367. *Studies in the Xanthone Series. Part II.* Preparation and Reactions of 1-Formyl-2-hydroxyxanthone.*

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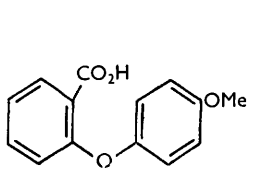
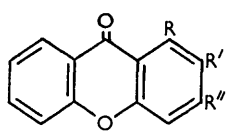
Reactions of 2-hydroxyxanthone leading to the preparation of 1-formyl-2-hydroxyxanthone (II; R = CHO, R′ = OH, R″ = H), furanoxanthones (V), and α-pyronoxanthones (VI) are discussed.

We have investigated reactions of 2-hydroxyxanthone in an attempt to find simple structural analogues of pharmacologically active chromones, such as khellin. We failed to obtain 2-hydroxyxanthone (II; R = R″ = H, R′ = OH) from salicylic acid and quinol,[1] but it was made by cyclisation of the diphenyl ether (I) (prepared from *o*-chlorobenzoic acid and *p*-methoxyphenol) with acetyl chloride–sulphuric acid or polyphosphoric acid, followed by demethylation.



(I)



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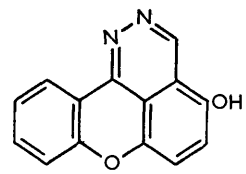

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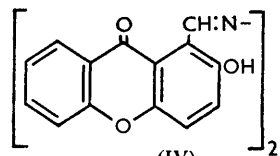


(IV)

o-Fluorobenzoic acid did not afford the ether (I), so it appears that fluorine prevents the carboxylate group from exerting its *ortho*-activating effect in the Ullmann copper-catalysed reactions of aryl halides with phenols. Recent observations that the *o*-carboxylate group is deactivating for methoxy-dechlorination [2,3] may be pertinent in this respect. Successful Ullmann reactions have been reported for *o*-fluorobenzoic esters.[4]

Attempts to cyclise 2-acetonyloxyxanthone (II; R = R″ = H, R′ = O·CH_2·COMe) with sulphuric acid or sulphuric acid–acetic acid were unsuccessful. Moreover, since neither bromoacetal nor ethyl β-bromopropionate condensed with 2-hydroxyxanthone, ring-closure of such ethers as a route to extended xanthone systems was abandoned.

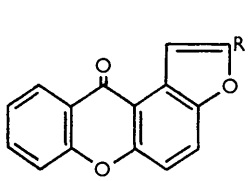
2-Hydroxyxanthone was readily formylated by a Duff reaction or, less conveniently, under Reimer–Tiemann conditions. The resulting aldehyde is 1-formyl-2-hydroxyxanthone (II; R = CHO, R′ = OH, R″ = H) for the following reasons: A Dakin reaction with the aldehyde yields a dihydroxyxanthone, convertible into a methylene ether. Moreover, the diacetyl and the dimethyl derivative differ from those of the alternative 2 : 3-dihydroxyxanthone (II; R′ = R″ = OH, R = H).[5,6] Treatment of the dihydroxy-compound with pyroboroacetate gives a monoacetyl derivative only, and one of the hydroxyl groups shows reduced reactivity (cf. Table: preparation of 2-substituted 1 : 2-dihydroxyxanthones). Both these results are explicable on grounds of chelation [7,8] and thus confirm the 1-position of the newly introduced hydroxyl group. That the two functional groups in the aldehyde are adjacent also follows from successful cyclisations of certain formylhydroxyxanthone derivatives (cf. below). Although the carbonyl reactivity

* Part I, *J.*, 1956, 2140.

