Polyketoenols and Chelates. The Mechanism by which Glaucophanic Enols are formed

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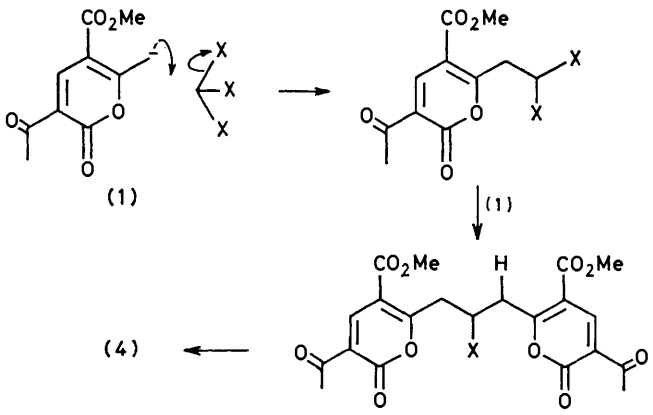
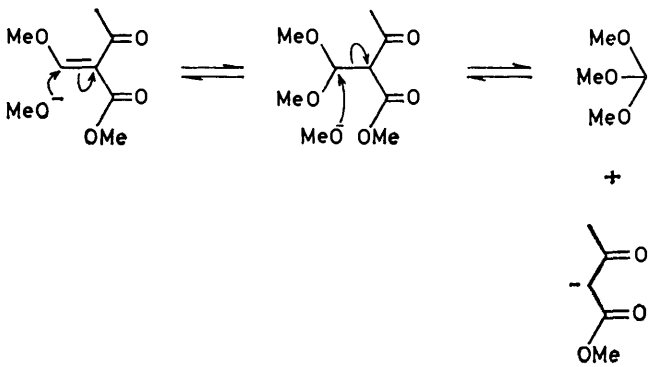
Attempts to make dimethyl glaucophanic enol (4) by coupling the anion from 3-acetyl-5-methoxycarbonyl-6-methyl-2-pyrone (2) (2 mol equiv.) through a one-carbon source were unsuccessful, as were attempts to derive it by treating the anion with dimethyl xanthophanic enol (5). However, a ' melt reaction ' between pyrone (2) (2 mol equiv.), methyl methoxymethyleneacetoacetate (1 mol equiv.), and dry sodium methoxide gave glaucyrone (4) (49%). By using methyl methoxy[^{14}C]methyleneacetoacetate in the reaction, labelled glaucyrone (4) and xanthyrone (5) were obtained with the same specific activities. The central (C-8) position of the label in (4) was shown by magnesium methoxide-catalysed transformation into the chalcone (7) which was ozonised to (8) and (9). Extraction of the atom, which corresponds to C-8 in (4), from the latter by Dakin reaction accounted for 89% of the original radioactivity. The two residual aromatic fragments each contain 4% of the activity, which can be explained by equilibration of the label into the pyrone rings of (4). A unified mechanism for the formation of xanthyrones and glaucyrones in ' melt reactions ' can now be advanced and factors favouring one or the other product understood. This is supported by comparison of the xanthyrone–glaucyrone-forming ability of five alkoxymethylene compounds.

STRUCTURE (4), 3,3'-diacetyl-5,5'-bismethoxycarbonylglaucyrone, was proposed earlier for the black crystalline dimethyl glaucophanic enol formed along with red dimethyl xanthophanic enol (5) when methyl methoxymethyleneacetoacetate is heated at 100 °C with solid methyl sodioacetoacetate.[1] The pathway by which dimethyl xanthophanic enol (3,3'-diacetyl-3,5'-dime thoxycarbonylxanthyrone) (5) arises is now fairly well established.[2,3] It involves formation of the pyrone (2) and Michael addition of its anion (1) to methyl methoxymethyleneacetoacetate (3) (*cf.* Scheme 5). On the other hand little is known about the way in which the glaucyrone (4) is formed.

