## 419. *Studies in the Xanthone Series. Part I.*

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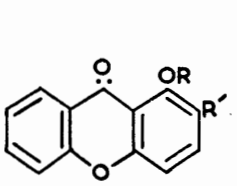
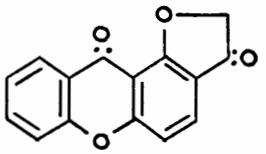
The preparation of a dihydro-oxofurano- (II) and a $\gamma$-pyrono-xanthone (III); R = H) from 1-hydroxyxanthone is described.

REACTIONS of 1-hydroxyxanthone (I; R = R′ = H) have been studied in order to prepare simple analogues of biologically active chromones, such as khellin,[1] for pharmacological testing. We failed to formylate 1-hydroxyxanthone by the usual methods but acetylated it by Fries rearrangement with aluminium chloride in cold or hot nitrobenzene and, in much better yield, by Friedel–Crafts reactions. These experiments gave 2-acetyl-1-hydroxyxanthone and an isomeric ketone, but there was not enough of the latter for

[1] Huttrer and Dales, *Chem. Reviews*, 1951, **48**, 543.

further investigation. Attempts to oxidise the former, for orientation, to 1 : 2-dihydroxyxanthone [2] by a Dakin reaction with one equivalent or excess of alkali,[3] gave only unchanged starting material: the structural analogue, 6-acetyl-5-hydroxyflavone, is also stable under these conditions.[4] The structure of the ketone was settled by cyclisation of its ω-monobromo-derivative (I; R = H, R′ = CO·$CH_2$Br) (prepared in good yield by use of


(I)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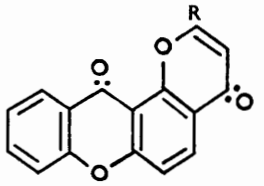
(III)

bromine in acetic acid [5]) to the furanoxanthone (II) in ethanol with sodium acetate. The compound (II) was also prepared as follows: Ethyl 9-oxo-1-xanthyloxyacetate (I; R = $CH_2$·$CO_2$Et, R′ = H) was obtained from 1-hydroxyxanthone and ethyl bromoacetate, and was converted into the acid chloride which was treated with aluminium chloride in benzene; reaction was with the solvent, giving 1-phenacyloxyxanthone (I; R = $CH_2$·COPh, R′ = H); but in carbon disulphide at high dilution ring-closure gave the furanoxanthone (II). Its enolic properties were shown by formation of an acetyl derivative.

The acid (I; R = $CH_2$·$CO_2$H, R′ = H) and the ketonic by-product (I; R = $CH_2$·COPh, R′ = H) could not be cyclised by conventional methods (cf. the failure to cyclise ω-phenoxyacetophenone [6]).

2-Acetyl-1-hydroxyxanthone did not condense with ethyl formate and ethyl acetate, but with ethyl oxalate and sodium, activated by a little ethanol, gave the diketo-ester (I; R = H, R′ = CO·$CH_2$·CO·$CO_2$Et). The pyronoxanthonecarboxylic acid (III; R = $CO_2$H) was obtained in good yield by cyclisation of the diketone in a mixture of hot glacial acetic and concentrated hydrochloric acid. Thermal decarboxylation furnished the pyronoxanthone (III; R = H), but the use of copper in quinoline gave intractable tars. Experiments designed to yield a pyronoxanthone from 2-acetyl-1-hydroxyxanthone by a Kostanecki–Robinson reaction failed.

## Experimental

*2-Acetyl-1-hydroxyxanthone.*—(*a*) Powdered aluminium chloride (5·3 g.) was added in portions to a solution of 1-acetoxyxanthone [7] (5 g.) in redistilled nitrobenzene (55 c.c.), and the whole kept at room temperature for 60 hr. and then poured into ice (250 g.) and 2N-hydrochloric acid (250 c.c.). The precipitate, crystallised from ethanol, gave *2-acetyl-1-hydroxyxanthone* as yellow needles (0·8 g., 16%), m. p. 203—204° (Found: C, 70·5; H, 4·0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%). It gave a deep-red ferric colour in ethanol. Its 2 : 4-*dinitrophenylhydrazone* crystallised as red spikes, m. p. 273—274°, from anisole (Found: N, 12·9. $C_{21}H_{14}O_7N_4$ requires N, 12·9%). The same procedure, but at 80° for 3 hr., gave a 24% yield of ketone. Chromatography (silica gel; benzene) of the crude product yielded a small quantity of an isomeric, unidentified ketone, m. p. 200° (corresponding to $C_{15}H_{10}O_4$ by analysis), which depressed the m. p. of the 2-acetyl compound.

