Studies of Chromens. Part 3.[1] Routes to 2,2-Dimethylchroman-3-ones and 4-Ethyoxycarbonyl-2,2-dimethylchromens. Synthesis of a Stable Chromenopyrazolinone

Panayiotis Anastasis and Philip E. Brown *
Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

2,2-Dimethyl-3,4-epoxychroman (6a) was converted into 2,2-dimethylchroman-3-one which readily underwent ethoxycarbonylation to 4-ethoxycarbonyl-2,2-dimethylchroman-3-one (5c). The derived 4-ethoxycarbonyl-2,2-dimethylchromen (1b) reacted with hydrazine to give the pyrazolidinone (4a), oxidation of which gave the stable pyrazolinone (11). Lead tetra-acetate acetoxylation of 7-methoxy-2,2-dimethylchroman-4-one, followed by metal hydride reduction, afforded the 3,4-diol as a mixture of isomers. The relative proportions of *cis* and *trans* isomers could be varied from 1 : 1 to 5 : 1, respectively, by the choice of reducing conditions. Acid-catalysed dehydration of the diol mixture gave 7-methoxy-2,2-dimethylchroman-3-one (5b). This was unstable and could not be ethoxycarbonylated, but 4-ethoxycarbonyl-7-methoxy-2,2-dimethylchroman-3-one (5d)/(1j) was obtained by a standard synthesis.

In Part 2[1] we described the synthesis of 7-methoxy-2,2-dimethylchromen-3-carboxylic acid (1a) and reported our failure to convert this into either the pyrazolinone (2) or its pyrazolidinone precursor (3). Our interest in such chromenopyrazolidinones arose from the possibility that they might slowly liberate biologically active chromens under mild oxidative conditions.[2,3] Consequently, we considered the alternative chromenopyrazolidinones (4a) and (4b) and their synthesis from the 4-ethoxycarbonyl-2,2-dimethylchromens (1b) and (1c).

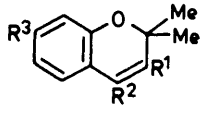
Alkylation of chroman-4-ones had proved to be of interest,[1] so we first investigated ethoxycarbonylation of 2,2-dimethylchroman-3-ones as a route to the chromens (1b) and (1c). 2-Unsubstituted and 2-monosubstituted chroman-3-ones undergo alkylation normally at both C-2 and C-4,[4,5] but very few 2,2-dimethylchroman-3-ones, or indeed any 2,2-disubstituted chroman-3-ones, appear to be known. We therefore thought it desirable to investigate both 2,2-dimethylchroman-3-one (5a) and 7-methoxy-2,2-dimethylchroman-3-one (5b) since carbanion formation in the latter may be affected by the 7-methoxy group.

Compound (6a) was obtained in 92% yield by epoxidation of the chromen (1d) with *m*-chloroperbenzoic acid in a sodium hydrogen carbonate buffered two-phase system.[6] Although the epoxide was sufficiently pure to be used directly, further purification could be accomplished by fast passage through a short alumina column, but prolonged contact caused dimerisation (t.l.c. and mass spectrometry). The epoxide has previously been reported as an unisolated component of a mixture obtained by the action of peracetic acid on the chromen [7] and as a low melting solid derived from the bromohydrin.[8] In the absence of sodium hydrogen carbonate, the mono *m*-chlorobenzoate (7a) was formed as a mixture of isomers consisting mainly (6 : 1) of the *trans* isomer. The predominance of the *trans* isomer indicates that the initially formed epoxide was being opened in a largely S_N2 manner by the *m*-chlorobenzoic acid produced in the reaction mixture.

The epoxide (6a) was readily converted into the chroman-3-one (5a) by a catalytic quantity of boron trifluoride–diethyl ether in dry benzene. Ethoxycarbonylation was accomplished by boiling the chroman-3-one (5a) with sodium hydride in diethyl carbonate. The complete enolisation of the resultant oxo-ester (5c) (1e) is in marked contrast to the oxo-ester (8a) which exists entirely in the keto form.[1]

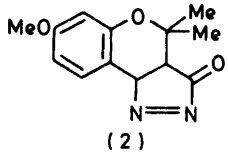
We explained the behaviour of the latter [1] by the steric strain introduced by enolisation. Similar conformational arguments may be used in the case of ester (5c) in which enolisation replaces the nearly eclipsed conformation (5c) with a more skewed conformation (1e) thereby somewhat relieving steric strain and reinforcing hydrogen bond and resonance effects (Figure 1).

Hydrogenation of the ester (1e) yielded the chromanol (7b)

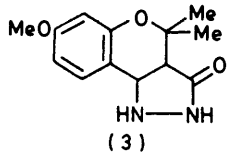


(1)

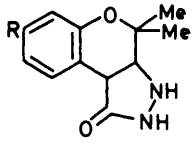
	R^1	R^2	R^3
a;	CO_2H	H	OMe
b;	H	CO_2Et	H
c;	H	CO_2Et	OMe
d;	H	H	H
e;	OH	CO_2Et	H
f;	H	H	OMe
g;	O·CO_2Et	H	OMe
h;	O·CO_2Et	H	H
i;	H	$CH{=}CH_2$	OMe
j;	OH	CO_2Et	OMe



(2)

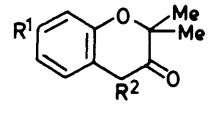


(3)



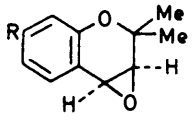
(4)

a; R = H
b; R = OMe

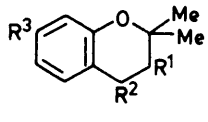


(5)

	R^1	R^2
a;	H	H
b;	OMe	H
c;	H	CO_2Et
d;	OMe	CO_2Et

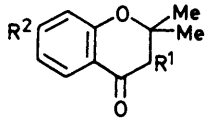


(6)



(7)

	R^1	R^2	R^3
a; R = H	a; OH	*m*-$ClC_6H_4{\cdot}CO_2$	H
b; R = OMe	b; OH	CO_2Et	H
	c; OH	*m*-$ClC_6H_4{\cdot}CO_2$	OMe
	d; OH	OH	OMe
	e; H	OH	OMe
	f; H	$CH{=}CH_2$	OMe



(8)

	R^1	R^2
a;	CO_2Et	OMe
b;	H	OMe
c;	O_2CMe	OMe

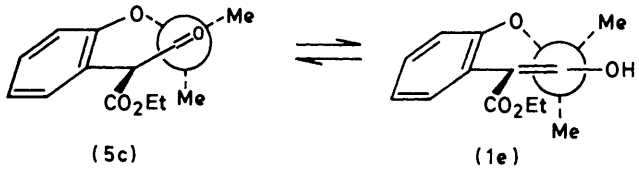
which on treatment with toluene-*p*-sulphonyl chloride in pyridine afforded the required chromen (1b).

