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STUDIES IN THE XANTHONE SERIES—IV*

PREPARATION AND REACTIONS OF 2-ALLYL-1-HYDROXYXANTHONE

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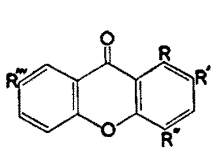
Abstract—Preparations of furano-(II and V) and pyranoxanthones (III) from 2-allyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) and the orientation of 2-formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H) and of 4-acetyl-1-hydroxyxanthone (I; R = OH, R′ = R‴ = H, R″ = Ac) are described. The ultra-violet absorption spectra of the new ring systems and their intermediates are briefly discussed.

FURTHER reactions of 1-hydroxyxanthones[1] have been investigated with a view to preparing simple analogues of pharmacologically active chromones such as khellin.[2] 2-Allyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) was made by a Claisen rearrangement of 1-allyloxyxanthone[3] (I; R = $OCH_2CH{:}CH_2$, R′ = R″ = R‴ = H) effected by heating the ether alone or with an even higher yield by refluxing it in dimethyl aniline. Claisen[4,5] rearranged the allyl ether of phenol with pyridine hydrochloride and obtained some 2-methylcoumaran (IV), but under similar conditions 1-allyloxyxanthone de-etherified.

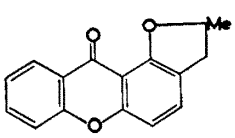
2-Allyl-1-hydroxyxanthone was made to react with hydrogen bromide under carefully chosen conditions in order to predetermine the direction of addition. Thus 2-β-bromoprpoyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CHBrCH_3$, R″ = R‴ = H) was prepared by saturating a solution of 2-allyl-1-hydroxyxanthone in glacial acetic acid kept under nitrogen with hydrogen bromide gas in the presence of a peroxide inhibitor (diphenylamine). Cyclization of this bromo-compound by refluxing in ethanolic sodium ethoxide occurred almost quantitatively and gave a furanoxanthone which must have the structure (II). This product was also obtained, but only in low yield, by refluxing 2-allyl-1-hydroxyxanthone in a mixture of hydrobromic (48%) and acetic acid followed by cyclization of the crude intermediate with sodium ethoxide. Anti-Markownikoff addition with hydrogen bromide was carried out not on the free phenol (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) since the hydroxyl group might have inhibited the free radical reaction, but on 1-acetoxy-2-allylxanthone (I; R = OAc, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) in hexane solution in presence of traces of dibenzoyl peroxide. The crude mixture of 2-γ-bromopropyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH_2CH_2Br$, R″ = R‴ = H) and its O-acetyl derivative (I; R = OAc, R′ = $CH_2CH_2CH_2Br$, R″ = R‴ = H) resulting from this reaction was cyclized in high yield to 5′:6′-dihydropyrano(2′:3′-1:2)xanthone (III).

* Part III. F. Lamb and H. Suschitzky, *Tetrahedron* **5**, 1 (1959).

[1] J. S. H. Davies, F. Scheinmann and H. Suschitzky, *J. Chem. Soc.* 2140 (1956).
[2] C. P. Huttrer and E. Dale, *Chem. Rev.* **48**, 543 (1951).
[3] A. Mustafa and Orkede H. Hishmat, *J. Amer. Chem. Soc.* **79**, 2225 (1957).
[4] L. Claisen, *Liebigs Ann.* **418**, 69 (1919).
[5] L. Claisen and E. Tietze, *Liebigs Ann.* **81**, 449 (1926).



I



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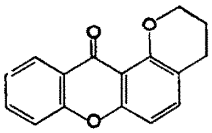
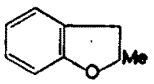


III



IV

Hurd and Hoffman[6] prepared methyl coumaran and chroman derivatives by an analogous route. The hydrogen bromide adducts were, however, not isolated and the endproducts were known beforehand. Their work confirms that, by using the "peroxide effect" the direction of the ring-closure in *o*-allylphenols may be reliably controlled.