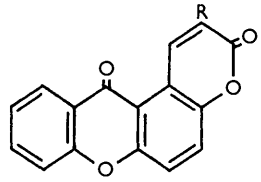
[1] von Kostanecki and Rutishauser, *Ber.*, 1892, **25**, 1648.
[2] Miller and Williams, *J.*, 1953, 1475.
[3] Bunnett, Morath, and Okamoto, *J. Amer. Chem. Soc.*, 1955, **77**, 5055.
[4] Dean and Whalley, *J.*, 1954, 4638.
[5] Liebermann and Lindenbaum, *Ber.*, 1904, **37**, 2735.
[6] Cavill, Robertson, and Whalley, *J.*, 1949, 1567.
[7] Robertson and Waters, *J.*, 1929, 2239.
[8] King, King, and Manning, *J.*, 1953, 3932.

of xanthones is stated to be increased in reactions that can lead to ring formation,[9] reaction with hydrazine gave the aldazine (IV) and not the pyridazine (III).

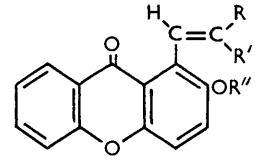
Cyclisation of 1-formyl-9-oxo-2-xanthyloxyacetate (II; R = CHO, R′ = O·CH_2·CO_2Et, R″ = H) (prepared from 1-formyl-2-hydroxyxanthone and ethyl bromoacetate) in ethanol with sodium ethoxide at room temperature gave 5′-ethoxycarbonylfurano(3′ : 2′-1 : 2)-xanthone (V; R = CO_2Et) in good yield. Hydrolysis of this ester, followed by decarboxylation, yielded the parent furanoxanthone (V; R = H), which was also obtained in one step by ring-closure of the xanthyloxyacetic acid (II; R = CHO, R′ = O·CH_2·CO_2H, R″ = H) owing to accompanying decarboxylation.



(V)



(VI)



(VII)

1-Formyl-2-hydroxyxanthone readily underwent a Perkin reaction with acetic or propionic anhydride, yielding the α-pyronoxanthone (VI; R = H) or its homologue (VI; R = Me) respectively. Methylation of the pyrono-compounds in acetone with dimethyl sulphate, a modification [10] of the method used by Canter and Robertson [11] for identifying coumarin structures, afforded the unsaturated esters (VII; R = CO_2Me, R′ = H, R″ = Me; and R = CO_2Me, R′ = R″ = Me). By analogy with the behaviour of coumarin these esters and the acids obtained from them by hydrolysis are assigned a *trans*-configuration. Unlike coumarin the α-pyronoxanthones were stable in refluxing 2N-sodium hydroxide or ethanolic sodium ethoxide.

Experimental

2-Hydroxyxanthone.—2-Carboxy-4′-methoxydiphenyl ether was obtained according to the method of Ullmann and Zlokasoff [12] in 30% yield. A 50% yield resulted when *o*-chlorobenzoic acid (62·4 g.) was condensed with *p*-methoxyphenol (59·6 g.) in hot pentyl alcohol (320 ml.), potassium carbonate (122 g.), and copper bronze (0·4 g.) for 5 hr. With *o*-fluorobenzoic acid in place of the chloro-acid no reaction occurred. The ether (35 g.) was first dissolved in acetyl chloride (350 ml.) and concentrated sulphuric acid (5·7 ml.), and most of the acetyl chloride (250 ml.) was then removed by distillation. On addition of water to the residue, 2-methoxyxanthone (30·5 g., 94%), m. p. 131°, separated. The ether was also cyclised by polyphosphoric acid at 100° in 1 hr., giving 2-methoxyxanthone (84%). Treatment of a solution of 2-methoxyxanthone in xylene with anhydrous aluminium chloride on a water-bath gave a quantitative yield of 2-hydroxyxanthone, m. p. 235—236° (von Kostanecki and Rutishauser [1] give m. p. 231°).

2-Acetonyloxyxanthone.—A mixture of 2-hydroxyxanthone (4·2 g.), redistilled chloroacetone (2·2 g.), and anhydrous potassium carbonate (13·8 g.) in anhydrous acetone (100 ml.) was heated under reflux and agitated for 5 hr. From the filtrate of the mixture *2-acetonyloxyxanthone* (3·6 g., 70%) was obtained as needles, m. p. 150—151° (from ethanol). It gave a positive iodoform test (Found: C, 71·3; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). Its 2 : 4-*dinitrophenylhydrazone* crystallised as yellow needles (from ethylene chloride), m. p. 225° (Found: C, 59·4; H, 3·6. $C_{22}H_{16}O_7N_4$ requires C, 58·9; H, 3·6%). 2-Acetonyloxyxanthone was cyclised neither by concentrated sulphuric acid at room temperature, nor under reflux in acetic acid containing a few drops of concentrated sulphuric acid. In the former case only starting material was recovered, in the latter de-etherification occurred.