This simple scheme has to be modified for the 7-methoxy analogues since the relevant epoxide (6b) is extremely labile and has only been prepared *via* the bromohydrin. In fact treatment of chromen (1f) with *m*-chloroperbenzoic acid, even under buffered conditions, leads to a mixture of the *cis* and *trans* diols (1 : 1) after hydrolysis of the initially formed monoesters (7c).[9] Opening of the epoxide is now an S_N1 process.

An essentially equivalent synthesis involving dehydration of chroman-3,4-diols has been used to prepare chroman-3-ones.[10] The requisite diol (7d) could not be obtained from the chromen by the action of either potassium permanganate or osmium tetraoxide, both reagents giving complex mixtures of products. Although epoxidation of chromen (1f) followed by hydrolysis provides a 1 : 1 mixture of *cis* and *trans* diols we sought a more direct route from the chroman-4-one (8b) which is the usual precursor of the chromen.

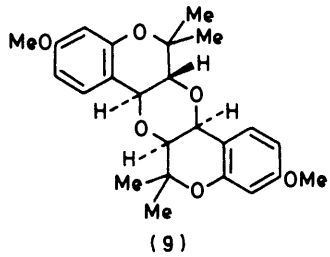
Oxidation of the chroman-4-one (8b) with lead tetra-acetate [11] afforded the 3-acetoxy derivative (8c) which was reduced by complex metal hydrides to mixtures of the *cis* and *trans* diols (7d). Although the stereochemistry is not of direct relevance, since the dehydration almost certainly proceeds by an *E*1 process, it was found that the *cis* : *trans* diol ratio was affected by the reducing conditions used. Sodium borohydride in ethanol gave a 3.4 : 1 *cis* : *trans* mixture, lithium aluminium hydride in tetrahydrofuran a 1 : 1 mixture, whilst with lithium aluminium hydride in diethyl ether a 5 : 1 *cis* : *trans* ratio of isomers was obtained. Over-reduction in ether solution [12] was prevented by using a short reaction time of 3 min.

The original workers [10] used copper sulphate at 200 °C to effect dehydration of the *cis* diol in order to avoid the dimer formation (90%) which they found to occur when dehydration was attempted by boiling in benzene with toluene-*p*-sulphonic acid for several hours. The chroman-3-one could, however, be isolated in reasonable yield (63%) with the latter reagent when the reaction time was reduced to 1 min.[12] This three stage ketone transposition can only be expected to be effective when,



(5c) (1e)

Figure 1. Enolisation of the ester (5c)



(9)

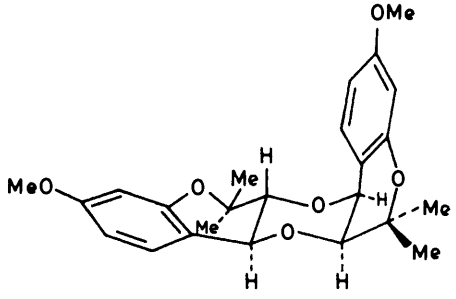


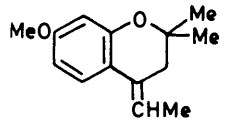
Figure 2. Configuration of the dimer (9)

as in the present work, dehydration of the intermediate diol is strongly regioselective, but in these cases it is competitive with other methods.[13]

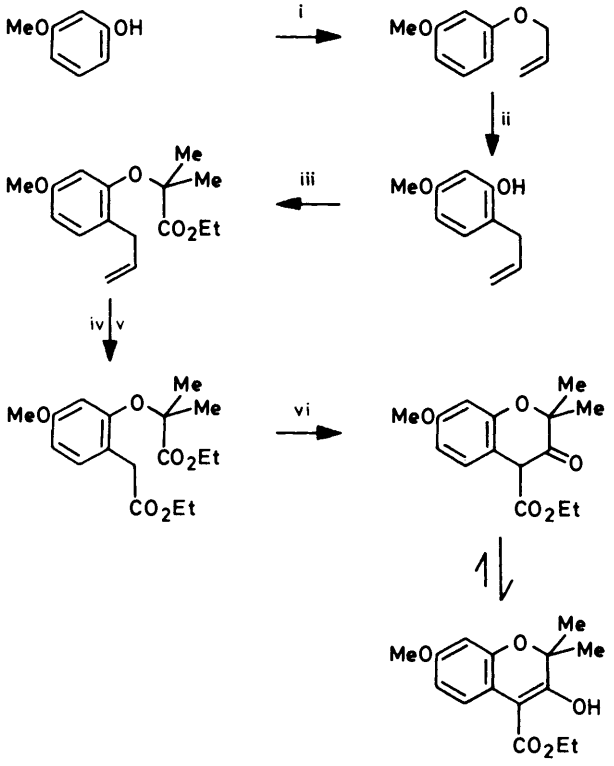
Under our conditions, formation of the dimer (9), in which the C(3)–O–C(4) linkages are assumed on mechanistic grounds, was restricted to 11%. Of interest was the asymmetric nature of the dimer as shown by its ^1H n.m.r. spectrum; the C-2 methyl groups appeared as four singlets, the C-5 aromatic protons as two doublets, and the C-3 and C-4 protons as four doublets, two indicating *cis* stereochemistry (*J* 4 Hz) and two *trans* stereochemistry (*J* 9 Hz). Examination of models shows that this configuration is one of two which does not involve severe steric strain and suggests that the *cis* ring junction should be 4-*eq*′,3-*ax*′ as shown in Figure 2. The alternative *trans*,-*trans* configuration may be kinetically disfavoured.

The 7-methoxy-2,2-dimethylchroman-3-one (5b) was unstable, decomposing at room temperature in a matter of days, and attempted ethoxycarbonylation with sodium hydride and diethyl carbonate, both at the boiling point and at room temperature, gave only complex mixtures. The action of dimsyl sodium and ethyl chloroformate did, however, provide the enol-ester (1g); similarly the 7-unsubstituted chroman-3-one (5a) afforded the enol-ester (1h) with these reagents. Attempted ethoxycarbonylation of the 7-methoxychroman-3-one (5b) *via* an enamine was also unsuccessful.

