Polyketoenols and Chelates. Glaucyrones and their Reactions with Magnesium Methoxide

By **S. Richard Baker** and **Leslie Crombie,*** Department of Chemistry, University of Nottingham, Nottingham NG7 2RD

Using the pyrone melt procedure of the preceding paper, 3,3′,5,5′-tetrakismethoxycarbonylglaucyrone (2) and the tautomerically unsymmetrical 3′-acetyl-3,5,5′-trimethoxyglaucyrone (5) have been prepared. Conditions can be adjusted to prevent complete ester exchange in the reaction of 3,3′-diacetyl-5,5′-bisethoxycarbonylglaucyrone (1) with excess of magnesium methoxide, in accord with the mechanism proposed. On reaction with the latter reagent, the two new glaucyrones give aromatic penta-esters (11) and (14), and their mechanisms of formation are discussed. Heating these penta-esters effects cyclisation to xanthyrones having aromatic side-chain termini, (13) and (16), respectively.

Up to the present, the only known glaucyrones have been esters of structure (1). Development of a procedure for making these compounds from suitable substituted pyrones, together with an understanding of the mechanism of the original 'melt reaction' between alkyl sodioacetoacetates alkoxymethyleneacetoacetates, and sodium alkoxides,[1,2] has encouraged us to make other types and to examine transformations induced by magnesium methoxide.

3,5-Bismethoxycarbonyl-6-methyl-2-pyrone (3) (2 mol equiv.), dimethyl methoxymethylenemalonate (1 mol equiv.), and dry sodium methoxide (2 mol equiv.) were heated at 100° for 3 h and after treatment with chloroform–4M-acetic acid a black sodium salt was isolated. Treatment of the latter with chloroform–8M-sulphuric acid gave 3,3′-5,5′-tetrabismethoxycarbonylglaucyrone. It formed red needles, m.p. 156—157 °C, from ether and on keeping, the crystals crumbled to a grey powder: crystallised from benzene, however, it gave black plates with a green sheen, m.p. 104—106 °C. Some 3,3′,3′,5-tetrakismethoxycarbonylxanthyrone [3] is also formed in this reaction. N.m.r. data ($CDCl_3$) show that none of the four ester groups is enolised but an AB quartet is present, τ 2.46, *ca.* 2.94 (*J* 15 Hz), with the high-field proton coupled to a methylene at τ 5.84 (*J* 6.5 Hz). The two pyrone hydrogens resonate as singlets at τ 1.32 and 1.33. It is therefore assigned at 7′-H structure (2) in this solvent, though like (1) it is tautomerically symmetrical.

Synthesis of a tautomerically unsymmetrical glaucyrone, the 3′-acetyl-3,5,5′-trismethoxycarbonyl derivative (5), was attempted. An equimolar mixture of pyrones (3) and (4) was employed in a melt reaction similar to that above, and the sodium salts were shaken with chloroform–4M-sulphuric acid (10 min). The sodium salt then remaining was mainly that of the tetraester glaucyrone (2) but from the chloroform layer it was possible to isolate in low yield, 3′-acetyl-3,5,5′-trismethoxycarbonylglaucyrone (5), together with the other symmetrical glaucyrone (1; R = Me). The new 'unsymmetrical' glaucyrone (5) had an n.m.r. spectrum resembling that of (1; R = Me) with an AMX system, τ 2.73, 2.00, 3.18 (*J* 15 and 11 Hz), representing the bridge-chain, an enolised acetyl (τ — 3.90), and pyrone-hydrogen singlets at τ 1.38 and 2.40.

In earlier work [4,5] a striking difference between the reaction of xanthyrones with methoxide ion in the presence of magnesium, as opposed to sodium as a counterion, has been discussed and the role of magnesium as a chelating ion has been emphasised. Diethyl and dimethyl glaucophanic enols (1; R = Me or Et) on treatment with excess of methanolic magnesium methoxide give one and the same triester (6; R = Me) in *ca.* 78% yield. This reaction was envisaged as involving methoxide opening of the pyrone rings with magnesium chelation of the open-chain product. One end cyclises by aldol-type reaction, the other by Claisen. In the original proposal the aldol reaction was shown as nucleophilic attack on a chelated carbonyl.[6] Experience has indicated this to be a less probable mode of attack and we have modified the process to that pictorially summarised in (7). Because of the tautomeric symmetry of the chain, only two conjugated bis-chelates are possible and equilibration between them is envisaged in solution.