[9] Campbell, McCallum, and Mackenzie, *J.*, 1957, 1922.
[10] Shah and Shah, *J. Univ. Bombay*, 1938, **7**, Pt. 3, 213.
[11] Canter and Robertson, *J.*, 1931, 1876.
[12] Ullmann and Zlokasoff, *Ber.*, 1905, **38**, 2111.

1-*Formyl*-2-*hydroxyxanthone*.—(a) *By a Duff reaction*. 2-Hydroxyxanthone (21·2 g.), hexamine (98 g.), and acetic acid (800 ml.) were heated on a steam-bath for 7 hr. After addition of boiling aqueous hydrochloric acid (1 : 1; 400 ml.) the mixture was kept under reflux for 10 min., then poured into water (4 l.) and set aside overnight. Crystallisation of the precipitate from light petroleum (b. p. 100—120°) gave 1-*formyl*-2-*hydroxyxanthone* (8·1 g., 34%) as pale yellow needles, m. p. 163° (Found: C, 70·0; H, 3·0. $C_{14}H_8O_4$ requires C, 70·0; H, 3·4%). It gave a red colour with ethanolic ferric chloride and a 2 : 4-*dinitrophenylhydrazone*, m. p. 295° (from anisole), as orange needles (Found: N, 13·7. $C_{20}H_{12}O_7N_4$ requires N, 13·3%).

(b) *By a Reimer–Tiemann reaction*. 2-Hydroxyxanthone (1·0 g.), sodium hydroxide (1·4 g.), chloroform (2·1 ml.), and water (30 ml.) were heated under reflux with stirring for 4 hr. The precipitate obtained by driving off the solvent and acidifying the aqueous suspension with dilute hydrochloric acid yielded on extraction with light petroleum (b. p. 100—120°) the aldehyde (16%), m. p. and mixed m. p. 163°.

2-*Acetoxy*-1-*formylxanthone*, obtained as white needles, m. p. 186°, by boiling a solution of 1-formyl-2-hydroxyxanthone in acetic anhydride–pyridine for 2 hr., crystallised from ethanol (Found: C, 68·4; H, 3·8. $C_{16}H_{10}O_5$ requires C, 68·1; H, 3·6%), had a negative ferric reaction, and gave a yellow precipitate with Brady's reagent.

1 : 2-*Dihydroxyxanthone*.—To 1-formyl-2-hydroxyxanthone (1·2 g.), pyridine (10 ml.), sodium hydroxide (0·4 g.), and water (5 ml.), hydrogen peroxide (6% w/v; 11·3 ml.) was added during 0·5 hr. with shaking. By addition of dilute hydrochloric acid (1 : 1; 50 ml.) 1 : 2-*dihydroxyxanthone* was obtained (1·04 g., 91%), crystallising as yellow needles (from aqueous ethanol), m. p. 166—167° (Found: C, 68·7; H, 3·6. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%). It gave a dark green ethanolic ferric reaction.

For various *derivatives* see the Table.

Substituted 1 : 2-*dihydroxyxanthones*.