Three attempts were made to generate the required chromen ester (1c) from readily available materials. Direct addition of hydrogen cyanide to 7-methoxychroman-4-ones had previously been shown not to take place [14] so we first attempted to replace the hydroxy group of chromanol (7e) by a cyano group using sodium cyanide catalysed by iodide ion.[15] Even under these mild conditions the chromen (1f) was isolated in 94% yield, elimination taking place very much more rapidly



(10)

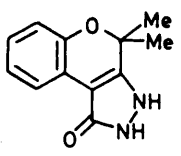


Scheme. *Reagents:* i, CH_2=$CHCH_2Br$–K_2CO_3–acetone; ii, heat/$PhNMe_2$; iii, EtO^-–EtOH–$BrCMe_2CO_2Et$; iv, O_3–MeOH–H_2O_2–HOAc; v, $SOCl_2$–EtOH; vi, EtO^-–EtOH

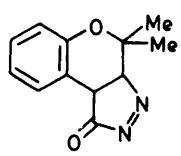
than substitution. In the second approach, ozonolysis of 7-methoxy-2,2-dimethyl-4-vinylchroman-4-ol followed by an oxidative work-up gave only a complex mixture of products. An attempt to convert the vinylchromanol into the vinylchroman (7f) with lithium aluminium hydride [12] so that ozonolysis might proceed normally, to be followed by dehydrogenation, gave a mixture of alkenes in which the 4-ethylidenechroman (10) predominated. The required 4-vinylchroman (7f) was present only as a minor component together with the 4-vinylchromen (1i).

4-Ethoxycarbonyl-7-methoxy-2,2-dimethylchroman-3-one (5d) was eventually synthesised by a traditional route involving Dieckmann ring closure (Scheme). Oxidation of the olefin (step iv) was attempted with potassium permanganate, but over-oxidation to the benzoic acid could not be prevented. The chroman-3-one was found to exist entirely in the enol form (1j).

Conversion into the chromen carboxylic ester (1c) was not attempted because although the 7-unsubstituted carboxylic ester (1b) readily formed the pyrazolidinone (4a), oxidation of this gave the pyrazolinone (11) rather than the required tautomer (12) and this isomerisation to the aryl-conjugated pyrazolinone was expected to be even more favourable in the case of the 7-methoxy compound. Although isomerisation had been expected it had been hoped that sufficient of the tautomer (12) would be present to undergo elimination of nitrogen and carbon monoxide. The product obtained (11) was highly



(11)



(12)

stable however and showed no sign of decomposition up to its melting point of 242—243 °C, though the pyrazolidinone (4a) did begin to decompose at 195 °C, just below its melting point. This stability is in marked contrast to simpler pyrazolinones which decomposed slowly above −20 °C and explosively above 0 °C.[2,3]

These results were not promising with respect to our aim of developing a method of protecting the labile olefinic bond of biologically active chromens with groups that would slowly decompose to release the chromen, and work with chromopyrazolinones was not pursued further.

Experimental

M.p.s are uncorrected. I.r. spectra of solids (KBr) and liquids (film) were recorded on a Hilger and Watts Infrascan. U.v. spectra were determined with a Perkin-Elmer Model 137 Spectrometer. N.m.r. spectra were obtained on a Varian EM 360 Spectrometer (60 MHz) with tetramethylsilane as internal standard. Mass spectra were obtained on a MS9 instrument. Homogeneity of non-crystalline compounds was established by t.l.c. in at least three solvent systems of differing polarities.

Reaction of 2,2-*Dimethyl*-2H-*chromen* (1d) *with* m-*Chloroperbenzoic Acid.*—(*a*) *In the absence of sodium hydrogen carbonate.* A solution of the chromen (1d) (0.100 g, 0.63 mmol) in dry dichloromethane (5 ml) was treated with *m*-chloroperbenzoic acid (0.108 g, 0.63 mmol) dissolved in dichloromethane (5 ml) at 0 °C. After 1 h at room temperature the mixture was diluted with chloroform and washed with sodium hydrogen carbonate solution followed by water. Evaporation of the dried ($MgSO_4$) organic layer afforded a gum which consisted of a mixture of two isomers (*ca.* 1 : 6 *cis* : *trans* by n.m.r. spectroscopy) (0.199 g, 96%). An attempt to separate the isomers by silica-gel chromatography was unsuccessful and the products were characterised as an isomeric mixture of 4-(m-*chlorobenzoyloxy*)-2,2-*dimethylchroman*-3-*ols* (7a); $\nu_{max.}$ (film) 3 480, 1 720, 1 705, 1 615, 1 585, and 1 490 cm^{-1}; $\lambda_{max.}$ (EtOH) 211 (ε 22 000), 224 (17 000), 279 (3 600), and 286 nm (3 800); *major isomer* δ ($CDCl_3$) 1.35 and 1.50 (each 3 H, s), 3.30br (1 H, s), 3.90 (1 H, d, *J* 7 Hz, 3-H), 6.12 (1 H, d, *J* 7 Hz, CHO·CO), 6.68—7.37 (4 H, m), and 7.4—8.1 (4 H, m); *minor isomer*, as for the major isomer except δ 1.43 and 1.50 (each 3 H, s), 4.05 (1 H, d, *J* 4 Hz), and 6.27 (1 H, d, *J* 4 Hz) (addition of D_2O caused the signal at δ 3.30 to disappear) (Found: M^+, 332.0831. $C_{18}H_{17}ClO_4$ requires *M*, 332.0815).

(*b*) *In the presence of sodium hydrogen carbonate.* *m*-Chloroperbenzoic acid (1.21 g, 7.00 mmol) was added slowly in small portions to a vigorously stirred mixture of the chromen (1d) (1.00 g, 6.25 mmol) in dichloromethane (60 ml) and 0.5M-aqueous sodium hydrogen carbonate (25 ml) at 0 °C. The mixture was left to reach room temperature and the two phases separated. The organic phase was washed with sodium hydrogen carbonate solution and water. Evaporation of the dried ($MgSO_4$) solution afforded (±)-2,2-dimethyl-3,4-epoxychroman (6a) (1.01 g, 92%) as a foam. Purification to give homogeneous material (t.l.c.) was achieved by quickly chromatographing the epoxide on alumina; δ ($CDCl_3$) 1.20

and 1.52 (each 3 H, s), 3.50 and 3.90 (each 1 H, d, *J* 4.5 Hz), and 6.80—8.20 (4 H, m).