(*b*) A solution of 1-hydroxyxanthone [7] (8·5 g.) in *s*-tetrachloroethane (60 c.c.) was added dropwise to a stirred suspension of powdered aluminium chloride (26·6 g.) in redistilled acetic anhydride (10 g.) and *s*-tetrachloroethane (60 c.c.). The red mixture was then heated on a

[2] Davies, Lamb, and Suschitzky, unpublished work.
[3] Baker and Flemons, *J.*, 1948, 2138.
[4] Baker, *J.*, 1934, 1953.
[5] Buu-Hoï and Lavitt, *J.*, 1955, 18.
[6] Stoermer and Atenstädt, *Ber.*, 1902, **35**, 3560.
[7] Michael, *J. Amer. Chem. Soc.*, 1883, **5**, 91.

steam-bath for 3 hr. and poured on crushed ice and concentrated hydrochloric acid (100 c.c.). The residue, after being extracted with ether, gave 2-acetyl-1-hydroxyxanthone on recrystallisation from benzene (mixed m. p. 203—204°; 4·1 g., 41%). The ether extract contained a little of the ketone, m. p. 200°. In another preparation, a solution of acetyl chloride (3·7 g.) in nitrobenzene (5 c.c.) was added dropwise to an ice-cooled, stirred mixture of powdered aluminium chloride (8·0 g.), 1-hydroxyxanthone (4·2 g.), and nitrobenzene (35 c.c.). The mixture was kept at room temperature for 5 days, and, when worked up as above, yielded 2-acetyl-1-hydroxyxanthone (1·8 g., 36%).

1-*Acetoxy*-2-*acetylxanthone*, white needles, m. p. 134°, obtained by means of boiling acetic anhydride–pyridine (2 hr.), crystallised from ethanol or light petroleum (b. p. 40—60°) (Found: C, 68·6; H, 4·0. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

4′ : 5′-*Dihydro*-4′-*oxofurano*(2′ : 3′-1 : 2)*xanthone* (II).—(*a*) 2-Acetyl-1-hydroxyxanthone (1·3 g.) in glacial acetic acid (120 c.c.) was treated dropwise with bromine (0·8 g.) in glacial acetic acid (10 c.c.), and the mixture was heated on a water-bath at 80° for 1 hr. The yellow crystals which gradually separated were collected, washed with boiling ethanol (100 c.c.), and recrystallised from glacial acetic acid. 2-ω-*Bromoacetyl*-1-*hydroxyxanthone* crystallised as yellow needles, m. p. 216—217° (decomp.) (0·7 g., 41%), from glacial acetic acid (Found: C, 54·1; H, 2·7; Br, 23·7. $C_{15}H_9O_4Br$ requires C, 54·1; H, 2·7; Br, 24·0%). It gave a red colour with ethanolic ferric chloride and an orange precipitate with Brady's reagent. Its *acetyl derivative* was obtained in the usual way as pale-yellow crystals, m. p. 143—145°, from ethanol (Found: C, 54·8; H, 3·0; Br, 21·1. $C_{17}H_{11}O_5Br$ requires C, 54·4; H, 3·0; Br, 21·3%). A solution of the bromo-ketone (0·2 g.) in ethanol (150 c.c.) was refluxed for 0·75 hr. in presence of crystalline sodium acetate (0·2 g.). After cooling and concentration of the mixture, the red precipitate obtained by addition of water was collected and extracted with chloroform. Removal of the dried ($MgSO_4$) solvent, followed by crystallisation of the residue from alcohol, gave 4′ : 5′-*dihydro*-4′-*oxofurano*(2′ : 3′-1 : 2)*xanthone* as white needles, m. p. 253—255° (0·08 g., 50%) (Found: C, 71·3; H, 3·4. $C_{15}H_8O_4$ requires C, 71·5; H, 3·2%). It had a negative ferric reaction and yielded an *acetyl derivative*, from boiling acetic anhydride, as white needles, m. p. 230—231° (Found: C, 69·0; H, 3·2. $C_{17}H_{10}O_5$ requires C, 69·4; H, 3·4%).

(*b*) Ethyl bromoacetate (1·25 g.) and 1-hydroxyxanthone (1 g.) in acetone (50 c.c.) containing anhydrous potassium carbonate (2 g.) were boiled under reflux with stirring for 6 hr. After filtration and evaporation of the filtrate the yellow residue was recrystallised from ethanol and gave 9-*oxo*-1-*xanthyloxyacetate* as a mixture of white cubes (m. p. 130°) and needles (m. p. 128—130°) (1·35 g., 90·5%) (Found: C, 68·1; H, 4·9. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·8%). Recrystallisation from excess of ethanol yielded only vitreous cubes. Hydrolysis of the dimorphic ester with 2N-sodium hydroxide gave 9-*oxo*-1-*xanthyloxyacetic acid* (91%) as needles, m. p. 195° (Found: C, 66·9; H, 3·9%; equiv., 268. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%; equiv., 270). Attempts to prepare the acid directly by condensation of 1-hydroxyxanthone with monochloroacetic acid or to cyclise the acid by concentrated sulphuric acid or polyphosphoric acid gave only starting materials.