Addition of bromine to 2-allyl-1-hydroxyxanthone gave the dibromo-adduct (I; R = OH, R′ = $CH_2CHBrCH_2Br$, R″ = R‴ = H) from which two molecules of hydrogen bromide were eliminated by treatment with ethanolic sodium ethoxide to give a cyclic ether. By analogy with the results of Adams and Rindfusz[7] who cyclized *o*-allylphenols by the same method, we assign the furano-structure (V) to our product although attempts to convert the furanoxanthone (II) by dehydrogenation into V failed.

Other methods of synthesizing extended xanthones were studied: thus condensations of 1-hydroxyxanthone with ethyl acetoacetate under Pechmann and Simonis conditions were unsuccessful. Experiments to cyclize 1-acetonyloxyxanthone (I; R = OCH_2COCH_3, R′ = R″ = R‴ = H) with polyphosphoric,[8] sulphuric,[9] or with hydrobromic acid in glacial acetic acid[10] gave only starting material in the first two cases and 1-hydroxyxanthone in the third case. When it was found that ethyl bromopropionate could not be made to condense with 1-hydroxyxanthone (cf. ethyl bromoacetate condensation[1]) the preparation of extended xanthones by ring-closure of ethers was not further pursued.

Successful formylations of hydroxyxanthones with hexamine in glacial acetic acid have been reported recently; thus 1-formyl-2-hydroxyxanthone[11] (I; R = CHO, R′ = OH, R″ = R‴ = H) was prepared by this method in about 34 per cent yield and 1-hydroxy-7-methoxyxanthone (I; R = OH, R′ = R″ = H, R‴ = OMe) gave a formyl derivative in similar yields.[12] However, formylation of 1-hydroxyxanthone under similar and modified conditions gave mainly starting material and only a small amount of 2-formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H). The structure of this aldehyde follows from its analysis and a comparison of its ultraviolet spectrum with the spectra of the 2- and the 4-acetyl-1-hydroxyxanthone (see Fig. 1).

We reported earlier[1] that in the preparation of 2-acetyl-1-hydroxyxanthone (I; R = OH, R′ = Ac, R″ = R‴ = H) a small amount of an unidentified ketone was also isolated. Mustafa and Hishmat[3] repeated our work but were unable to obtain the unidentified substance which we have now shown to be 4-acetyl-1-hydroxyxanthone (I; R = OH, R′ = R‴ = H, R″ = Ac) by the following unambiguous

[6] C. D. Hurd and W. A. Hoffman, *J. Org. Chem.* **5**, 212 (1940).
[7] R. Adams and R. E. Rindfusz, *J. Amer. Chem. Soc.* **41**, 648 (1919).
[8] W. Davies and S. Middleton, *Chem. & Ind.* 599 (1957).
[9] H. Curd and A. Robertson, *J. Chem. Soc.* 714, 1173 (1933).
[10] C. K. Bradsher and W. J. (Jr.) Jackson, *J. Amer. Chem. Soc.* **76**, 734 (1954) and other papers in this series.
[11] J. S. H. Davies, F. Lamb and H. Suschitzky, *J. Chem. Soc.* 1790 (1958).
[12] E. M. Philbin, J. Swirski and T. S. Wheeler, *J. Chem. Soc.* 4455 (1956).