2,2-*Dimethylchroman*-3-*one* (5a).—A solution of the epoxide (6a) (1.00 g, 5.68 mmol) in dry benzene (250 ml) was treated with a catalytic quantity of freshly distilled boron trifluoride–diethyl ether at room temperature for 20 min. The solution was washed with sodium hydrogen carbonate solution and water. The dried ($MgSO_4$) organic solvent was evaporated to afford a syrup. Fractionation on silica gel (benzene as eluant) afforded the title chroman-3-one (5a) as a clear homogeneous (t.l.c.) *oil* (0.890 g, 89%); $\nu_{max.}$ (film) 1 730, 1 612, 1 590, and 1 490 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 11 000), 219sh (9 100), and 280 nm (2 200); δ ($CDCl_3$) 1.40 (6 H, s), 3.58 (2 H, s), and 6.80—7.25 (4 H, m) (Found: M^+, 176.0832. $C_{11}H_{12}O_2$ requires *M*, 176.0837).

4-*Ethoxycarbonyl*-2,2-*dimethyl*-2H-*chromen*-3-*ol* (1e).—A mixture of the chromanone (5a) (0.800 g, 4.55 mmol), sodium hydride (0.135 g, 5.87 mmol) and diethyl carbonate (15 ml) was boiled under reflux under nitrogen for 2 h. The cooled suspension was diluted with 50% acetic acid and extracted with benzene. Evaporation of the dried ($MgSO_4$) extract afforded the enol-ester (1e) (0.553 g, 49%) as a homogeneous (t.l.c.) *foam*; $\nu_{max.}$ (film) 2 600—3 400, 1 720, 1 645, 1 615, 1 575, and 1 494 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 9 890), 242 (9 520), 250sh (8 420), 285 (4 520), and 292 sh nm (4 090); δ ($CDCl_3$) 1.37 (3 H, t), 1.43 (6 H, s), 4.30 (2 H, q), 6.67—7.07 (3 H, m), 7.53—7.82 (1 H, dd, *J* 7, *J'* 2 Hz), and 13.20 (1 H, s) (addition of D_2O caused the signal at δ 13.20 to disappear) (Found: M^+, 248.1026. $C_{14}H_{16}O_4$ requires *M*, 248.1048).

(±)-4-*Ethoxycarbonyl*-2,2-*dimethylchroman*-3-*ol* (7b).—The ester (5c) (0.500 g, 2.02 mmol) in ethanol (50 ml) was hydrogenated in the presence of a platinum catalyst (0.075 g). After 12 h the solution was filtered through Hi-flow and on evaporation afforded the chromanol (7b) (0.490 g, 97%) as a homogeneous (t.l.c.) *gum*; $\nu_{max.}$ (film) 3 500 and 1 745 cm^{-1}; $\lambda_{max.}$ (EtOH) 211 (ε 7 100), 218sh (7 200), 225sh (5 800), 277 (2 000), and 284 nm (1 900); δ ($CDCl_3$) 1.20 and 1.47 (each 3 H, s), 1.33 (3 H, t), 3.13br (1 H, s), 3.97 (2 H, s), 4.27 (2 H, q), 6.63—7.23 (4 H, m) (addition of D_2O caused the signal at δ 13.13 to disappear) (Found: M^+, 250.1212. $C_{14}H_{18}O_4$ requires *M*, 250.1205).

4-*Ethoxycarbonyl*-2,2-*dimethyl*-2H-*chromen* (1b).—Toluene-*p*-sulphonyl chloride (0.381 g, 2.0 mmol) was added to a stirred solution of the chromanol (7b) (0.450 g, 1.8 mmol) in dry pyridine (15 ml). Work-up after 12 h afforded the chromen (1b) (0.355 g, 85%) as a homogeneous (t.l.c.) *syrup*; $\nu_{max.}$ (film) 1 720, 1 630, 1 605, and 1 570 cm^{-1}; $\lambda_{max.}$ (EtOH) 225 (ε 10 000), 278 (3 100), and 317 nm (1 700); δ ($CDCl_3$) 1.37 (3 H, t), 1.43 (6 H, s), 4.30 (2 H, q), 6.57 (1 H, s), 6.68—7.27 (3 H, m), and 7.92 (1 H, dd, *J* 8, *J'* 2 Hz) (Found: M^+, 232.1105. $C_{14}H_{16}O_3$ requires *M*, 232.1099).

Attempted Hydroxylation of the Chromen (1f).—(*a*) *With potassium permanganate*. To a stirred solution of the chromen (1f) (0.200 g, 1.1 mmol) in ethanol (3 ml) at −20 °C was added dropwise a solution of potassium permanganate (0.132 g) and magnesium sulphate (0.099 g) in water (5 ml). After 1 h the solution was treated with sulphur dioxide and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid followed by water, and dried ($MgSO_4$). Evaporation of the solvent gave a residue (0.180 g) which was a complex mixture of products (t.l.c. and n.m.r. spectroscopy).

(*b*) *With osmium tetraoxide*. A solution of the chromen (1f) (0.200 g, 1.1 mmol) in methanol (10 ml) was stirred with osmium tetraoxide (10 mg) and barium chlorate (0.200 g, 1.1 equiv.) in water (2 ml) at 50 °C. T.l.c. showed that a mixture of products was formed as the reaction proceeded. After 6 h, when all the starting material had reacted, work-up gave only a complex mixture of products as a black oil.

(±)-3-*Acetoxy*-7-*methoxy*-2,2-*dimethylchroman*-4-*one* (8c).—The chromanone (8b) (6.0 g, 29 mmol) in glacial acetic acid (50 ml) was heated at 80 °C with lead tetra-acetate (12.9 g, 29 mmol) for 4 h. The cooled mixture was diluted with water and extracted with ethyl acetate. The organic solution was washed with water and sodium hydrogen carbonate solution. The dried ($MgSO_4$) solution was evaporated to afford the crystalline acetoxychromanone (8c) (4.8 g, 63%), m.p. 129—131 °C (ethyl acetate) (lit.,[11] 129 °C); $\nu_{max.}$ (KBr) 1 740, 1 690, 1 600, 1 570, and 1 488 cm^{-1}; δ ($CDCl_3$) 1.35 and 1.53 (each 3 H, s), 2.27 (3 H, s), 3.85 (3 H, s), 5.57 (1 H, s), 6.38 (1 H, d, *J* 2 Hz), 6.57 (1 H, dd, *J* 2, *J'* 10 Hz), and 7.77 (1 H, d, *J* 10 Hz) (Found: M^+, 264.0993. Calc. for $C_{14}H_{16}O_5$: *M*, 264.0998).