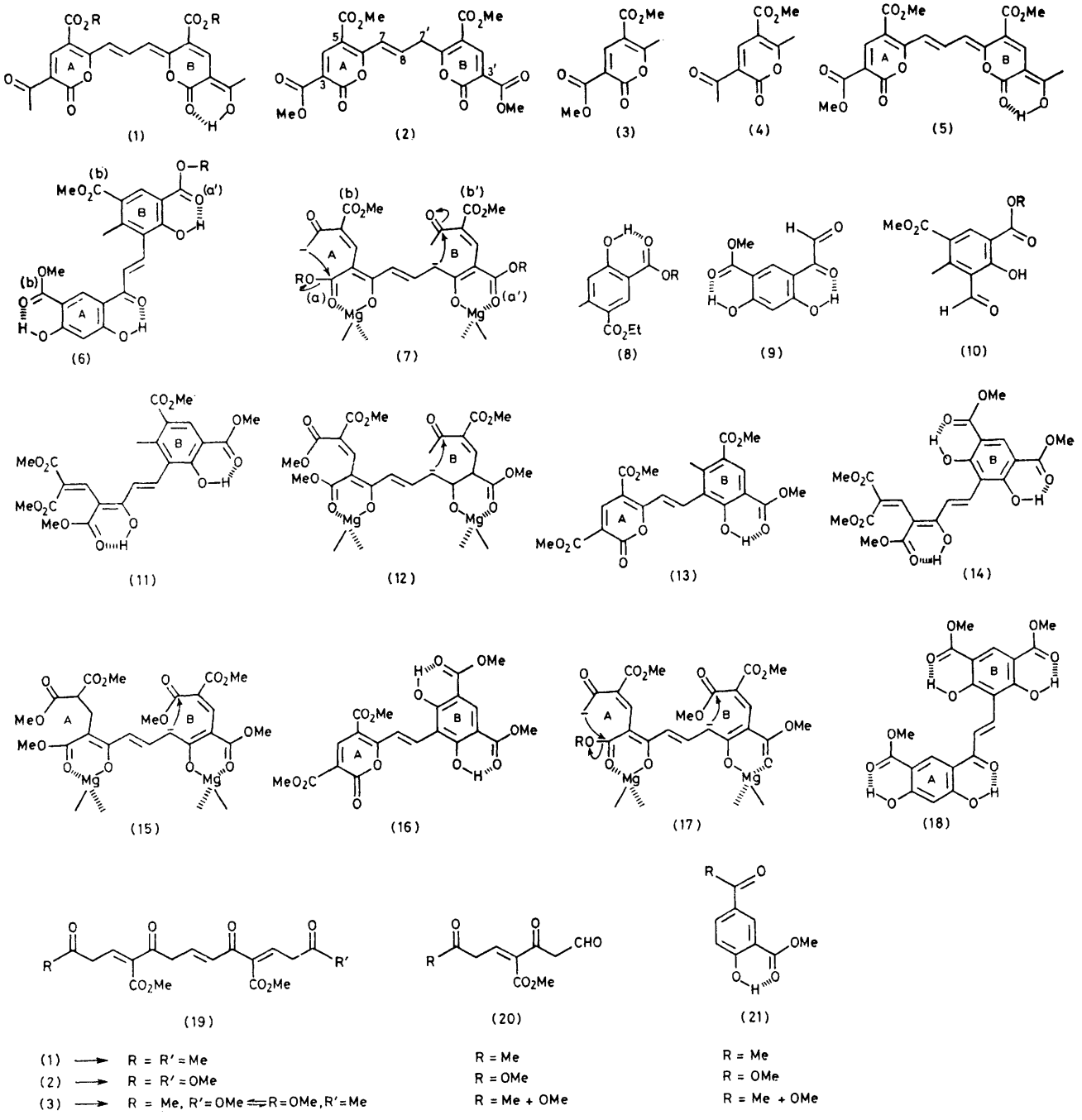
In (7) the esters (b) and (b′) are produced by opening the pyrone ring. Ester (a) is lost in the Claisen ring closure forming ring A. Ester (a′) however should be retained in the product (6). Unfortunately it is subject to ready ester exchange probably because of the enhanced electrophilicity of the carbonyl centre of the magnesio-chelated ester, the same factor promoting Claisen attack in ring A. Thus treatment of diethyl 6-hydroxy-4-methylisophthalate (8; R = Et) with methanolic magnesium methoxide permits formation of methyl 3-ethoxycarbonyl-4-methyl-6-hydroxybenzoate (8; R = Me), exchange involving only the chelated ester to any appreciable extent.