One hypothesis is that two pyrone units might be coupled *via* their anions (1) through a one-carbon source present in the ' melt reaction ' mixture (Scheme 1). A possible one-carbon source is trimethyl orthoformate formed from methyl methoxymethyleneacetoacetate in the equilibrium shown (Scheme 2). However, only trace amounts of the glaucyrone (4) were obtained when 3-acetyl-5-methoxycarbonyl-6-methyl-2-pyrone (2) was treated with trimethyl orthoformate in the presence of bases (sodium methoxide in methanol, lithium diisopropylamide in tetrahydrofuran, potassium t-butoxide in t-butyl alcohol). ' Melt reaction ' between pyrone (2), sodium methoxide, and trimethyl orthoformate was also unsuccessful, the naphthalene (6) being formed in low yield. Iodoform was also not successful as a carbon source and no experimental support for Scheme 1 could be obtained.



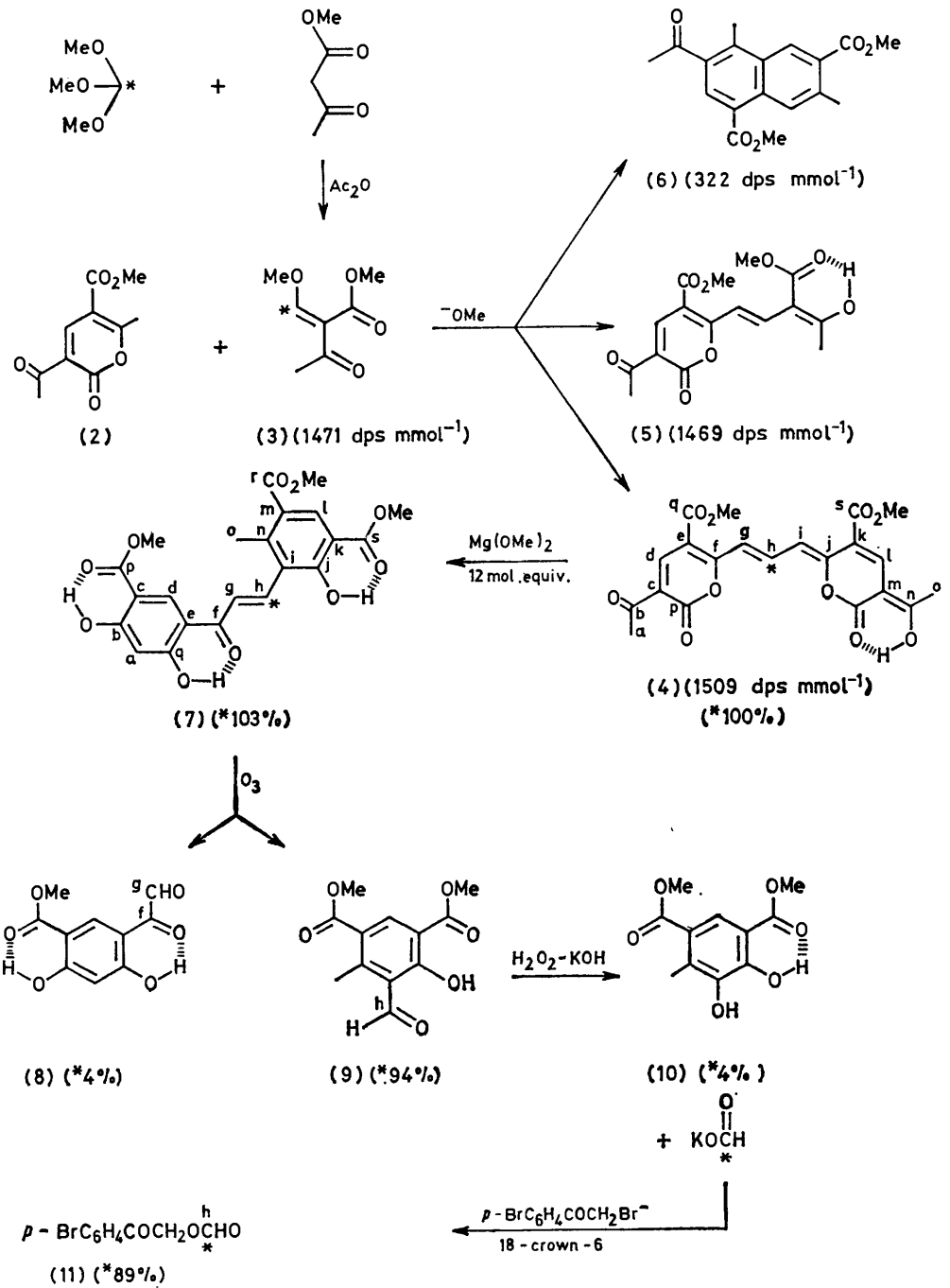
SCHEME 1



SCHEME 2

A possible route to glaucyrones is *via* the corresponding xanthyrones, but heating dimethyl xanthophanic enol (5) with sodium methoxide and the pyrone (2) at 100 °C under ' melt conditions ' gave only unchanged xanthyrone, the naphthalene (6), and traces of glaucyrone. Various exploratory reactions were then undertaken but only one yielded the desired glaucyrone in anything but traces. This was a reaction, under ' melt conditions ', between the pyrone (2) (2 mol equiv.) and methyl methoxymethyleneacetoacetate (1 mol equiv.) in the presence of dry sodium methoxide (2 mol equiv.). The glaucyrone (4) was produced in good yield (49%) as compared with that from the original melt procedure (*ca.