Metal Hydride Reduction of the Acetoxychroman-4-*one* (8c).—(*a*) Sodium borohydride (0.030 g, 0.79 mmol) was added to a solution of the acetoxychromanone (8c) (0.100 g, 0.38 mmol) in dry ethanol (3 ml). After 24 h the mixture was diluted with ethyl acetate, washed with dilute hydrochloric acid followed by water and dried ($MgSO_4$). Evaporation of the solvent gave a solid which consisted of *cis* and *trans* isomers of the diol (7d)[9] (0.076 g, 89%) (*ca.* 3.4 : 1 *cis* : *trans* by n.m.r. spectroscopy); $\nu_{max.}$ (KBr) 3 380, 3 440, 1 620, 1 588, and 1 505 cm^{-1}; δ ($CDCl_3$) (*trans* isomer) 1.13 and 1.40 (each 3 H, s), 2.93—4.00 (3 H, m, 3-H and 2 × OH), 3.70 (3 H, s), 4.37 (1 H, d, *J* 8 Hz), 6.12—6.57 (2 H, m), and 7.03—7.38 (1 H, m); (*cis* isomer), as for the *trans* except δ 1.22 and 1.40 (each 3 H, s), 4.63 (1 H, d, *J* 4 Hz) (addition of D_2O caused the broad complex at δ 2.93—4.00 to collapse to give two doublets at δ 3.45, *J* 8 Hz, and at δ 3.57, *J* 4 Hz) (Found: M^+, 224.1042. Calc. for $C_{12}H_{16}O_4$: *M*, 224.1049).

(*b*) Lithium aluminium hydride (0.144 g, 3.79 mmol) was added to a solution of the chromanone (8c) (1.00 g, 3.79 mmol) in dry diethyl ether (20 ml) and the mixture boiled under reflux for 3 min. The cooled solution was diluted with diethyl ether followed by water and acidified with dilute hydrochloric acid. The organic extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded a 5 : 1 mixture of *cis* and *trans* isomers (by n.m.r. spectroscopy) of the diol (7d) (0.772 g, 91%).

(*c*) Lithium aluminium hydride (0.057 g, 1.5 mmol) was added to a solution of the chromanone (8c) (0.100 g, 0.379 mmol) in dry tetrahydrofuran (5 ml). Work-up after 6 h afforded a 1 : 1 mixture of isomers (by n.m.r. spectroscopy) of the diol (7d) (0.071 g, 84%), m.p. 112—115 °C (chloroform–light petroleum).

Reaction of the Diol (7d) *with Toluene*-p-*sulphonic Acid*.—A solution of *cis* and *trans* isomers (*ca.* 5 : 1) of the diol (7d) (0.750 g, 3.35 mmol) in dry benzene (150 ml) was heated to boiling for 1 min with a trace of toluene-*p*-sulphonic acid. Work-up afforded a gum (0.680 g) consisting of a mixture of two components (t.l.c. and n.m.r. spectroscopy) which was fractionated by silica-gel chromatography (benzene as eluant).

The first material eluted, obtained as a white crystalline solid, was the dimer 6a,13,13a,14a-*tetrahydro*-3,10-*dimethoxy*-6,6,13,13-*tetramethyl*-6H,7aH-*bischromeno*[3,4-b:3',4'-e]-[1,4]*dioxin* (9) (0.142 g, 11%), m.p. 119—120 °C (from $CHCl_3$); $\nu_{max.}$ (KBr) 1 620, 1 585, and 1 507 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 25 000), 220sh (17 000), 276 (5 800), and 280sh nm (5 200); δ ($CDCl_3$) 1.25, 1.30, 1.47, and 1.60 (each 3 H, s),

3.30 and 4.67 (each 1 H, d, *J* 9 Hz), 3.68 (6 H, s), 3.83 and 4.97 (each 1 H, d, *J* 4 Hz), 6.13—6.8 (4 H, m), 7.22 and 7.30 (each 1 H, each d, *J* 8 Hz, 2 × 5-H) (Found: C, 69.75; H, 6.75%; M^+, 412.1891. $C_{24}H_{28}O_6$ requires C, 69.88; H, 6.84%; *M*, 412.1886).

The second constituent, obtained as a homogeneous (t.l.c.) oil (0.435 g, 63%), was 7-*methoxy*-2,2-*dimethylchroman*-3-*one* (5b); $\nu_{max.}$ (film) 1 735, 1 620, 1 590, and 1 506 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 15 000), 226 (7 300), 282 (2 100), and 288 nm (2 000); δ ($CDCl_3$) 1.40 (6 H, s), 3.53 (2 H, s), 3.77 (3 H, s), 6.43—6.70 (2 H, m), and 6.95 (1 H, d, *J* 8 Hz) (Found: M^+, 206.0958. $C_{12}H_{14}O_3$ requires *M*, 206.0943). Separation of the two components was also possible by crystallisation from chloroform–light petroleum.

Reaction of the Chroman-3-*one* (5b) *with Sodium Hydride in Diethyl Carbonate.*—(*a*) The chromanone (5b) (0.100 g, 0.49 mmol) was boiled under reflux in a mixture of diethyl carbonate (5 ml) and sodium hydride (0.017 g, 0.74 mmol) under nitrogen for 2 h. The cooled suspension was diluted with aqueous acetic acid and extracted with benzene. Evaporation of the dried ($MgSO_4$) solvent afforded a complex mixture of products. Attempts to purify the crude mixture by silica-gel chromatography were unsuccessful.

(*b*) The chromanone (5b) (0.050 g, 0.24 mmol) was added to a solution of diethyl carbonate (2.5 ml) and sodium hydride (0.010 g, 0.44 mmol) under nitrogen. Work-up after 6 h resulted in a syrup composed of a number of products which could not be separated by silica-gel chromatography.