Since ester exchange occurring when (1; R = Et) is converted into (6; R = Me) deprives us of a useful mechanistic pointer [6] we have found conditions under which it can be partly avoided. Treatment of (1; R = Et) in chloroform with magnesium methoxide (6 mol equiv.) in methanol for 1 h allowed the isolation of a *ca.* 3 : 1 mixture (by n.m.r.) of the dimethyl-ethyl triester (6; R = Et) and the trimethyl ester (6; R = Me). Precipitation, presumably of the tris-magnesio-chelate, occurred, and doubtless protects the ethyl ester from more extensive exchange. The position of the unexchanged ethyl ester could be located by the small shift (τ — 1.81 ⟶ — 1.96) on the resonance position of

the chelated hydroxy-proton assigned to the ring-B system of (6). As the two esters (6; R = Me) and (6; R = Et) were difficult to separate, the location of the unexchanged ethyl ester on ring B was established by ozonolysis, which gave the α-keto-aldehyde (9) from ring A and a *ca.* 3 : 1 mixture (by n.m.r.) of the esters (10; R = Et) and (10; R = Me).

Reaction of the tautomerically unsymmetrical glaucyrone (5) with 12 mol equiv. of magnesium methoxide in methanol gave (80% yield) a yellow compound $C_{23}H_{24}O_{12}$ which was somewhat unstable towards crystallisation from methanol, or keeping. It showed i.r. absorptions 1 723 and 1 678 cm^{-1} assigned to esters and chelated esters. The compound had five methyl ester resonances (τ 6.08—6.35) and two chelated hydroxys (τ — 1.40 and —2.80). There was an AB system, τ 2.90, 2.31 (*J* 16 Hz), proton singlets at τ 1.73 and 2.29, assigned as aromatic and olefinic protons, and an aromatic methyl signal at τ 7.56.

Structure (11) accommodates these data. The origins of ring B in (11) are shown in (12) which parallels those in (7). However the system is now not capable of the



ring-A-forming Claisen condensation in (7) which leads to (6), and with no carbocyclisation possibilities open the monocyclic (11) results.

Refluxing (11) in xylene (3 h) gave a new orange crystalline compound, $C_{22}H_{20}O_{11}$, with mass spectral fragmentation similar to that of (11). I.r. data were also similar but a new absorption was present at 1 773 cm^{-1} assigned to a 2-pyrone carbonyl. The n.m.r. features expected for ring B were present: two methyl esters τ 6.10, 6.04, chelated hydroxy, τ −1.65, aromatic singlet, τ 1.62, and aromatic methyl, τ 7.28. A bridge AB quartet, τ 1.78, 2.10 (J 16 Hz), was present. For ring A there were two further methyl esters at τ 6.10 and a pyrone proton at τ 1.41. It is clear that (11) has been transformed into the pyrone (13) which represents a new xanthyrone type having the side-chain terminated by a chelated aromatic system.