* 25%).[1] With this method available, the fate of the methoxymethylene carbon atom in methyl methoxymethyleneacetoacetate was traced radiochemically using ^{14}C labelling.

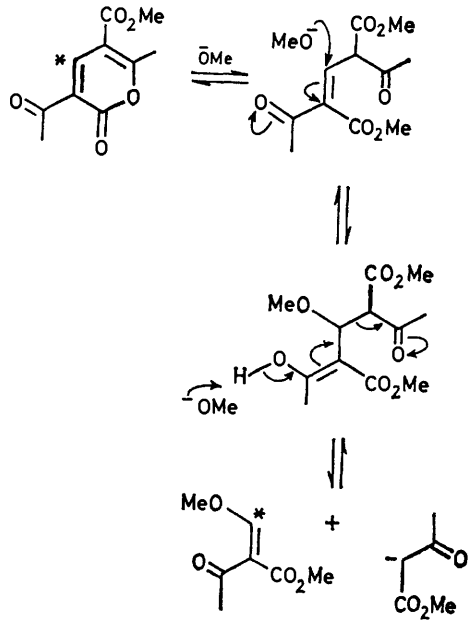
Ethyl [^{14}C]formate was converted into [^{14}C]formamide by treatment with liquid ammonia and a catalytic quantity of sodium methoxide, and then with methanol and ethyl chloroformate [4] to give trimethyl [^{14}C]orthoformate. After distillation, the latter was converted into methyl methoxy[^{14}C]methyleneacetoacetate using methyl acetoacetate in acetic anhydride. The product, m.p. 56—58 °C, had a specific activity of 1 471 dps mmol^{-1} and was converted into the glaucyrone (4) using pyrone (2) and the method above. After recrystallisation, the glaucyrone, m.p. 206—207 °C, had specific activity 1 509 dps mmol^{-1}. Also formed in the reaction was 3,3'-diacetyl-3',5-bismethoxycarbonylxanthyrone (5)



Scheme 3

The specific activities of the xanthyrone (5) and glaucyrone (4) show that the methylene carbon atom of 1 mol equiv. of methyl methoxymethyleneacetoacetate

is involved in the formation of each (Scheme 3). The location of the [^{14}C]label in the glaucyrone was then tracked by converting it into the chalcone (7) by treatment with 12 mol equiv. of magnesium methoxide.