3-*Ethoxycarbonyloxy*-7-*methoxy*-2,2-*dimethyl*-2H-*chromen* (1g).—A solution of the chromanone (5b) (0.100 g, 0.49 mmol) in dry tetrahydrofuran (2 ml) was treated with 1.1 equiv. of dimsyl sodium as for (1h) below. Work-up and column chromatography of the resulting syrup afforded the title chromen (1g) (0.123 g, 90%) as a homogeneous (t.l.c.) *oil*; $\nu_{max.}$ (film) 1 764, 1 620, 1 575, and 1 506 cm^{-1}; δ ($CDCl_3$) 1.37 (3 H, t), 1.47 (6 H, s), 3.73 (3 H, s), 4.23 (2 H, q), 6.23 (1 H, s), 6.30—6.50 (2 H, m), and 6.83 (1 H, d, *J* 9 Hz) (Found: M^+, 278.1149. $C_{15}H_{18}O_5$ requires *M*, 278.1154.)

3-*Ethoxycarbonyloxy*-2,2-*dimethyl*-2H-*chromen* (1h).—A solution of the chromanone (5a) (0.100 g, 0.57 mmol) in dry tetrahydrofuran (2 ml) was added at 0 °C to a solution of dimsyl sodium [prepared by heating sodium hydride (0.014 g, 0.60 mmol) at 65 °C in dimethyl sulphoxide (3 ml) under nitrogen for 30 min] diluted with dry tetrahydrofuran (2 ml). After 0.5 min ethyl chloroformate (0.095 ml, 1.00 mmol) was added to the light yellow mixture which was stirred for a further 5 min. The reaction mixture was diluted with ethyl acetate and washed well with water (6 × 10 ml). After evaporation of the solvent the resultant syrup was chromatographed on silica (benzene as eluant) to give the title chromen (1h) (0.130 g, 92%) as a homogeneous (t.l.c.) colourless *oil*; $\nu_{max.}$ (film) 1 767, 1 612, 1 579, and 1 490 cm^{-1}; $\lambda_{max.}$ (EtOH) 224 (ε 22 000), 267 (6 100), 276 sh (5 300), 304 (3 600), and 312sh nm (2 000); δ ($CDCl_3$) 1.37 (3 H, t), 1.47 (6 H, s), 4.27 (2 H, q), 6.33 (1 H, s), and 6.63—7.20 (4 H, m) (Found: M^+, 248.1060. $C_{14}H_{16}O_4$ requires *M*, 248.1049).

Reaction of the Chroman-3-*one* (5b) *with Pyrrolidine followed by Ethyl Chloroformate.*—A solution of the chromanone (5b) (0.100 g, 0.49 mmol) and pyrrolidine (0.050 ml, 0.60 mmol) in dry benzene (30 ml) was boiled under reflux with azeotropic removal of water. After 8 h ethyl chloroformate (0.062 ml, 0.65 mmol) was added and the mixture boiled under reflux for a further 6 h. Water was added to the cooled solution which was then diluted with diethyl ether. The organic phase was washed with sodium hydrogen carbonate solution followed by water and dried ($MgSO_4$). Evaporation of the solvent afforded a gum which was fractionated by silica-gel chromatography (benzene–diethyl ether as eluant) to afford starting material (0.036 g, 36%) (t.l.c. and n.m.r. spectroscopy) as the only isolated product.

Attempted Preparation of 4-*Cyano*-7-*methoxy*-2,2-*dimethyl*-2H-*chromen.*—The chromanol (7e) (0.100 g, 0.48 mmol), sodium cyanide (0.050 g, 1.0 mmol), and sodium iodide (2 mg) were mixed with deaerated acetonitrile (2 ml) and dimethylformamide (2 ml) and treated at room temperature with trimethylsilyl chloride (0.108 g, 1.0 mmol). The mixture was slowly heated to 65 °C under argon for 2 h. When it had cooled the mixture was poured onto ice–water (20 ml) and the aqueous layer extracted with diethyl ether. Evaporation of the dried ($MgSO_4$) solvent afforded the known [16] chromen (1f) (0.086 g, 94%) as the only product (t.l.c. and n.m.r.).

Ozonolysis of 7-*Methoxy*-2,2-*dimethyl*-4-*vinylchroman*-4-*ol.*—7-Methoxy-2,2-dimethyl-4-vinylchroman-4-ol [17] (0.100 g, 4.3 mmol) in dry dichloromethane (10 ml) was treated with ozone at −78 °C. After 10 min the excess of ozone was removed by a stream of nitrogen and the solvent carefully removed. The oily residue was dissolved in formic acid (98%; 1 ml) and hydrogen peroxide (37%; 1 ml) was added. After being stirred at room temperature for 1 h, water (5 ml) was added and the aqueous solution extracted with ethyl acetate. The organic phase was washed well with water and dried ($MgSO_4$). Removal of the solvent afforded a complex oil (t.l.c. and n.m.r.).

Lithium Aluminium Hydride Reduction of 7-*Methoxy*-2,2-*dimethyl*-4-*vinylchroman*-4-*ol.*—The vinylchroman (1.00 g, 4.30 mmol) in dry dimethoxyethane (25 ml) was boiled under reflux under argon with lithium aluminium hydride (1.00 g, 26 mmol). After 24 h work-up afforded an oil (0.900 g, 97%) which consisted of a mixture of three components. The major component appeared to be 4-ethylidene-7-methoxy-2,2-dimethylchroman (10) (75%) by n.m.r.; δ ($CDCl_3$) 1.27 (6 H, s), 1.74 (3 H, d, *J* 5 Hz, $=CHCH_3$), 2.37 (2 H, s, CH_2), 5.95 (1 H, d, *J* 5 Hz, $=CHCH_3$), 6.2—6.5 (2 H, m), and 7.25 (1 H, d, *J* 6 Hz, 5-H). The required vinylchroman (7f) was present only as a minor component (*ca.* 15%) by n.m.r.; δ ($CDCl_3$) 1.33 and 1.37 (each s, 2-Me_2) and other signals. The third component was considered to be the vinylchromen (1i) (*ca.* 10%) by n.m.r.; δ ($CDCl_3$) 7.10 (d, *J* 6 Hz, 5-H) and other signals.