The tetraester glaucyrone (2) when treated with 12 mol equiv. of magnesium methoxide gave in 81% yield a yellow, rather unstable compound, $C_{22}H_{22}O_{13}$, clearly related to (11). It was formulated as (14). Assignments to ring B in the n.m.r. are: two methyl esters, τ, 6.09, two chelated hydroxys, τ −1.83, and an aromatic singlet, τ 1.70. The AB quartet, τ 2.10, 2.90, had J 16 Hz and there were three further methyl esters, τ 6,19, 6.24, 6.25, together with a chelated hydroxy, τ −2.83, and an olefinic singlet, τ 2.29. Its origin follows previously described lines, double pyrone opening by alkoxide giving (15). The latter cannot now cyclise by an aldol mechanism as in (7) and (12), and the slower Claisen process supervenes giving (14).

On heating in xylene (14) gave the orange xanthyrone (16), $C_{21}H_{18}O_{12}$, $\nu_{max.}$ 1 778 cm^{-1}. Ring B is identified by the two methyl esters, τ 6.10, and two chelated hydroxys, τ −1.93, along with an aromatic proton, τ 1.62. The bridge AB, system τ 1.45, 1.83 (J 16 Hz), was present and two methyl esters for the pyrone ring A resonated at τ 6.16 with the pyrone proton at τ 1.40. The behaviour of (11) and (14) on heating is thus parallel.

It is of interest to compare the aromatic cyclisation of 3′-acetyl-3,5,5′-trismethoxycarbonylglaucyrone (5) with that of the 3,3′,5,5′-tetrakismethoxycarbonyl- and 3,3′-diacetyl-5,5′-bismethoxycarbonylglaucyrones (2) and (1; R = Me). If a ring B cyclisation [summarised in (17)], parallel to that found for the tetrakismethoxycarbonyl case (15) occurred, a similar isophthalate ring would be formed. Aromatic closure to form ring A could also take place using the Claisen pathway postulated in (7) for the 3,3′-diacetyl-5,5′-bismethoxycarbonyl case. This would give the chalcone (18), in magnesium-complexed form. It thus appears that the aldol reaction of (12), giving (11) is considerably faster than other Claisen pathways: with ring B formed the magnesium complex of (11) results. In the formation of (6) from (1) it thus becomes highly likely that ring B forms first *via* aldol reaction, *cf.* (7), and ring-A cyclisation follows by Claisen condensation. It is of course possible that one pyrone ring, *e.g.* in (1) opens and cyclises by aldol condensation before the second pyrone opens: (7) would then represent a summary of events.

Like xanthyrones,[7] glaucyrones undergo decarboxylation on boiling with water to release a reactive chain: this may be represented as undergoing cleavage by retroaldol reaction, the newly formed formyl group reacting by aldol condensation to give an aromatic product. Thus (1) gives the acetophenone (21; R = Me)[6] whilst (2) gives the isophthalic ester (21; R = OMe). The 'mixed' xanthyrone (5), because of glutaconic type tautomerism of the central double bond in (19), can yield both (20; R = Me) and (20; R = OMe) and hence gives the mixture (21; R = Me) and (21; R = OMe). The timing of pyrone decarboxylation and retroaldol cleavage is uncertain: the latter might alternatively be written as an earlier event.

EXPERIMENTAL

3,3′,5,5′-*Tetrakismethoxycarbonylglaucyrone* (2).—The preparation of this sodium salt has been described.[3] The salt (4.3 g) was ground and shaken with chloroform (500 ml) and 8M-sulphuric acid (100 ml) for 2 days in the dark. The red chloroform layer was filtered, washed with water (50 ml), dried, and evaporated to low bulk. Ether was added and the solution was set aside at 0 °C to give 3,3′,5,5′-*tetrakismethoxycarbonylglaucyrone* (2) (3.71 g), m.p. 156—157°, as red needles. Crystallised from benzene it formed black plates with a green sheen, m.p. 104—106° (Found: C, 54.5; H, 4.0%; M^+, 462. $C_{21}H_{18}O_{12}$ requires C, 54.5; H, 3.9%; M, 462), $\nu_{max.}$ (KBr) 1 765 and 1 710 cm^{-1}. For further spectral data see the following paper.