SCHEME 4

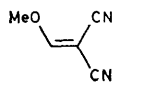
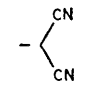
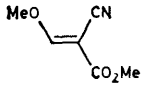
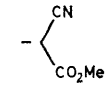
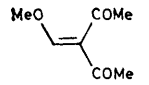
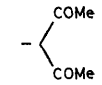
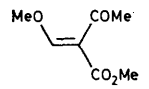
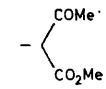
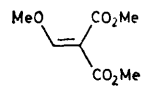
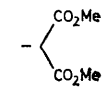
This reaction and its mechanism are discussed elsewhere,[1,6] and the position of the erstwhile central carbon of the main chain of the glaucyrone is starred. The lettering on (7) shows the derivation of its constituent carbon atoms from glaucyrone (4). Ozonolysis of the chalcone (7) gave the keto-aldehyde (8) carrying only 4% of the label, and the formyl hydroxyisophthalic ester (9) carrying 94% of the label. That the label was mainly contained in the formyl group of the latter was shown by Dakin oxidation with alkaline hydrogen peroxide. This gave the catechol (10) carrying 4% of the radioactivity, together with potassium formate. The latter was characterised as the crystalline *p*-bromophenacyl ester (11) and, counted in this form, contained 89% of the label present in the original glaucophanic enol (4).

These results clearly demonstrate that the primary source of the central carbon of the latter, as produced in the melt reaction between pyrone (2) and methyl methoxymethyleneacetoacetate, is the methylene carbon of the latter. There is a small escape of label, *ca.* 4%, into each pyrone ring as shown by the residual counts in (8) and (10). This is not entirely surprising as one is dealing with various equilibria in the formation of glaucophanic and xanthophanic enols. Thus formation of acetoacetate anion by Scheme 2, or by Scheme 4 (omitting radiolabelling asterisks), allows building of the radiolabel into C-3 of the pyrone (2) by reaction with labelled methyl methoxymethyleneacetoacetate (Scheme 4, with asterisks, run in reverse).

With this information to hand, a unified mechanism for the formation of xanthyrones and glaucyrones can be proposed, as shown in Scheme 5. Michael reaction between the pyrone anion (1) and methyl methoxymethyleneacetoacetate leads to (12). Anion (12) eliminates methoxide ion to give the xanthyrone (5) which forms the sodio-derivative: the equilibrium is very much in favour of the latter. On the other hand, the anion may competitively protonate (13) (or tautomer) and then becomes susceptible to attack by (1) with displacement of methyl acetoacetate anion leading to (14). Alternatively the 1′-anion from (13) may be viewed as eliminating acetoacetate anion giving the alkoxymethylene pyrone (15): Michael addition of (1) then leads to the anion of (14). Subsequent elimination of methoxide ion and enolisation gives the glaucyrone (4) which forms its sodio-derivative. Xanthyrone (5) was a poor source of glaucyrone (4) as mentioned earlier, and there is no rapid regressive degradation of glaucyrone sodio-derivative to xanthyrone under the ' melt conditions ' employed. In such a ' melt reaction ', the overall system is driven by distillation of methanol.