Ethyl (2-*Allyl*-5-*methoxyphenoxy*)*dimethylethanoate.*—Sodium ethoxide (15.0 mmol) was added to a solution of 2-hydroxy-4-methoxyallylbenzene (obtained by Claisen rearrangement of the allyl ether) (2.00 g, 12.2 mmol) in dry ethanol (30 ml) and the mixture boiled under reflux for 30 min. Ethyl 2-bromoisobutyrate (3.12 g, 16.0 mmol) in dry ethanol (10 ml) was added and boiling under reflux continued for 8 h. The resulting white solid was filtered off and the filtrate evaporated to a small volume. Diethyl ether was added and the organic layer washed with water and dried over $MgSO_4$. Evaporation of the solvent afforded an oil which was purified by silica-gel chromatography (benzene as eluant) to afford the ester (2.68 g, 79%) as a homogeneous (t.l.c.) *oil*; $\nu_{max.}$ (film) 1 732, 1 633, and 1 595 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 16 000), 219 (11 000), 272 (973), and 279 nm (973); δ ($CDCl_3$) 1.27 (3 H, t), 1.57 (6 H, s), 3.35 (2 H, d, *J* 7 Hz), 3.72 (3 H, s), 4.27 (2 H, q), 4.83—5.27 (2 H, m), 5.60—6.22 (1 H, m), 6.30 (1 H, d, *J* 2.5 Hz), 6.47 (1 H, dd, *J* 2, *J'* 8 Hz), and 7.05 (1 H,

d, J' 8 Hz) (Found: M^+, 278.1525. $C_{16}H_{22}O_4$ requires M, 278.1518).

Reaction of the Alkene Ester with Potassium Permanganate.—The above alkene ester (0.200 g, 0.72 mmol) was dissolved in a mixture of ethanol (10 ml) and water (3 ml) and the solution cooled to 0 °C. To this solution was added dropwise during 1 h a solution of potassium permanganate (0.455 g, 2.88 mmol) in 90% aqueous ethanol (15 ml). Sulphur dioxide was passed into the solution until it was colourless and ethyl acetate was then added. The organic layer was successively washed with 1M-hydrochloric acid and water and then dried ($MgSO_4$). Evaporation of the organic solvent gave a syrup which contained two components (*ca.* 1 : 1 by n.m.r. spectroscopy). Addition of carbon tetrachloride–light petroleum to the mixture afforded the crystalline *ethyl (2-carboxy-5-methoxyphenoxy)dimethylethanoate* (0.055 g, 27%), m.p. 95—97 °C (from chloroform–light petroleum); $\nu_{max.}$ 3 100—2 840, 1 736, 1 685br, 1 605, 1 573, and 1 510 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 21 000), 253 (10 800), and 283 nm (2 550); δ ($CDCl_3$) 1.28 (3 H, t), 1.77 (6 H, s), 3.82 (3 H, s), 4.27 (2 H, q), 6.38 (1 H, d, J 2 Hz), 6.63 (1 H, dd, J 9, J' 2 Hz), 8.12 (1 H, d, J 9 Hz), and 10.79br (1 H, s) (addition of D_2O caused the signal at δ 10.79 to disappear) (Found: C, 59.3; H, 6.45; M^+, 282. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43%; M, 282).

The mother-liquors were fractionated by silica-gel chromatography. The first-eluted material was the above acid (0.010 g, 5%) while the second-eluted material was *ethyl [2-(carboxymethyl)-5-methoxyphenoxy]dimethylethanoate* (0.034 g, 16%), m.p. 87.5—88.5 °C (from chloroform–light petroleum); $\nu_{max.}$ (KBr) 3 300br, 1 710, 1 745, 1 620, 1 590, and 1 510 cm^{-1}; $\lambda_{max.}$ (EtOH) 210 (ε 16 000), 228 (11 000), 280 (3 200), and 285 nm (2 000); δ ($CDCl_3$) 1.25 (3 H, t), 1.60 (6 H, s), 3.62 (2 H, s) 3.73 (3 H, s), 4.23 (2 H, q), 6.27 (1 H, d, J' 2 Hz), 6.45 (1 H, dd, J 9, J' 2 Hz), 7.08 (1 H, d, J 9 Hz), and 9.03br (1 H, s) (addition of D_2O caused the signal at δ 9.03 to disappear) (Found: C, 60.55; H, 6.8%; M^+, 296.1291. $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.80%; M, 296.1260).

Reaction of the Alkene Ester with Ozone.—Ozonised oxygen was passed for 1 h through a cooled (acetone–solid CO_2) solution of the above alkene ester (1.00 g, 3.60 mmol) in methanol (40 ml). After the solution had been flushed with oxygen the solvent carefully removed, hydrogen peroxide (30 ml, 35%) and acetic acid (30 ml) were added at 0 °C and the mixture then stirred for 12 h at room temperature. Diethyl ether (100 ml) was added and the mixture washed with water (3 × 10 ml). The organic solvent was extracted with saturated sodium hydrogen carbonate solution (3 × 40 ml). The aqueous layer was acidified with 2M-hydrochloric acid and extracted with diethyl ether. Evaporation of the dried ($MgSO_4$) solvent afforded ethyl [2-(carboxymethyl)-5-methoxyphenoxy]dimethylethanoate (0.724 g, 68%).

Ethyl [2-(Ethoxycarbonylmethyl)-5-methoxyphenoxy]dimethylethanoate.—Thionyl chloride (0.10 ml, 1.40 mmol) was added to dry ethanol (7 ml) at 0 °C and stirred for 10 min, after which a solution of the above acid (0.400 g, 1.35 mmol) in dry ethanol (5 ml) was added and the mixture left to attain room temperature. After 12 h the solvent was evaporated to afford a syrup which was purified by silica-gel chromatography (benzene as eluant) to give the title diester as a homogeneous (t.l.c.) *oil* (0.411 g, 94%); $\nu_{max.}$ (film) 1 740, 1 611, 1 598, and 1 507 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 15 000), 222sh (11 000), 279 (3 400), and 286 nm (3 200); δ ($CDCl_3$) 1.23 (6 H, t), 1.57 (6 H, s), 3.57 (2 H, s), 3.72 (3 H, s), 3.93—4.43 (4 H, m), 6.25 (1 H, d, J' 2 Hz), 6.43 (1 H, dd, J 8, J' 2 Hz), and 7.07 (1 H, d, J 8 Hz) (Found: M^+, 324.1554. $C_{17}H_{24}O_6$ requires M, 324.1573).

