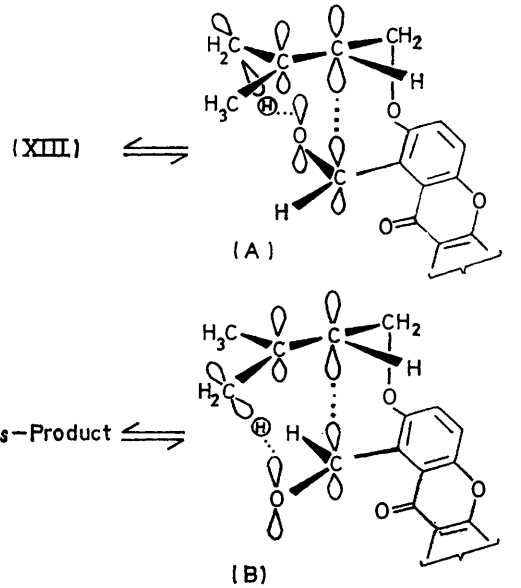


FIGURE 2 Ene-reaction transition states leading to (A) *cis*- and (B) *trans*-cyclisation product

which would lead to a *trans*-product, is unlikely under the reaction conditions in chloroform owing to unfavourable electrostatic interactions between the aldehyde and xanthone carbonyl groups.

We have already suggested that the corresponding dihydropyran ring in shamixanthone (I) arises biogenetically by cyclisation of an *O*-prenylaldehyde residue.[1] Indeed the co-occurrence of the variecoxanthones supports this hypothesis. However, shamixanthone is the *trans*-product. Although the mechanism of an enzyme-controlled reaction is difficult to predict, an ' ene-reaction ' mechanism would require a transition state of the type shown in Figure 2(B). It is possible that *in vivo* this could be stabilised by hydrogen-bonding of the xanthone and aldehyde carbonyl groups. Alternatively this could be favoured if dihydropyran ring formation preceded xanthone formation, in which case the carbonyl group of the precursor benzophenone could rotate away from the aldehyde group.

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were measured for solutions in chloroform with a Perkin-Elmer 125 instrument, u.v. spectra for solutions in ethanol with a Unicam SP 800 instrument, ^{1}H n.m.r. spectra with a Varian HA-100 or XL-100 instrument for solutions in acid-free deuteriochloroform

[10] H. M. R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8**, 556.

[11] G. Ohloff, *Tetrahedron Letters*, 1960, **11**, 10.

[12] O. Achmatowicz and B. Szechner, *J. Org. Chem.*, 1972, **37**, 964.

[13] N. H. Anderson Hong-Sun Hu, S. E. Smith, and P. G. M. Wuts, *J.C.S. Chem. Comm.*, 1972, 956.

containing tetramethylsilane as internal standard, ^{13}C n.m.r. spectra with a Varian XL-100-15 FT spectrometer for similar solutions, mass spectra with an A.E.I. MS 12 instrument at 70 eV, and accurate masses with an A.E.I. MS9 instrument. T.l.c. was performed on silica gel GF (Merck). M.p.s were determined with a Kofler hot-stage instrument.