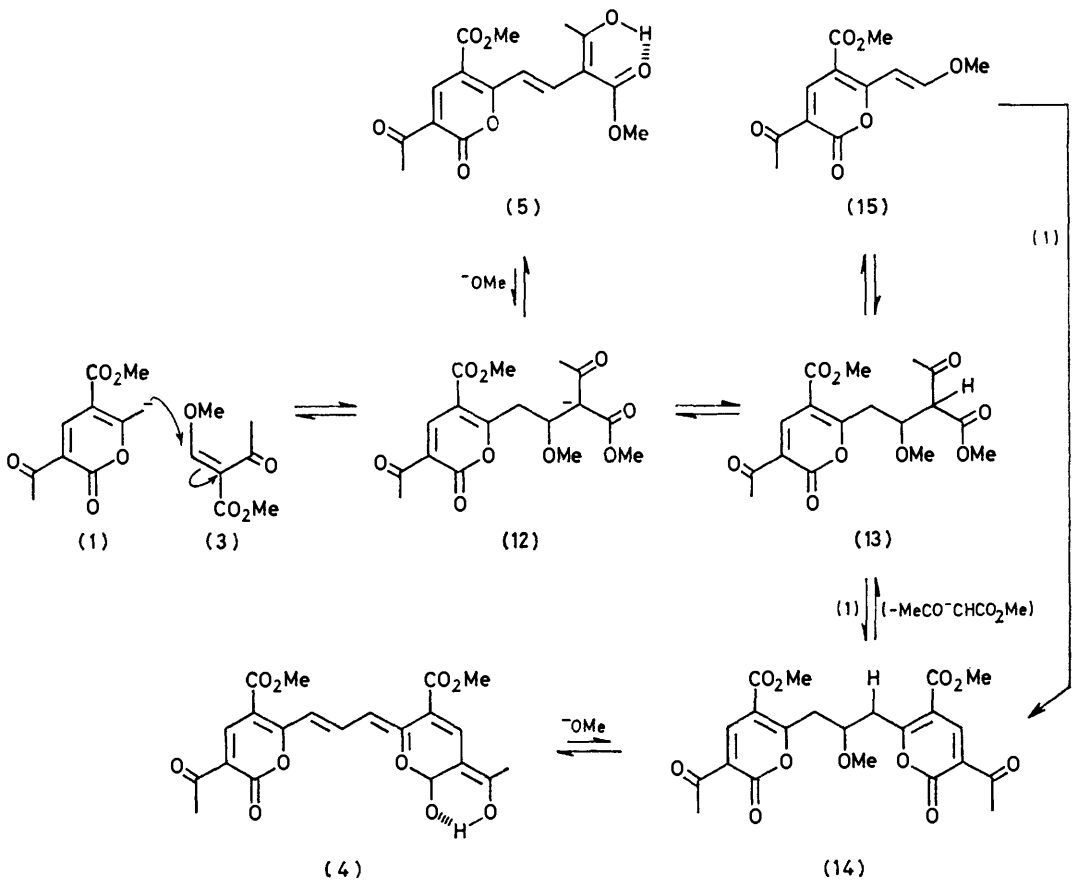
A feature of the proposed scheme for glaucyrone formation is the necessity for competitive protonation of the initially formed anion (12), and the role of the acetoacetate anion as leaving group. In order to probe this further, the methoxymethylene compounds listed in the Table were in turn allowed to react with pyrone

Methoxymethylene compounds as sources of the central carbon of glaucyrone (4)

Carbon source	Leaving group	Yield of glaucyrone (%)	Yield of xanthyrone (%)
		Nil	86
		Trace	88
		2	85
		49	44
		56	4

(2) in the presence of dry sodium methoxide under the conditions mentioned earlier. Only in the cases of methyl methoxymethyleneacetoacetate and dimethyl methoxymethylenemalonate was glaucyrone (4) found in good yield. The yield of the latter appears to *decrease* as the stability of the leaving anion increases, while the reverse trend is shown in the formation of the various

xanthyrones. For glaucyrones, the key intermediate in Scheme 5 is (13), and increased acidity at the 3'-position (or of the corresponding enolised proton) encourages the largely irreversible loss of methoxide ion from (12). The susceptibility of (13) and related compounds to the displacement or 1'-initiated elimination required is dependent on an adequate supply of the unionised species and so glaucyrone formation is suppressed in those cases with more acidic termini, despite the fact that they provide good potential leaving groups. Moderate acidity achieves the required compromise.



SCHEME 5 Delocalised or tautomeric forms assumed

Attempts have been made to employ methanol as a solvent in the sodium methoxide catalysed reaction between pyrone (2) and methyl methoxymethyleneacetoacetate, but the major product was xanthyrone (5) with only trace quantities of glaucyrone. In a similar reaction in methanol using dimethyl methoxymethylenemalonate, however, the glaucyrone (4) was obtained, but in rather low yield (11%).