4-Ethoxycarbonyl-7-methoxy-2,2-dimethyl-2H-chromen-3-ol (1j).—The above diester (0.200 g, 0.62 mmol) in dry ethanol (10 ml) was treated with sodium ethoxide (0.62 mmol) and boiled under reflux for 3 h. Work-up gave a syrup which was purified by silica-gel chromatography to yield the crystalline *enol ester* (1j) (0.147 g, 85%), m.p. 73.5—74.5 °C (from chloroform–light petroleum); $\nu_{max.}$ (KBr) 3 460, 1 735, 1 645, 1 636, 1 570, and 1 507 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 22 000), 248 (15 000), 297 (5 100), 305 (5 400), and 316sh nm (3 900); δ ($CDCl_3$) 1.40 (3 H, t), 1.47 (6 H, s), 3.80 (3 H, s), 4.43 (2 H, q), 6.43—6.73 (2 H, m), 7.73 (1 H, d, J 9 Hz), and 13.20 (1 H, s) (addition of D_2O caused the signal at δ 13.20 to disappear) (Found: C, 64.85; H, 6.7%; M^+, 278.1149. $C_{15}H_{18}O_5$ requires C, 64.74; H, 6.54%; M, 278.1154).

(±)-*3,3a,4,9b-Tetrahydro-4,4-dimethylchromeno[3,4-c]pyrazol-1(2H)-one* (4a).—The chromen ester (1b) (0.100 g, 0.43 mmol) was boiled under reflux in hydrazine hydrate (5 ml) for 3 h. When it had cooled, water (25 ml) was added and the resulting crystals filtered off (0.056 g, 60%). Extraction of the filtrate with ethyl acetate afforded a further quantity of the *pyrazolidinone* (4a) (0.015 g, 16%), m.p. 203—206 °C (slight decomp. at 195 °C) (from EtOH); $\nu_{max.}$ (KBr) 3 200, 3 236, 1 685, 1 650, 1 610, and 1 583 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 11 300), 220sh (8 700), 277 (2 100), and 284 nm (2 100); δ ($CDCl_3$) 1.30 and 1.40 (each 3 H, s), 3.47—4.67 (4 H, m, 3- and 4-H + 2 × NH), 6.60—7.60 (4 H, m) (addition of D_2O caused the signals at δ 3.47—4.67 to collapse to an ABq at δ 3.55 and 3.87, J 7 Hz) (Found: C, 65.9; H, 6.3; N, 12.75%; M^+, 218.1055. $C_{12}H_{14}N_2O_2$ requires C, 66.04; H, 6.47; N, 12.84%; M, 218.1055).

3,4-Dihydro-4,4-dimethylchromeno[3,4-c]pyrazol-1(2H)-one (11).—To a stirred suspension of lead tetra-acetate (0.142 g, 0.32 mmol) in anhydrous dichloromethane 5 ml) at −50 °C was added a solution of the pyrazolidinone (4a) (0.050 g, 0.23 mmol) in anhydrous dichloromethane. The mixture was maintained at this temperature under nitrogen for 3 h and then filtered. The filtrate was washed with cold (−15 °C) ammonium chloride solution and dried ($MgSO_4$). Evaporation at −15 °C gave a gum which slowly solidified to afford the title *pyrazolinone* (11) (0.039 g, 78%), m.p. 242—243 °C (from chloroform–light petroleum); $\nu_{max.}$ (KBr) 3 340—3 560 and 1 660—1 605 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 17 400), 255 (5 300), 273 (6 000), 294 (6 200), and 302 nm (6 000); δ [$(CD_3)_2CO$] 1.03 (6 H, s), 6.23—6.50 (3 H, m, ArH + NH), 6.77—7.73 (3 H, m, ArH + NH) (addition of D_2O caused the signals at δ 6.23—7.73 to simplify and integrate for 4 H) (Found: C, 66.6; H, 5.45; N, 12.75%; M^+, 216.0906. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.59; N, 12.96%; M, 216.0899).

Acknowledgements

We thank the S.R.C. for a studentship (to P. A.).

References

1 P. Anastasis and P. E. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1983, 197.
2 B. T. Gillis and R. Weinkam, *J. Org. Chem.*, 1967, **32**, 3321; R. H. Kent and J-P. Anselme, *Can. J. Chem.*, 1968, **46**, 2322.
3 W. Nagata and S. Kamata, *J. Chem. Soc. C*, 1970, 540.
4 N. S. Vul'fson, T. N. Podrezova, and L. B. Senyavina, *J. Gen. Chem. USSR*, 1964, **34**, 2676.
5 R. Verhe and N. Schamp, *Bull. Soc. Chim. Belg.*, 1973, **82**, 283.

6 W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, 1973, **38**, 2267.
7 A. J. Birch, M. Maung, and A. Pelter, *Aust. J. Chem.*, 1969, **22**, 1923.
8 R. Livingstone, *J. Chem. Soc.*, 1962, 76.
9 R. J. Jennings and A. P. Ottridge, *J. Chem. Soc., Chem. Commun.*, 1979, 920; R. A. Halpin, S. F. El-Naggar, K. M. McCombe, K. P. Vyas, D. R. Boyd, and D. M. Jerina, *Tetrahedron Lett.*, 1982, 1655.
10 F. Baranton, G. Fontaine, and P. Maitte, *Bull. Soc. Chim. Fr.*, 1968, 4203; *C.R. Acad. Sci. Ser. C*, 1967, **264**, 410.
11 G. W. K. Cavill, F. M. Dean, A. McGookin, B. M. Marshall, and A. Robertson, *J. Chem. Soc.*, 1954, 4573.
12 P. Anastasis and P. E. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2013.
13 J. A. Marshall and H. Roebke, *J. Org. Chem.*, 1969, **34**, 4188; B. M. Trost, K. Hiroi, and S. Kurozumi, *J. Am. Chem. Soc.*, 1975, **97**, 438.
14 M. Miyano and M. Matsui, *Bull. Chem. Soc. Jpn.*, 1958, **31**, 267.
15 R. Davis and K. G. Untch, *J. Org. Chem.*, 1981, **46**, 2985.
16 J. R. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, 1971, **24**, 2347; *Tetrahedron Lett.*, 1969, 1369.
17 T. R. Kasturi, A. Srinavasan, and K. M. Damodaran, *Indian J. Chem.*, 1970, **8**, 877; O. Dann, K. W. Hagedorn, and H. Hofmann, *Chem. Ber.*, 1971, **104**, 3313.

Received 12*th November* 1982; *Paper* 2/1897