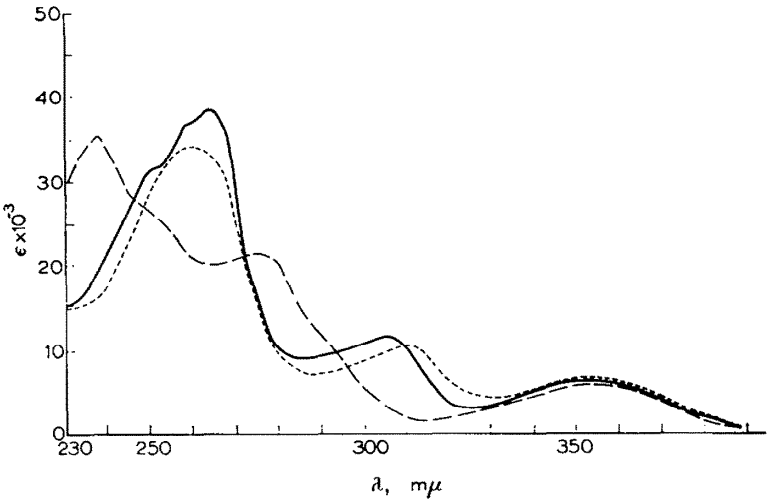
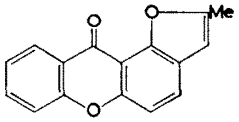
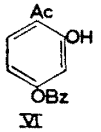


FIG. 1. Ultra-violet spectra of 2-acetyl-1-hydroxy (—); 2 formyl-1-hydroxy (- - - -) and 4-acetyl-1-hydroxyxanthone (— —).

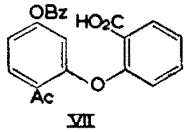
synthesis: *o*-chlorobenzoic acid and 4-benzyloxy-2-hydroxyacetophenone (VI) were condensed under Ullmann conditions and gave the diphenylether (VII) which, by treatment with tetraphosphoric acid, was cyclized and debenzylated in one step yielding 4-acetyl-1-hydroxyxanthone (I; R = H, R′ = R‴ = H, R″ = Ac).



V



VI



VII

A discussion and interpretation of the ultra-violet spectra of xanthones with a conjugated angular ring or with groups in the 1 and 1:2 positions capable of chelation have been given previously.* It will again be noticed from some further examples quoted below (Table 1) that such xanthones show a marked drop in the intensity of the principal absorption band without appreciable shift in the wavelength of the maximal absorption when compared with the spectrum of xanthone. This behaviour is ascribed to steric interference with the planarity of the molecule. The spectrum of 1-hydroxyxanthone has previously been measured by Mull and Nord[13] and is in good agreement with ours, but these authors report a spectrum for 1-methoxyxanthone almost identical with that for 1-hydroxyxanthone. We suspected this result since the marked hypochromic effect in the principal maximum of 1-hydroxyxanthone (Table 1) is undoubtably due to chelation and should disappear when hydrogen bonding is prevented (cf. 1-acetoxyxanthone, Table 1), We, therefore, measured the spectrum of 1-methoxy-xanthone and observed the expected intensity increase relative to 1-hydroxyxanthone.

EXPERIMENTAL

Ultra-violet spectra were measured in methanol on a Unicam S.P. 500 spectrophotometer, except the spectrum of γ-pyrono(2′:3′-1:2)xanthone-6′-carboxylic acid, which was determined in peroxide free dioxan. The spectra are quoted as λ_{max} (mμ) with ε in parentheses.

* See footnote on p. 31.

[13] R. P. Mull and F. F. Nord, *Arch. Biochem.* **4**, 419 (1944).

1-Allyloxyxanthone (I; R = $OCH_2CH{:}CH_2$, R′ = R″ = R‴ = H)

A mixture of 1-hydroxyxanthone (8·48 g), allyl chloride (6·0 g), sodium iodide (12·0 g) and potassium carbonate (16·6 g) in dry acetone (350 cc) was boiled under reflux (ca. 30 hr) until a test sample did not give the characteristic ferric chloride colouration of 1-hydroxyxanthone. The inorganic residue was filtered off, the solvent removed from the filtrate and the residual, white solid (10·1 g) gave on recrystallization (petroleum ether b.p. 60–80°) 1-allyloxyxanthone as fine, white needles, m.p. 86° (Mustafa and Hishmat[3] give m.p. 86–87°) (Found: C, 76·2: H, 4·9. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%).