EXPERIMENTAL

3,3'-Diacetyl-5,5'-bismethoxycarbonylglaucyrone (4) *from 3-Acetyl-5-methoxycarbonyl-6-methyl-2-pyrone* (2) *by Melt Procedure.*—The pyrone (2) (2.1 g), methyl methoxymethyleneacetoacetate (3) (0.79 g), and dry sodium methoxide (0.54 g) were heated together for 3 h at 100 °C. The black solid was ground and extracted with acetic acid (4M; 100 ml) and chloroform (200 ml). Filtration gave, after washing with chloroform, the sodio-derivative of 3,3'-diacetyl-5,5'-bismethoxycarbonylglaucyrone (4) (1.1 g, 49%). Evaporation of the chloroform solution gave 3,3'-diacetyl-3',5-bismethoxycarbonylxanthyrone (5) (0.74 g, 44%). Treatment of the sodioglaucyrone with 4M-sulphuric acid in chloroform gave the glaucyrone (4), m.p. and mixed m.p. 204—205° (lit.,[1] 207°), i.r. spectrum identical with that of an authentic sample.

Replacement of methyl methoxymethyleneacetoacetate by methyl methoxymalononitrile in the above procedure (1/20th scale) gave no glaucyrone (4): the chloroform layer gave 3-acetyl-3,3'-dicyano-5-methoxycarbonylxanthyrone [7] (86%). Similarly, methoxymethyleneacetylacetone gave the sodio-derivative of glaucyrone (4) (2.5%) and 3,3',3'-triacetyl-5-methoxycarbonylxanthyrone [8] (85%). Employment of methyl methoxymethylenecyanoacetate gave only traces of glaucyrone (4) identified by t.l.c., and 3-acetyl-3'-cyano-3',5-bismethoxycarbonylxanthyrone [7] (88%). When (3) was replaced by dimethyl methoxymethylenemalonate in the above reaction, the sodio-derivative of glaucyrone (4) (56%), and 3-acetyl-3',3',5-trismethoxycarbonylxanthyrone [7] (4%) were obtained.

Formation of 3,3'-Diacetyl-5,5'-bismethoxycarbonylglaucyrone (4) *in Methanol.*—3-Acetyl-5-methoxycarbonyl-2-pyrone (448 mg) and dimethyl methoxymethylenemalonate

(348 mg) were added to sodium methoxide (108 mg) in dry methanol. After refluxing (15 min) the solution was evaporated and treated with 4M-acetic acid and chloroform to give the sodio-derivative of glaucyrone (4) (11%). 3-Acetyl-3′,3′,5-trismethoxycarbonylxanthyrone [7] was also formed.

Refluxing pyrone (2) (112 mg) with potassium t-butoxide [from potassium (18 mg) and t-butyl alcohol (20 ml)] and ethyl ethoxymethyleneacetoacetate (46.5 mg) for 2 h gave 3,3′-diacetyl-3′,5-bisethoxycarbonylxanthyrone with only traces of glaucyrone (4). Potassium t-butoxide in dimethylformamide gave similar results, as did reactions employing sodium methoxide in dry toluene or dimethyl sulphoxide.

Attempts to form Glaucyrone (4) *from Pyrone* (2) (2 mol equiv.) *by One-carbon Supply* (1 mol equiv.). Butyllithium (64 mg) in hexane was added to di-isopropylamine (101 mg) in dry tetrahydrofuran (10 ml) under nitrogen at −78 °C followed by 3-acetyl-5-methoxycarbonyl-6-methyl-2-pyrone (2) (210 mg) in tetrahydrofuran (10 ml). Trimethyl orthoformate (53 mg) in tetrahydrofuran (10 ml) was added, the temperature being kept at −78 °C for 2 h. The mixture was allowed to warm to room temperature (overnight) and then refluxed (2 h). Work up gave no glaucyrone (4), only xanthyrone (5) and naphthalene (6) being formed.

Pyrone (2) (210 mg), refluxed (2 h) in dry methanol (50 ml) containing sodium methoxide (54 mg) and trimethyl orthoformate (53 mg) gave naphthalene (6) as major product and no glaucyrone (4). Similar experiments using potassium t-butoxide in t-butyl alcohol gave similar results, as did replacement of orthoformate by iodoform.

Melt reaction (100 °C; 3 h) between pyrone (2) (210 mg), trimethyl orthoformate (56 mg), and sodium methoxide (54 mg) gave only traces of (4), and iodoform produced no improvement.