Isolation of Variecoxanthones A—C [(IV)—(VI)].—*Aspergillus variecolor*, strain CBS 135·55, was grown in static culture for 15 days at 25°, as previously described for strain IMI 112543.[2] The dried mycelium (*ca.* 6 g l^{-1}) was ground and continuously extracted with light petroleum (b.p. 60—80°). The resulting semi-solid was triturated with warm methanol and the solution evaporated to give a yellow solid which was fractionated by preparative t.l.c. [toluene–ether (97 : 3 v/v)]. Sterigmatocystin was eluted from the band of R_F 0·25 and afforded pale yellow needles (5·0 mg l^{-1}) from methanol, m.p. and mixed m.p. 242—243° (lit.,[5] 246°), identical (i.r., u.v., and ^1H n.m.r. spectra) with an authentic sample. *Variecoxanthone C* was eluted from the band of R_F 0·3 and gave yellow needles (0·8 mg l^{-1}) from methanol, m.p. 118—120°, $\nu_{max.}$ 3500—3100 and 1641 cm^{-1}, $\lambda_{max.}$ 252, 258, 274, 294, and 376 nm (ε 30,700, 24,700, 30,000, 27,800, and 15,000) (Found: M^+, 424·188. $C_{25}H_{28}O_6$ requires M, 424·188). *Variecoxanthone A* was eluted from the band of R_F 0·5 and gave pale yellow needles (11·5 mg l^{-1}) from methanol, m.p. 135°, $\nu_{max.}$ 3500—3100 and 1643 cm^{-1} (Found: C, 70·5; H, 5·9%; M^+, 340·130. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%; M, 340·131). The band of R_F 0·58—0·62 was eluted and the material re-chromatographed [four-fold development with benzene–ether (98 : 2 v/v)]. Arugosins A and B were eluted from the band of R_F 0·43 and obtained as a yellow oil (2·05 mg l^{-1}), identical (i.r., u.v., and ^1H n.m.r. spectra) with an authentic sample.[3] *Variecoxanthone B* was eluted from the band of R_F 0·55 and afforded yellow prisms (0·7 mg l^{-1}) from methanol, m.p. 113—115°, $\nu_{max.}$ 3520—3100 and 1640 cm^{-1}, $\lambda_{max.}$ 253, 258, 275, 294, and 380 nm (ε 26,600, 28,400, 30,400, 28,400, and 15,400) (Found: C, 73·4; H, 7·0%; M^+, 408·195. $C_{25}O_{28}H_5$ requires C, 73·5; H, 6·9%; M, 408·194). Shamixanthone was eluted from the band of R_F 0·66, giving yellow needles (1·45 mg l^{-1}) from methanol, m.p. and mixed m.p. 154—156° (lit.,[2] 154—156°), identical (i.r., u.v., and ^1H n.m.r. spectra) with an authentic sample.

Methylation of Variecoxanthones A—C.—On reaction with methyl iodide and anhydrous potassium carbonate in acetone, variecoxanthone A (30 mg) gave 1-*hydroxymethyl*-8-*methoxy*-3-*methyl*-2-(3-*methylbut*-2-*enyloxy*)*xanthone*, needles (24 mg) from benzene–hexane, m.p. 143—145°, $\nu_{max.}$ 3500 and 1645 cm^{-1}, τ 2·5 (1H, t, J 9 and 9 Hz), 2·85 (1H, s), 3·07 (1H, d, J 9 Hz), 3·3 (1H, d, J 9 Hz), 4·43 (1H, t, J 8 Hz), *ca.* 5·00 (3H), 5·58 (2H, d, J 8 Hz), 6·03 (3H, s), 7·62 (3H, s), 8·23 (3H, s), and 8·31 (3H, s) (Found: M^+, 354·146. $C_{21}H_{22}O_5$ requires M, 354·147). Similarly variecoxanthone B (12 mg) gave 1-*hydroxymethyl*-8-*methoxy*-3-*methyl*-5-(3-*methylbut*-2-*enyl*)-2-(3-*methylbut*-2-*enyloxy*)*xanthone* (VII), needles (8 mg) from benzene–hexane, m.p. 147—148°, $\nu_{max.}$ 3505 and 1646 cm^{-1}, τ 2·57 (1H, d, J 9 Hz), 3·04 (1H, s), 3·28 (1H, d, J 9 Hz), 4·4 (1H, t, J 8 Hz), 4·74 (1H, t, J 8 Hz), 4·90 (2H, s), *ca.* 5·0 (1H), 5·54 (2H, d, J 8 Hz), 6·03 [3H, s, τ (C_6D_6) 6·43], 6·48 (2H, d, J 8 Hz), 7·57 (3H, s), and 8·22—8·28 (12H) (Found: M^+, 422·211. $C_{26}H_{30}O_5$ requires M, 422·209), and variecoxanthone C (14 mg) gave 5-(2,3-*epoxy*-3-*methylbutyl*)-1-*hydroxymethyl*-8-*methoxy*-3-*methyl*-2-(3-*methylbut*-2-*enyloxy*)*xanthone* (VIII), needles (11 mg) from benzene–hexane, m.p. 148—150°, $\nu_{max.}$ 3500 and 1639 cm^{-1}, $\lambda_{max.}$ 240, 251, 285, and 354 nm (ε 30,050, 29,400, 8300, and 7350), τ 2·56 (1H, d, J 9 Hz), 2·80 (1H, s), 3·30 (1H, d, J 9 Hz), 4·47 (1H, t, J 9 Hz), *ca.* 5·00 (1H), 5·01 (2H, s), 5·57 (2H, d, J 9 Hz), 6·05 [3H, s, τ (C_6D_6) 6·54], 6·98 (3H, s), 7·61 (3H, s), 8·23 (3H, s), 8·31 (3H, s), 8·57 (3H, s), and 8·61 (3H, s) (Found: M^+, 438·205. $C_{26}H_{30}O_6$ requires M, 438·204).