When the etherification was carried out with allyl bromide instead of allyl chloride and sodium iodide the yields of allyl ether were lower (cf. Mustafa and Hishmat, *loc. cit.*).

Claisen rearrangement of 1-allyloxyxanthone

(a) *By heating alone.* 1-Allyloxyxanthone (2·5 g) was heated at 195–200° (2·5 hr). On recrystallization of the product from aqueous methanol *2-allyl-1-hydroxyxanthone* (I; R = OH, R′ = CH_2CH:

TABLE 1.—PRINCIPAL ABSORPTION MAXIMA OF XANTHONES AND RELATED COMPOUNDS IN METHANOL

Compound	λ_{max}(mμ)	ε_{max}
Xanthone	238	44,200
1-Acetoxyxanthone	238	44,100
1-Methoxyxanthone	236	40,300
Xanthones with conjugated angular rings or chelating groups		
1-Hydroxyxanthone	230	30,600
4-Acetyl-1-hydroxyxanthone	238	35,500
2-Formyl-1-hydroxyxanthone	260	34,400
4-Acetoxyfurano(2′:3′-1:2)xanthone[1]	262	31,000
γ-Pyrono(2′:3′-1:2)xanthone-6′-carboxylic acid[1] ..	226	19,900
Xanthones with non-conjugated angular ring systems		
4′:5′-Dihydro-4′-oxofurano(2′:3′-1:2)xanthone ..	255	38,200
4′:5′-Dihydro-5′-methylfurano(2′:3′-1:2)xanthone ..	254	39,600

CH_2, R″ = R‴ = H) (1·83 g; 73%) was obtained as fine, yellow needles, m.p. 105° (Found: C, 75·8; H, 4·8. $C_{16}H_{12}O_3$ requires: C, 76·2; H, 4·8%). It decolourizes bromine in carbon tetrachloride, gives a green ferric reaction and forms an insoluble sodium salt. It also gives a positive reaction with 2:6-dichlorobenzoquinone chloroimide (Gibbs Reagent) which indicates that the position *para* to the hydroxyl group is unsubstituted.[14]

(b) *By heating in dimethylaniline.* 1-Allyloxyxanthone (1 g) in dimethylaniline (7 cc) was heated under reflux for 3 hr. Acidification with aqueous hydrochloric acid (2 N) precipitated 2-allyl-1-hydroxyxanthone in theoretical yield. Recrystallization from aqueous methanol gave yellow needles, m.p. 104–105°, undepressed on admixture with a sample obtained from method (a).

(c) *By heating with pyridine hydrochloride.* A mixture of 1-allyloxyxanthone (1 g) and dry pyridine hydrochloride (3·5 g) was heated at 200–205° for 2 hr. The product was triturated with water and the residue (0·8 g) m.p. 140–143°, was shown to be impure 1-hydroxyxanthone.

1-Acetoxy-2-allylxanthone

This was obtained as vitreous cubes, m.p. 107–109° from boiling acetic anhydride containing 1 drop of syrupy phosphoric acid and recrystallized from petroleum ether (b.p. 40–60°) (Found: C, 73·5; H, 5·0. $C_{18}H_{14}O_4$ requires: C, 73·5; H, 4·8%).

[14] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).

4′:5′-Dihydro-5′-methylfurano(2′:3′-1:2)xanthone (II)