Attempts to form Glaucyrone (4) *from* 3,3′-*Diacetyl*-3′,5-*bismethoxycarbonylxanthyrone* (5).—The following experiment is typical. Xanthyrone (5) (168 mg), pyrone (2) (105 mg), and dry sodium methoxide (27 mg) were heated 100°; 2 h) in a melt reaction. Acidification with 4M-hydrochloric acid, and extraction with chloroform, gave unchanged xanthyrone (109 mg) and only traces of glaucyrone (4), detected by t.l.c.

Methyl Methoxy[^{14}C]*methyleneacetoacetate* (3).—Ethyl [^{14}C]formate (250 μCi) was diluted with trimethyl orthoformate (20 ml) and used as a stock solution. As assayed by formation of methyl methoxymethyleneacetoacetate, exchange between the formate and othoformate, catalysed by toluene-*p*-sulphonic acid, boron trifluoride–ether, or zinc chloride was slow and incomplete so the following procedure was adopted.

A portion (5 ml; 50 μCi) of the stock solution was diluted with trimethyl orthoformate (20 ml), and treated with sodium methoxide (5 mg) and liquid ammonia (5 ml). After keeping (36 h) *ca.* 2 ml of orthoformate was distilled to remove excess of ammonia, and methanol (1 ml) and ethyl chloroformate (3 ml) [4] were added, the mixture being warmed at 40 °C (2 h). Trimethyl orthoformate was distilled and collected as three fractions: (a) b.p. 96—98 °C (10.3 g; 1 281 dps mmol^{-1}), (b) b.p. 98—99 °C (4.6 g; 1 251 dps mmol^{-1}), (c) b.p. 99—100 °C (6.2 g; 1 309 dps mmol^{-1}).

Trimethyl [^{14}C]orthoformate (14.9 g) was treated with methyl acetoacetate (16.3 g) and acetic anhydride (24 g) under reflux (90 min).[3] Vacuum distillation gave methyl methoxy[^{14}C]methyleneacetoacetate (3) (10.2 g, 46%), b.p. 80—84° at 0.15 mmHg, 1 389 dps mmol^{-1}. A second vacuum distillation gave crystalline material (8.11 g), b.p. 82—84 °C at 0.15 mmHg, m.p. 57—59 °C (lit.,[3] 56—58 °C), 1 471 dps mmol^{-1}.

Melt Reaction Between Methyl Methoxy[^{14}C]*methyleneacetoacetate,* 3-*Acetyl*-5-*methoxycarbonyl*-6-*methyl*-2-*pyrone, and Sodium Methoxide.*—Methyl methoxy[^{14}C]methyleneacetoacetate (1.58 g), pyrone (2) (4.2 g), and dry sodium methoxide (1.08 g) were heated together at 100 °C for 2 h. Work-up as above gave 3,3′-diacetyl-5,5′-bismethoxycarbonyl[8-^{14}C]glaucyrone (4) (0.89 g), crystallised four times to constant activity, m.p. 206—207 °C (lit.,[1] 207 °C), 1 509 dps mmol^{-1}. From the chloroform layer (see above) a yellow solid was obtained which was washed with light petroleum (b.p. 60—80°) and the washings were kept. The residual solid (1.2 g) was crystallised three times from benzene to constant activity, forming 3,3′-diacetyl-3′,5-bismethoxycarbonyl[^{14}C]xanthyrone (5), m.p. 185—186 °C (lit.,[2] 185 °C), 1 469 dps mmol^{-1}. Evaporation of the light petroleum washings gave, after four recrystallisations, three from methanol and one from light petroleum (b.p. 60—80°), 2-acetyl-4,7-bismethoxycarbonyl-1,6-dimethyl-[^{14}C]naphthalene (6) (106 mg), m.p. 132 °C (lit.,[5] 135 °C), 322 dps mmol^{-1}.