Xanthone	M. p.	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H	Ethanolic $FeCl_3$
1 : 2-Diacetoxy	190°	64·9	3·9	$C_{17}H_{12}O_6$	65·4	3·9	—
1 : 2-Dimethoxy	130	70·4	4·9	$C_{15}H_{12}O_4$	70·3	4·7	—
1 : 2-Methylenedioxy	212	70·3	3·3	$C_{14}H_8O_4$	70·0	3·4	—
2-Acetoxy-1-hydroxy [a]	191	66·8	3·7	$C_{15}H_{10}O_5$	66·6	3·7	Dark green
2-Acetoxy-1-methoxy [b]	148	67·6	4·2	$C_{16}H_{12}O_5$	67·6	4·3	—
2-Hydroxy-1-methoxy [c]	171	69·0	4·6	$C_{14}H_{10}O_4$	69·4	4·2	—
1-Hydroxy-2-methoxy [d]	158	69·4	4·3	$C_{14}H_{10}O_4$	69·4	4·2	Dark green
1-Acetoxy-2-methoxy	144	67·6	4·3	$C_{16}H_{12}O_5$	67·6	4·3	—
2-Benzyloxy-1-hydroxy [e]	147	75·6	4·6	$C_{20}H_{14}O_4$	75·5	4·4	Dark green
1 : 2-Dibenzyloxy	126	78·9	5·1	$C_{27}H_{20}O_4$	79·4	4·9	—

[a] Made by the pyroboroacetate method. [b] On admixture with 1-acetoxy-2-methoxyanthone the m. p. was depressed. [c] Obtained by hydrolysis of 2-acetoxy-1-methoxyxanthone with 2N-sodium hydroxide. [d] Prepared from equimolar quantities of dimethyl sulphate and 1 : 2-dihydroxyxanthone. [e] Obtained from equimolar quantities of benzyl bromide and 1 : 2-dihydroxyxanthone.

2-*Hydroxy*-9-*oxo*-1-*xanthylaldazine*.—Hydrazine sulphate (0·16 g.) and sodium acetate (0·54 g.) were boiled with 1-formyl-2-hydroxyxanthone (0·24 g.) in the minimum amount of ethanol for 5 min. Crystallisation of the yellow precipitate from anisole gave the *aldazine* (0·2 g.) as yellow needles, m. p. 365° (decomp.) (Found: C, 70·7; H, 3·4; N, 5·7. $C_{28}H_{16}O_6N_2$ requires C, 70·6; H, 3·4; H, 5·9%).

Ethyl 1-*Formyl*-9-*oxo*-2-*xanthyloxyacetate*.—1-Formyl-2-hydroxyxanthone (4·8 g.), ethyl bromoacetate (10·0 g.) and anhydrous potassium carbonate (16·6 g.) in anhydrous acetone (125 ml.) were kept under reflux for 14 hr. The filtrate obtained from the initially orange but finally pale yellow mixture deposited *ethyl* 1-*formyl*-9-*oxo*-2-*xanthyloxyacetate* (62%) as white needles, m. p. 143°, on evaporation (Found: C, 66·4; H, 4·4. $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3%). Hydrolysis with aqueous sodium hydroxide yielded the corresponding *acid*, m. p. 221° (Found: C, 64·5; H, 3·6. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%).

Furano(3′ : 2′-1 : 2)*xanthone*-5′-*carboxylic Acid*.—(*a*) Cyclisation of 1-formyl-9-oxo-2-xanthyloxyacetic acid (1·2 g.) was carried out with fused sodium acetate (3·0 g.) in boiling acetic anhydride for 2 hr. Addition of water (120 ml.), followed by neutralisation with sodium hydrogen carbonate, gave a precipitate which on recrystallisation from acetic acid yielded

furano(3′ : 2′-1 : 2)*xanthone-5′-carboxylic acid* as white needles (0·5 g., 45%), m. p. 322° (decomp.) (Found: C, 68·7; H, 2·8. $C_{16}H_8O_5$ requires C, 68·6; H, 2·9%). The acid is soluble in warm aqueous sodium hydrogen carbonate and sparingly soluble in cold dilute ammonia solution.

(*b*) A suspension of ethyl 1-formyl-9-oxo-2-xanthyloxyacetate (0·66 g.) in ethanol (35 ml.) containing sodium ethoxide (0·15 g.) was agitated for 1·5 hr. A pale yellow precipitate obtained by dilution with water (100 ml.) yielded on crystallisation from ethyl acetate 5′-*ethoxycarbonylfurano*(3′ : 2′-1 : 2)*xanthone* as white needles (56%), m. p. 207° (Found: C, 70·2; H, 4·0. $C_{18}H_{12}O_5$ requires C, 70·1; H, 3·9%). Hydrolysis of the ester with 4% ethanolic sodium hydroxide yielded the acid (88%) whose mixed m. p. with a sample from (*a*) was undepressed.