Besides the glaucyrone (2) and the tetrakismethoxycarbonylxanthyrone already described,[3] trimethyl toluene-1,3,5-tricarboxylate,[7] 2,4,7-trismethoxycarbonyl-1-methyl-6-hydroxynaphthalene, and 3′-acetyl-3,3′,5-trismethoxycarbonylxanthyrone[7] were observed as products of the 'melt reaction'.

3′-*Acetyl*-3,5,5′-*trismethoxycarbonylglaucyrone* (5).—3-Acetyl-5-methoxycarbonyl-6-methyl-2-pyrone (4) (0.99 g), 3,5-bismethoxycarbonyl-6-methyl-2-pyrone (3) (1.06 g), methoxymethyleneacetoacetate (0.27 g), and sodium methoxide (0.39 g) were mixed and heated at 100 °C (2 h). On cooling, the black solid was crushed and washed with 4M-acetic acid and chloroform until the washings were no longer coloured. The black residue (0.82 g) was shaken with 4M-sulphuric acid (100 ml) and chloroform (200 ml) for 30 min and filtered. The residual sodio-derivative was mainly that of the tetrakismethoxycarbonylglaucyrone (2). After washing and drying the chloroform layer was evaporated and the residue crystallised from benzene. The first crop yielded 3′-*acetyl*-3,5,5′-*trismethoxycarbonylglaucyrone* (5) (23 mg), black plates, m.p. 178—180 °C (Found: C, 55.95; H, 4.0%; M^+, 446. $C_{21}H_{18}O_{11}$ requires C, 56.50; H, 4.05; M, 446), $\nu_{max.}$ (KBr) 1 758 and 1 718 cm^{-1}. The remainder of the material was mainly 3,3′-diacetyl-5,5′-bismethoxycarbonylglaucyrone (1; R = Me).

Treatment of 3,3′-*Diacetyl*-5,5′-*bisethoxycarbonylglaucyrone* (1; R = Et) *with Excess of Magnesium Methoxide*.—The glaucyrone (1; R = Et) (2.29 g) in chloroform (50 ml) was added to magnesium methoxide solution [from magnesium (0.72 g) and dry methanol (100 ml)] and stirred for 1 h at 20 °C. The product was poured into iced 4M-hydrochloric acid and extracted with chloroform. Washing, evaporation,

and crystallisation from ether gave a mixture of dimethyl ethyl ester (6; R = Et) and trimethyl ester (6; R = Me) (*ca.* 75 : 25 by n.m.r.) m.p. 209—210° (Found: C, 59.9; H, 4.5. Calc. for, 75 : 25 mixture of $C_{23}H_{22}O_{10}$ and $C_{22}H_{20}O_{10}$: C, 59.05; H, 4.75%), $\nu_{max.}$ 1 721, 1 678, 1 641, 1 608, and 1 572 cm^{-1}, $\lambda_{max.}$ (EtOH) 226 (ε 35 700), 254 (36 900), 303 (17 800), and 349 (19 500) nm, τ($CDCl_3$) −3.20 (1 H, s), −1.96 (*ca.* 0.75 H, s), −1.81 (*ca.* 0.25 H, s), and −1.02 (1 H, s). The retained ethyl ester resonated at τ 8.52, 5.51 (*J* 7 Hz) and the exchanged methyl ester at this position at τ 5.97. There was an AB quartet, τ 1.94, 2.13 (*J* 16 Hz), an aromatic methyl, τ 7.24, and aromatic protons, τ 1.50, 1.54, 3.53: two other methyl esters resonated at τ 6.00 and 6.08.