Hydrogenolysis of Variecoxanthone A.—This compound (80 mg) in ethyl acetate (25 ml) was hydrogenated at room temperature and 1 atm over palladium–carbon (100 mg; 10%) for 14 h. The solvent was removed and the residue was separated into two components by preparative t.l.c. [toluene–ether (97 : 3 v/v)]. 8-*Hydroxy*-1,3-*dimethyl*-2-(3-*methylbutoxy*)*xanthone* (IX) was eluted from the band at R_F 0·8, giving pale yellow prisms (11 mg) from hexane, m.p. 67—68°, $\nu_{max.}$ 3496 and 1644 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 265, 288, 310, and 368 nm (ε 30,000, 15,200, 8800, and 9100), τ −3·02 (1H, s), 2·54 (1H, t, J 9 and 9 Hz), 2·95 (1H, s), 3·25 (1H, d, J 9 Hz), 3·34 (1H, d, J 9 Hz), 6·26 (2H, t, J 8 Hz), 7·20 (3H, s), 7·61 (3H, s), 8·25 (2H, t, J 8 Hz), *ca.* 8·3 (1H, m), and 9·00 (6H, d, J 9 Hz) (Found: M^+, 326·152. $C_{20}H_{22}O_4$ requires M, 326·152). 2,8-Dihydroxy-1,3-dimethylxanthone (X), was eluted from the band at R_F 0·4, affording yellow needles (26 mg) from methanol, m.p. 211°, $\nu_{max.}$ 3496 and 1642 cm^{-1}, $\lambda_{max.}$ 238, 247, 259, 267, 290, 312sh, and 380 nm (ε 21,700, 22,400, 25,000, 22,250, 9850, 3700, and 5700), identical (m.p., mixed m.p.; i.r., u.v., and ^1H n.m.r. spectra) with the compound prepared as previously described[6] (lit., m.p. 212—215°).

Oxidation of Variecoxanthone A.—(*a*) This compound (200 mg) in acetone (50 ml) was titrated with Jones reagent in the usual way.[7] After adding ethanol (2 ml), the mixture was poured into water and the product isolated in ether and purified by preparative t.l.c. [toluene–ether (97 : 3 v/v)]. The band at R_F 0·45 gave starting material (35 mg) and the band at R_F 0·55 gave 1-*formyl*-8-*hydroxy*-3-*methyl*-2-(3-*methylbut*-2-*enyloxy*)*xanthone* (XI), yellow needles (95 mg) from methanol, m.p. 143—145°, $\nu_{max.}$ 3467, 1708, and 1644 cm^{-1}, τ −2·06 (1H, s), −0·61 (1H, s), 2·42 (1H, t, J 8·6 and 8·6 Hz), 2·6 (1H, s), 3·1 (1H, dd, J 8·6 and 1·4 Hz), 3·23 (1H, dd, J 8·6 and 1·4 Hz), 4·49 (1H, t, J 7·6 Hz), 5·5 (2H, d, J 7·6 Hz), 7·53 (3H, s), 8·22 (3H, s), and 8·28 (3H, s) (Found: C, 70·7; H, 5·4%; M^+, 338·115. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·4%; M, 338·115).

(*b*) Variecoxanthone A (80 mg) in dichloromethane (15 ml) was treated with Collins reagent[8] (400 mg; 6 : 1 molar ratio) for 1 h at room temperature. Isolated in the usual way, the product was purified as described above giving starting material (25 mg) and the aldehyde (XI) (20 mg), m.p. and mixed m.p. 143—145°.

The Decarbonylation Product (XII).—The aldehyde (XI) (58 mg) in benzene (20 ml) was heated under reflux for 4 h in an atmosphere of nitrogen with chlorotristriphenylphosphinerhodium(I) (80 mg). Removal of the solvent left a crude oil which was purified by preparative t.l.c., the band at R_F 0·58 [toluene–ether (97 : 3 v/v)] being eluted to give 8-*hydroxy*-3-*methyl*-2-(3-*methylbut*-2-*enyloxy*)*xanthone* (XII), which separated from chloroform–methanol in yellow needles (17 mg), m.p. 154—156°, $\nu_{max.}$ 3470 and 1648 cm^{-1}, τ −2·76 (1H, s), 2·49 (1H, t, J 8·6 and 8·6 Hz), 2·51 (1H, s), *ca.* 2·8 (1H, s), 3·14 (1H, dd, J 8·6 and 1·4 Hz), 3·28 (1H, dd, J 8·6 and 1·4 Hz), 4·51 (1H, t, J 7·4 Hz), 5·41 (2H, d, J 7·4 Hz), 7·64 (3H, s), and 8·2 (6H, s) (Found: M^+, 310·120. $C_{19}H_{18}O_4$ requires M, 310·121).