Treatment of 3,3′-*Diacetyl*-5,5′-*bismethoxycarbonyl*[8-^{14}C]-*glaucyrone* (4) *with Excess of Magnesium Methoxide.*—The [8-^{14}C]glaucyrone (0.86 g) in chloroform (15 ml) was added to magnesium methoxide solution [from magnesium (0.58 g) and dry methanol (100 ml)] and stirred at 20° (1 h). The product was poured into ice-cold 4M-hydrochloric acid and extracted with chloroform. Evaporation and crystallisation from chloroform–ether gave the chalcone (7) (0.73 g, 82%), yellow-green needles, m.p. 226—227 °C (lit.,[1] 226—227 °C). It was crystallised four times to constant specific activity, 1 550 dps mmol^{-1}.

Ozonolysis of Chalcone (7).—Chalcone (7) (0.5 g) in chloroform (100 ml) was ozonised for 15 min, the solution becoming colourless. Dimethyl sulphide (0.5 ml) and water (50 ml) were added and the chloroform was evaporated. The aqueous solution was refluxed (30 min), the hot water decanted, and the residual oil washed with further hot water (50 ml) and decanted. The oil was extracted with ether and evaporated to give crude dimethyl 5-formyl-6-hydroxy-4-methylbenzene-1,3-dicarboxylate (9) (123 mg, 44%). This was purified by p.l.c. (HF 254 silica; $CHCl_3$) and crystallised four times from methanol to constant activity, m.p. 125—126° (lit.,[1] 124—125.5 °C), 1 419 dps mmol^{-1}.

On cooling, the hot aqueous decantations deposited crystalline oxo-aldehyde (8) (207 mg, 84%), crystallised three times to constant activity, m.p. 199—200 °C (lit.,[1,9] 200—201 °C), 58.2 dps mmol^{-1}.

Dakin Oxidation of Dimethyl 5-*Formyl*-6-*hydroxy*-4-*methylbenzene*-1,3-*dicarboxylate* (9).—The labelled aldehyde (9) (13.5 mg), in potassium hydroxide (3 mg) in water (5 ml), was treated with 28% hydrogen peroxide solution (50 mg), stirred for 3 h at 40°, and then cooled and extracted with chloroform, the aqueous layer being reserved. Evaporation gave the catechol (10) (9.7 mg) which was crystallised three times from chloroform to constant activity, m.p. 139—140 °C, 59 dps mmol^{-1}.

For characterisation purposes, the degradation was repeated using unlabelled aldehyde (9) and gave *catechol* (10), m.p. 141—142 °C (Found: M^+, 240.060 1. $C_{11}H_{12}O_6$ requires *M*, 240.063 4), $\nu_{max.}$ (KBr) 1 715, 1 681, and 1 607

cm^{-1}, $\tau(CDCl_3)$ −1.00 (1 H), 1.92 (1 H), 4.20br (1 H), 6.03 (3 H, s), 6.11 (3 H, s), and 7.48 (3 H, s).

The aqueous layer (above) was evaporated and the residue thoroughly azeotroped with benzene. *p*-Bromophenacyl bromide (16 mg) and 18-crown-6 (3 mg) were added to the benzene solution (10 ml) and the mixture stirred and refluxed (3 days). The solution was concentrated and applied to a pre-washed ($CHCl_3$) t.l.c. plate (20 × 20 cm; silica HF 254) and eluted with chloroform. The *p*-bromophenacyl formate (3.7 mg), m.p. 99—100 °C (lit.,[10] 100—101 °C) was counted (1 315 dps $mmol^{-1}$) and then washed with a little cold methanol, dried, and counted (1 353 dps $mmol^{-1}$).

Counting Conditions.—Samples were counted in polythene scintillation vials (15 ml) using Nuclear Enterprises 233 toluene-based fluid. Oxo-aldehyde (9) and catechol (10) were dissolved in a little 1,4-dioxan before addition to the fluid. Glaucyrone (4) and xanthyrone (5) quench considerably and difficulties were overcome by adding sodium isopropoxide in propan-2-ol to the scintillation fluid before adding the compound. The sample was allowed to stand for a few hours, just acidified with acetic acid, and counted immediately

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