The above mixture (0.5 g) was ozonised in chloroform (100 ml) for 15 min, dimethyl sulphide (0.5 ml) and water (50 ml) were added, and chloroform was evaporated. The aqueous solution was refluxed (30 ml) and the water decanted off. The oily residue was extracted with ether and the product crystallised as a mixture of (10; R = Et) and (10; R = Me) (*ca.* 3 : 1), m.p. 68—70°, τ −0.60, 1.59, 6.09, 7.19 with the chelated hydroxy doubled, τ −2.04, −2.00, a methyl ester at τ 6.00, and a corresponding ethyl ester at τ 8.59 and 5.51 (*J* 7 Hz). The aqueous fractions gave keto-aldehyde (9) [6] on cooling, m.p. and mixed m.p. 199—200°, i.r. spectrum identical with that of an authentic specimen.

Treatment of 3,3′,5,5′-*Tetrakismethoxycarbonylglaucyrone* (2) *with Excess of Magnesium Methoxide*.—The glaucyrone (2) (400 mg) in chloroform (50 ml) was added to magnesium methoxide solution [from magnesium (247 mg) and methanol (50 ml)] and stirred overnight. The product was poured into 4M-hydrochloric acid and extracted with chloroform to give the *pentaester* (14) (343 mg, 81%), yellow needles which underwent a change at 170 °C and melted at 250 °C (decomp.) (Found: M^+, 494.106, $C_{22}H_{22}O_{13}$ requires *M*, 494.106), $\nu_{max.}$ (KBr) 3 500, 1 737, 1 718, 1 623, and 1 603 cm^{-1}, $\lambda_{max.}$ (EtOH) 379 (ε 18 700) and 254 (22 500) nm, τ($CDCl_3$) −2.83 (1 H, chelated hydroxy), −1.83 (2 H, chelated hydroxys), 1.70 (1 H, aromatic H), 2.29 (1 H, olefinic singlet), 2.10, 2.90 (2 H, olefinic AB, *J* 16 Hz), 6.09 (6 H, two methyl esters), 6.19, 6.24, 6.35 (each 3 H, three methyl esters).

Pentaester (14) (20 mg) was refluxed in xylene (20 ml) for 3 h. Evaporation and crystallisation from benzene gave *pyrone* (16) (18 mg), orange needles, m.p. 245—250° (decomp.) (Found: C, 54.8; H, 3.85%; M^+, 462. $C_{21}H_{18}O_{12}$ requires C, 54.55; H, 3.9%; *M*, 462), $\nu_{max.}$ 1 778, 1 725, 1 675, 1 603, and 1 583 cm^{-1}; $\lambda_{max.}$ (EtOH) 410 (ε 28 800) and 256 (31 400) nm, τ($CDCl_3$) −1.93 (2 H, chelated hydroxys), 1.40 (1 H, pyrone 4 H), 1.62 (1 H, aromatic H), 1.45, 1.83 (2 H, olefinic AB, *J* 16 Hz), 6.10 (6 H, two methyl esters), and 6.16 (6 H, two methyl esters).

Treatment of 3-*Acetyl*-3′,5,5′-*trismethoxycarbonylglaucyrone* (5) *with Excess of Magnesium Methoxide*.—Glaucyrone (5) (50 mg) in chloroform (10 ml) was added to magnesium methoxide solution [from magnesium (31 mg) and methanol (25 ml)] and stirred at 20° (3 h). Work up as above gave the *pentaester* (11) (43 mg, 80%), yellow crystals from chloroform–methanol, m.p. 110—112 °C (decomp.) (Found: M^+, 492. $C_{23}H_{24}O_{12}$ requires *M*, 492). The *M* − H_2O ion was measured as 474.115, $C_{23}H_{22}O_{11}$ requires 474.116. The ester had $\nu_{max.}$ (KBr) 3 480, 1 723, 1 678, 1 640, and 1 603 cm^{-1}, $\lambda_{max.}$ (EtOH) 364 (ε 17 600), 290 infl. (12 800), and 253 (11 800) nm, τ($CDCl_3$) −2.80, −1.40 (each 1 H, chelated hydroxys), 1.73 (1 H, aromatic H), 2.29 (1 H, olefinic H), 2.31, 2.90 (2 H, olefinic AB, *J* 16 Hz), 6.08, 6.18, 6.26, 6.29, 6.35 (each 3 H, five methyl esters), and 7.56 (aromatic methyl).