Acid-catalysed Cyclisation of the Aldehyde (XI).—This

compound (90 mg) was dissolved in a solution of hydrogen chloride (0·002M) in chloroform (50 ml) at room temperature. After 1 h the solution was washed with 2M-sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated. The residue was purified by preparative t.l.c., the band at R_F 0·65 [light petroleum–acetone (4 : 1 v/v)] being eluted to give 1,2-cis-2,3-*dihydro*-1,11-*dihydroxy*-2-*isopropenyl*-5-*methylpyrano*[3,2-a]*xanthene*-12(1H)-*one* (XIII), which separated from benzene–hexane in yellow needles (56 mg), m.p. 141°, $\nu_{max.}$ 3500 and 1648 cm^{-1}, $\lambda_{max.}$ 239, 249, 265, 294, and 384 nm (ε 24,500, 25,700, 30,900, 12,600, and 9500) (Found: C, 70·3; H, 5·3%; M^+, 338·115. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%; *M*, 338·115).

Hydrogenation of Compound (XIII).—This compound (60 mg) in ethyl acetate (40 ml) was hydrogenated at room temperature and 1 atm over 10% palladium–carbon (20 mg) for 2 h to give a mixture of two products which were separated by preparative t.l.c. [light petroleum (b.p. 40—60°)–acetone (4 : 1 v/v)]. The band at R_F 0·72 gave 1,2-cis-2,3-*dihydro*-1,11-*dihydroxy*-2-*isopropyl*-5-*methylpyrano*[3,2-a]*xanthen*-12(1H)-*one* (XIV) as fine yellow needles (38 mg) from methanol, m.p. 173—174°, $\nu_{max.}$ 3480 and 1640 cm^{-1}, $\lambda_{max.}$ 238, 249, 265, 270sh, 292, and 384 nm (ε 18,200, 18,600, 22,400, 21,900, 8900, and 5400), τ −2·69 (1H, s), 2·50 (1H, t, *J* 8·4 and 8·4 Hz), 2·85 (1H, s), 3·20 (1H, dd, *J* 8·4 and 1·3 Hz), 3·28 (1H, dd, *J* 8·4 and 1·3 Hz), 8·84 (3H, d, *J* 6·8 Hz), and 8·96 (3H, d, *J* 6·8 Hz) (Found: C, 70·8; H, 6·0%; M^+, 340·130. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%; *M*, 340·130). The band at R_F 0·80 gave 2,3-*dihydro*-11-*hydroxy*-2-*isopropyl*-5-*methylpyrano*[3,2-a]*xanthen*-12(1H)-*one* (XV) as yellow needles (2 mg) from methanol, m.p. 95—96°, $\nu_{max.}$ 1642 cm^{-1}, $\lambda_{max.}$ 241, 247, 264, 269, 289, and 382 nm (ε 18,600, 20,000, 22,900, 22,900, 10,500, and 6200) (Found: M^+, 324·136. $C_{20}H_{20}O_4$ requires *M*, 324·136).

3-*Isopropyl*-6-*methylchromen*-4-*one* (XVIII).—3-Methylbutanoyl chloride (5 g) was added slowly to 4-methylphenol (4·5 g) and, after evolution of hydrogen chloride had ceased, the mixture was heated to 100° for 12 h and then added slowly to aluminium chloride (6·1 g) in carbon disulphide (7 ml). After heating under reflux for 3 h the solvent was evaporated off and the residue heated to 170—180° for 1 h and then hydrolysed with 50% concentrated hydrochloric acid in water (12 ml) at 100° for 1 h. After dilution of the mixture with water, the product was isolated in ether (5 × 20 ml); the solution was washed with water, dried (Na_2SO_4), and evaporated to give an oil which was purified by distillation giving 4-(2-*hydroxy*-4-*methylphenyl*)-2-*methylbutan*-2-*one* (b.p. 85° at 0·1 mmHg) (6·4 g), $\nu_{max.}$ 3400—2800 and 1640 cm^{-1}, $\lambda_{max.}$ 227, 255, and 339 nm (ε 5400, 7600, and 3800), τ −2·23 (1H, s), 2·42 (1H, d, *J* 2·5 Hz), 2·72 (1H, dd, *J* 2·5 and 7·9 Hz), 3·11 (1H, d, *J* 7·9 Hz), 7·23 (2H, d, *J* 7·0 Hz), 7·76 (1H, m), and 9·03 (6H, d, *J* 7·0 Hz) (Found: C, 74·6; H, 8·3. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%).