The *acid chloride* was obtained, by refluxing the acid with thionyl chloride in benzene, as yellow needles, m. p. 173° (decomp.), unstable to heat and air. It was characterised by its *amide*, white needles, m. p. 252—254° (decomp.), from ethanol (Found: C, 66·9; H, 4·2; N, 4·9. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1; N, 5·2%). Cyclisation was effected as follows: A solution of the acid chloride (3·2 g.) in warm carbon disulphide (1·4 c.c.; freshly distilled over $P_2O_5$) was added during 2 hr. to a warm stirred suspension of powdered aluminium chloride (1·8 g.) in carbon disulphide (100 c.c.), and the mixture was boiled under reflux for 4 hr. and then kept at room temperature overnight. The filtered mixture was poured into ice (100 g.) and concentrated hydrochloric acid (50 c.c.). Organic material was taken up in chloroform, and the chloroform solution extracted with aqueous sodium hydrogen carbonate (20%), which removed 9-oxo-1-xanthyloxyacetic acid (1·0 g.; m. p. 192—194°). Washing with water, drying ($MgSO_4$), and removal of the solvent left a yellow residue which, on repeated recrystallisation from ethanol gave a xanthone, m. p. 253—255° (0·45 g., 16%) alone or mixed with a sample prepared by route (*a*).

*Cyclisation in Benzene.*—When a solution of the acid chloride (1·3 g.) in benzene (70 c.c.) in the presence of powdered aluminium chloride (1·2 g.) was kept at room temperature for 4 days, and the mixture was worked up as described under (*b*), 1-*phenacyloxyxanthone*, m. p. 187—188° (0·4 g., 27%), was obtained as white needles from ethanol (Found: C, 76·1; H, 4·6. $C_{21}H_{14}O_2$ requires C, 76·3; H, 4·3%). Its 2 : 4-*dinitrophenylhydrazone* formed orange needles (from chlorobenzene), m. p. 203° (decomp.) (Found: C, 63·6; H, 3·4; N, 10·9. $C_{27}H_{18}O_7N_4$

requires C, 63·5; H, 3·5; N, 11·0%). This ketone was not cyclised on treatment with concentrated sulphuric acid [8] or by methods used by Stoermer and Atenstädt.[6]

*4'-Pyrono(2' : 3'-1 : 2)xanthone* (III; R = H).—2-Acetyl-1-hydroxyxanthone (1·3 g.) was treated with ethyl oxalate (10 c.c.), ethanol (5 drops), and powdered sodium (0·5 g.) with stirring and gentle heating for 1 hr. After cooling, a brown sodium salt was collected and treated with aqueous acetic acid (20%), and the resulting yellow solid crystallised from benzene–ethanol (1 : 1), giving *2-ethoxalylacetyl-1-hydroxyxanthone* as lemon-yellow needles, m. p. 202—204° (1·5 g., 88%) (Found: C, 64·6; H, 4·0. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·0%). The diketone (0·6 g.) was cyclised in glacial acetic acid (2·5 c.c.) containing concentrated hydrochloric acid (2·5 c.c.) under reflux (0·5 hr.). The solid obtained by addition of water furnished on crystallisation from acetic acid *4'-pyrono(2' : 3'-1 : 2)xanthone-6'-carboxylic acid* (III; R = $CO_2H$) as white needles, m. p. 300—302° (decomp.) (0·4 g., 73%) (Found: C, 66·1; H, 2·8. $C_{17}H_8O^9$ requires C, 66·2; H, 2·6%). Heating the acid gently above its m. p. gave *4'-pyrono(2' : 3'-1 : 2)xanthone* as white sublimed needles, m. p. 327° (Found: C, 72·8; H, 3·2. $C_{16}H_8O_4$ requires C, 72·7; H, 3·1%). Decarboxylation by copper in quinoline produced an intractable oil.

Condensation of 2-acetyl-1-hydroxyxanthone with ethyl formate or ethyl acetate under the conditions described for ethyl oxalate or with sodium hydride or sodamide as condensing agents failed.

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[8] Curd and Robertson, *J.*, 1933, 714, 1173.