(a) A solution of 2-allyl-1-hydroxyxanthone (8 g) in glacial acetic acid (300 cc) was kept under nitrogen and saturated with hydrogen bromide gas (prepared by the bromine–tetralin method) in the presence of traces of diphenylamine. When the reaction mixture was set aside in the dark at room temp for 5 days 2-β-bromopropyl-1-hydroxyxanthone (6·7 g, 63%) m.p. 145–148° separated from the solution and was used in the subsequent cyclization experiment without further purification. The bromocompound crystallizes from aqueous acetic acid or from ethanol as plates or needles, m.p. 148–151°, and gives an intense green colour with aqueous ferric chloride (Found: C, 57·2; H, 4·4; Br, 23·6. $C_{16}H_{13}O_3Br$ requires: C, 57·7; H, 4·0, Br 24·0%). 2-β-bromopropyl-1-hydroxyxanthone (6·7 g) was cyclized by refluxing in ethanolic sodium ethoxide (1 g of sodium in 450 cc of ethanol) for 2 hr. Most of the solvent was removed and addition of water (1 l.) precipitated a pale-yellow solid (4·5 g, 90%), which on recrystallization (petroleum ether, b.p. 100–120°) gave *4′:5′-dihydro-5′-methylfurano-(2′:3′-1:2)xanthone*, m.p. 181°, λ_{max} 234 (31,300), 254 (39,600), 364 (7,200) (Found: C, 76·1; H, 4·7. $C_{16}H_{12}O_3$ requires: C, 76·2; H, 4·8%).

(b) A mixture of 2-allyl-1-hydroxyxanthone (0·75 g) bromine-free aqueous hydrobromic acid (48%, 15 cc) and glacial acetic acid (5 cc) was boiled under reflux for 0·75 hr. The crude material obtained by pouring the reaction mixture into ice water was boiled in ethanolic sodium ethoxide ((0·4 g of sodium in 100 cc of ethanol) for 1 hr and then most of the solvent was removed. Addition of water precipitated a residue from which 4′:5′-dihydro-5′-methylfurano(2′:3′-1:2)xanthone (0·15 g, 20%) was extracted with hot benzene.

5′:6′-Dihydropyrano(2′:3′-1:2)xanthone (III)

1-Acetoxy-2-allylxanthone (5 g) in *n*-hexane (550 cc) was saturated with hydrogen bromide gas in the presence of dibenzoyl peroxide (0·15 g) and the reaction mixture allowed to stand in sunlight for 3 days. The yellow solid (2·47 g) which had separated was combined with the residue obtained by evaporation of the mother-liquor. The combined fractions on recyrstallization from aqueous methanol furnished *2-γ-bromopropyl-1-hydroxyxanthone* as yellow needles, m.p. 125–126°, which gives a green ferric reaction (Found: C, 57·5; H, 4·1. $C_{16}H_{13}O_3Br$ requires: C, 57·7; H, 4·0%). Dilution of the aqueous methanolic filtrate with water precipitated a white solid which on repeated recrystallization from petroleum ether (b.p. 60–80°) gave *1-acetoxy-2-γ-bromopropylxanthone* as white needles, m.p. 116° (Found: C, 57·3; H, 4·2. $C_{18}H_{15}O_4Br$ requires: C, 57·6; H, 4·0%). A crude mixture of these products (5 g) was kept under reflux with sodium ethoxide (from 1 g of sodium) in ethanol (450 cc) for 1 hr. Most of the solvent was driven off and the solution was then poured into water (2·5 l.) yielding *5′:6′-dihydropyrano(2′:3′-1:2)xanthone* as fine, white needles, m.p. 166° (4·1 g, 85·5%), depressed on admixture with the isomeric 4′:5′-dihydro-5′-methylfurano-(2′:3′-1:2) xanthone (Found: C, 75·8; H, 4·8. $C_{16}H_{12}O_3$ requires: C, 76·2, H, 4·8%).

1-Acetonyloxyxanthone

Chloroacetone (3·62 g) was added to a stirred mixture of 1-hydroxyxanthone (6·37 g) and anhydrous potassium carbonate (12 g) in dry acetone (300 cc) and the reaction mixture boiled under reflux (9 hr). The yellow precipitate was collected and shown to be the sodium salt of 1-hydroxyxanthone (1·75 g). Removal of the solvent from the filtrate gave a residue which was extracted with chloroform. From the chloroform solution *1-acetonyloxyxanthone* was obtained as fine, white needles, m.p. 172–173° (Found: C, 71·7; H, 4·7. $C_{16}H_{12}O_4$ requires: C, 71·6; H, 4·5%).