Pentaester (11) (4 mg), refluxed in xylene (10 ml) for 2 h gave the *pyrone* (13) (2.9 mg), yellow-orange needles from chloroform–methanol, m.p. 240 °C (decomp.) (Found: M^+, 460.100. $C_{22}H_{20}O_{11}$ requires *M*, 460.100), $\nu_{max.}$ (KBr) 1 773, 1 714, 1 670, 1 605, and 1 580 cm^{-1}, $\lambda_{max.}$ (EtOH) 400 (ε 8 750), 351 (7 600), and 341 (7 600) nm, τ −1.65 (1 H, chelated hydroxy), 1.41 (1 H, pyrone 4-H), 1.62 (1 H, aromatic H), 1.78, 2.10 (2 H, olefinic AB, *J* 16 Hz), 6.10 (9 H, three ester methyls), 6.04 (3 H, ester methyl), and 7.28 (aromatic methyl).

Treatment of Diethyl 5-*Hydroxytoluene*-2,4-*dicarboxylate* (8; R = Et) *with Magnesium Methoxide* (*experiment by M. H. Knight*).—The ester (0.25 g) in benzene (1 ml) was added to magnesium methoxide solution [from magnesium (0.15 g) and methanol (3 ml)], kept 6 days, and poured into water. Acidification and extraction with benzene gave 2-ethoxycarbonyl-4-methoxycarbonyl-5-hydroxytoluene (8; R = Me) (0.19 g), needles from light petroleum (b.p. 40—60°), m.p. 58—59 °C (Found: C, 60.4; H, 5.7. Calc. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9%), $\nu_{max.}$ (mull) 1 709, 1 675, 1 658, 1 621, and 1 570 cm^{-1}. It did not depress the m.p. of an independently prepared specimen, but on admixture with diethyl 5-hydroxytoluene-2,4-dicarboxylate, m.p. 51—51.5 °C, a depression of 13 °C was recorded: the dimethyl ester has m.p. 114—115 °C.[2]

Treatment of 3,3′,5,5′-*Tetrakismethoxycarbonylglaucyrone* (2) *and* 3′-*Acetyl*-3,5,5′-*trismethoxycarbonylglaucyrone* (5) *with Boiling Water*.—The glaucyrone (2) (100 mg) was refluxed with water (20 ml) until the blue solution became pale yellow (3 h). Extraction with chloroform, followed by preparative t.l.c. (silica HF 254) eluting with chloroform–acetone–acetic acid (50 : 50 : 1), gave dimethyl 4-hydroxyisophthalate (21; R = OMe) (23 mg), m.p. and mixed m.p. 92—93 °C (lit.,[7] 94—95 °C).

Similarly glaucyrone (5) (3 mg) gave dimethyl 4-hydroxyisophthalate (21; R = OMe) and methyl 4-hydroxyacetophenone-3-carboxylate (21; R = Me),[7] identified by t.l.c. comparison with authentic specimens and n.m.r. examination of the mixture (approximately equal amounts).

One of us (S. R. B.) thanks the University of Nottingham for a Postgraduate Studentship.

[0/491 *Received*, 31*st March*, 1980]

REFERENCES

[1] S. R. Baker and L. Crombie, preceding paper; *J.C.S. Chem. Comm.*, 1980, 211, 213.
[2] L. Crombie, D. E. Games, and A. W. G. James, *J.C.S. Perkin I*, 1979, 464.
[3] S. R. Baker, L. Crombie, and R. V. Dove, *J.C.S. Perkin I*, 1981, 165.
[4] L. Crombie, M. Eskins, D. E. Games, and C. Loader, *J.C.S. Perkin I*, 1979, 472.
[5] L. Crombie, D. E. Games, and M. H. Knight, *J. Chem. Soc.* (*C*), 1967, 763.
[6] L. Crombie, D. E. Games, and M. H. Knight, *J. Chem. Soc.* (*C*), 1967, 773.
[7] L. Crombie, M. Eskins, D. E. Games, and C. Loader, *J.C.S. Perkin I*, 1979, 478.