Sodium hydride (50—60% oil dispersion; 0·25 g) was slowly added to the above ketone (0·5 g) in ethyl formate (20 ml) at −5° with stirring. After 20 min the mixture was allowed to warm to room temperature and, after 3 h, was added to water (100 ml); the product was isolated in ether. The solution was washed with water, dried (Na_2SO_4), and evaporated and the residue fractionated by preparative t.l.c. [benzene–ether (3 : 1 v/v)]. 3-*Isopropyl*-6-*methylchromen*-4-*one* (XVIII) was eluted from the band at R_F 0·65 and formed needles (34 mg) from hexane, m.p. 89°, $\nu_{max.}$ 1620 cm^{-1}, $\lambda_{max.}$ 234, 245, 265, and 307 nm (ε 9550, 7600, 3550, and 6600), τ 2·03br (1H, s), 2·36 (1H, s), 2·51 (1H, dd, *J* 2·1 and 8·1 Hz), 2·76 (1H, d, *J* 8·1 Hz), *ca.* 6·96 (1H, m), 7·67 (3H, s), and 8·88 (6H, d, *J* 7·0 Hz) (Found: C, 77·0; H, 6·8. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%). The band at R_F 0·30 gave 2-*hydroxy*-3-*isopropyl*-6-*methylchroman*-4-*one*, which formed needles (380 mg) from hexane, m.p. 106—108°, $\nu_{max.}$ (KBr) 3420 and 1665 cm^{-1}, $\lambda_{max.}$ 223, 252, and 328 nm (ε 7400, 8300, and 3200), τ 2·45 (1H, d, *J* 2·2 Hz), 2·81 (1H, dd, *J* 2·2 and 8·1 Hz), 3·27 (1H, d, *J* 8·1 Hz), 4·28 (1H, dd, *J* 2·3 and 4·2 Hz), 6·27 (1H, d, *J* 4·2 Hz), 7·68 (1H, dd, *J* 2·3 and 8·7 Hz), 7·80 (3H, s), 8·04 (1H, m), 8·97 (3H, d, *J* 7·5 Hz), and 9·14 (3H, d, *J* 7·5 Hz) (Found: C, 70·9; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

This compound (200 mg) was dehydrated by heating under reflux for 1 h with concentrated hydrochloric acid–acetic acid (1 : 15 v/v; 8 ml). Isolated in ether, the chromone (XVIII) formed needles (160 mg) from hexane, m.p. and mixed m.p. 89°.

cis- *and* trans-3-*Isopropyl*-6-*methylchroman*-4-*ol* (XVI) *and* (XVII).—(*a*) The chromone (XVIII) (150 mg) was reduced with sodium borohydride (500 mg) in refluxing ethanol (20 ml) for 3 h. Isolated in ether in the usual way, the product was separated into two components by preparative t.l.c. [light petroleum (b.p. 40—60°)–ether (9 : 1 v/v)]. cis-3-*Isopropyl*-6-*methylchroman*-4-*ol* (XVI) was eluted from the band at R_F 0·21 and crystallised from hexane to give needles (90 mg), m.p. 80°, $\nu_{max.}$ 3390 and 1620 cm^{-1}, $\lambda_{max.}$ 227, 283, and 290 nm (ε 4900, 2400, and 2800) (Found: C, 75·8; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%). The trans-*isomer* (XVII) was eluted from the band at R_F 0·14 and crystallised from hexane to give fine needles (38 mg), m.p. 97—99°, $\nu_{max.}$ 3390 and 1620 cm^{-1}, $\lambda_{max.}$ 227, 283, and 289 nm (ε 4500, 2300, and 2100) (Found: C, 75·8; H, 8·8%).

(*b*) Reduction of the chromone (XVIII) (30 mg) with sodium borohydride (100 mg) in propan-2-ol (7 ml) at room temperature for 10 h similarly gave the *cis*-isomer (XVI), needles (22 mg), m.p. and mixed m.p. 80°, and the *trans*-isomer (XVII), fine needles (2·4 mg), m.p. and mixed m.p. 97—99°.

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