Furano(3′ : 2′-1 : 2)*xanthone*.—(*a*) Evaporation of the acetic acid mother-liquor from which the acid was obtained in the above experiment (*a*) left a residue which afforded *furano*(3′ : 2′-1 : 2)*xanthone* as white needles (0·25 g., 27%), m. p. 144° (Found: C, 76·0; H, 3·4. $C_{15}H_8O_3$ requires C, 76·2; H, 3·4%).

(*b*) Heating furano(3′ : 2′-1 : 2)xanthone-5′-carboxylic acid (0·28 g.) in quinoline (5 ml.) with copper bronze (0·28 g.) under reflux for 10 min. gave the furanoxanthone (0·12 g.), m. p. and mixed m. p. 144°.

6′-*Pyrono*(3′ : 2′-1 : 2)*xanthone*.—1-Formyl-2-hydroxyxanthone (4·8 g.), freshly fused sodium acetate (1·64 g.), and acetic anhydride (3·8 ml.) were heated for 2 hr. at 120° and then for a further 5 hr. at 180°. On trituration of the mixture with water a solid remained which yielded no extract on treatment with 2N-sodium hydroxide. On recrystallisation from acetic acid it afforded 6′-*pyrono*(3′ : 2′-1 : 2)*xanthone* as white needles (5·2 g.), m. p. 251° (Found: C, 72·7; H, 3·3. $C_{16}H_8O_4$ requires C, 72·7; H, 3·1%), not affected by ethanolic sodium ethoxide solution (cf. Updegraff and Cassidy [13]).

5′-*Methyl*-6′-*pyrono*(3′ : 2′-1 : 2)*xanthone*.—A Perkin reaction with 1-formyl-2-hydroxyxanthone (2·4 g.), sodium propionate (0·96 g.), and propionic anhydride (2·6 g.), as described in the previous experiment, gave 5′-*methyl*-6′-*pyrono*(3′ : 2′-1 : 2)*xanthone* (2·7 g., 97%) as white needles, m. p. 248° (Found: C, 73·7; H, 3·7. $C_{17}H_{10}O_4$ requires C, 73·4; H, 3·6%), unaffected by ethanolic sodium ethoxide.

trans-*Methyl* β-(2-*Methoxy*-9-*oxo*-1-*xanthyl*)*acrylate*.—To a suspension of 6′-pyrono(3′ : 2′-1 : 2)xanthone (0·5 g.) in boiling acetone (50 ml.) was added dimethyl sulphate (10 ml.) and 20% aqueous sodium hydroxide (22 ml.) in three portions during 0·5 hr. After 1 hour's refluxing the solvent was driven off and the solid obtained from the residue by acidification with dilute hydrochloric acid was recrystallised from aqueous ethanol. trans-*Methyl* β-(2-*methoxy*-9-*oxo*-1-*xanthyl*)*acrylate* had m. p. 135° (white needles) (Found: C, 69·2; H, 4·4. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). Hydrolysis with ethanolic 2N-sodium hydroxide solution gave the *acid* as cream-coloured needles, m. p. 212° (Found: C, 69·4; H, 4·3. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

5′-Methyl-6′-pyrono(3′ : 2′-1 : 2)xanthone, treated as above, gave trans-*methyl* α-*methyl*-β-(2-*methoxy*-9-*oxo*-1-*xanthyl*)*acrylate* (47%), needles, m. p. 160° (Found: C, 70·0; H, 5·0. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%); the derived *acid* formed pale-yellow needles, m. p. 208° (decomp.) (Found: C, 70·1; H, 4·5; OMe, 10·0. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·6; OMe, 10·0%).

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[13] Updegraff and Cassidy, *J. Amer. Chem. Soc.*, 1949, **71**, 407.