Attempts to ring close 1-acetonyloxyxanthone (concentrated sulphuric or polyphosphoric acid) yielded starting material. Cyclization attempts by refluxing with aqueous hydrobromic (48%) and glacial acetic acid for 16 hr led to de-etherification.

2-Formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H)

A mixture of 1-hydroxyxanthone (1 g), hexamine (3 g) and glacial acetic acid (10 cc) was heated on a steam-bath (6 hr). Hydrochloric acid (18%, 10 cc) was now added and the heating continued for a further 0·5 hr. Dilution of the reaction mixture with water furnished a yellow precipitate (0·9 g) from which prolonged steam distillation removed 1-hydroxyxanthone (0·6 g) and left a residue which was repeatedly extracted with hot ethanol (10 cc portions). One extract, m.p. ca 170°, gave on repeated recrystallizations (ethanol and petroleum ether, b.p. 100–120°) *2-formyl-1-hydroxyxanthone* (0·02 g), as yellow needles, m.p. 186°, λ_{max} 260 (34,400), 310 (10,600), 355 (7,200) (Found: C, 69·8;

H, 3·3. $C_{14}H_8O_4$ requires: C, 70·0; H, 3·3%). It gives an orange, crystalline 2:4-dinitrophenylhydrazone, and a deep-red ferric reaction.

A by-product from the purification of 2-formyl-1-hydroxyxanthone gave a red gelatinous precipitate with Brady's reagent which suggests the presence of another formyl derivative. When the Duff reaction was carried out in glyceroboric acid or in a mixture of dimethyl formamide and acetic acid, or with more hexamine, the yields of formyl derivative were not improved. With 1-methoxyxanthone no reaction occurred but using 1-acetoxyxanthone the results were as for 1-hydroxyxanthone.

4-*Acetyl*-1-*hydroxyxanthone* (I; R = OH, R′ = R‴ = H, R″ = Ac)

4-Benzyloxy-2-hydroxyacetophenone (VI, 8·9 g) and *o*-chlorobenzoic acid (5·2 g) were refluxed in amyl alcohol (40 cc) in the presence of cuprous iodide (0·1 g), copper–bronze (0·1 g) and anhydrous potassium carbonate (9 g). The amyl alcohol-water azeotrope was distilled off and more amyl alcohol (30 cc) was added and the reaction mixture boiled under reflux for 3 hr. Finally the amyl alcohol was removed by steam distillation and the solid residue (which was 4-benzyloxy-2-hydroxyacetophenone, 6·7 g) collected. The filtrate when acidified to pH 2 yielded a gum which on trituration with ethanol gave 2-*acetyl*-2′-*carboxy*-5-*benzyloxydiphenyl ether* (0·32 g) as fine, white needles, m.p. 152–154° (aqueous ethanol) (Found: C, 72·5; H, 4·9. $C_{22}H_{18}O_5$ requires: C, 72·9; H, 5·0). The ether (0·1 g) and tetraphosphoric acid (3 cc) were heated on a water-bath at 84° for 0·8 hr and the reaction mixture then poured onto crushed ice. The yellow precipitate (0·08 g) when recrystallized twice from aqueous ethanol yielded 4-*acetyl*-1-*hydroxyxanthone*, m.p. 200°, identical with the unidentified substance isolated previously from Friedel–Crafts and Fries reactions on 1-hydroxyxanthone,[1] λ_{max} 238 (35,500), 248 (27,000), 276 (21,300), 358 (6200) (Found: C, 70·9; H, 4·0. $C_{15}H_{10}O_4$ requires: C, 70·9; H, 4·0%). Its 2:4-*dinitrophenylhydrazone* crystallized as orange needles, m.p. 273° (Found: N, 12·7. $C_{21}H_{14}O_7N_4$ requires: N, 12·9%).

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