99. *Anthoxanthins. Part XIV. ω-Hydroxyphloracetophenone and Certain Derivatives. Synthesis of Galangin under Milder Conditions than those used heretofore.*

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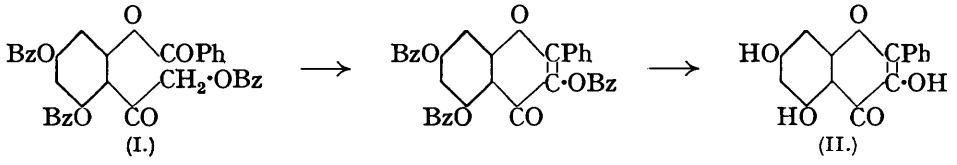
In order to extend the synthesis of flavonols described in this series of memoirs to the preparation of glucosides it is desirable (*a*) to devise a method of preparation of ω-glucosidoxyphloracetophenone and (*b*) to find conditions for the construction of the pyrone ring at a lower temperature than must now be employed in the melt with anhydrides of aromatic acids.

We have not yet succeeded in attempts to prepare the ω-hydroxy-2 : 4 : 6-triacetoxyacetophenone required for (*a*), but useful preliminary steps have been taken. On the other hand it has been found possible to dehydrate ω : 2 : 4 : 6-*tetrabenzoyloxyacetophenone* (I) by means of potassium acetate in boiling alcoholic solution, or, better, by means of boiling acetic anhydride in presence of sodium acetate. The product furnished galangin (II) on hydrolysis.



(I.) (II.)

This is not an improved synthesis of galangin itself (cf. Kalff and Robinson, J., 1925, **127**, 1972; Heap and Robinson, J., 1926, 2336, for better methods), but, unlike the older processes, it serves as a model for a flavonol-3-glucoside synthesis which it is hoped to realise.

ω : 2 : 4 : 6-*Tetrabenzoyloxyacetophenone* (I).—In the prepn. of benzoyloxyacetonitrile (Aloy and Raboux, *Bull. Soc. chim.*, **1913**, **13**, 457; Heap and Robinson, *loc. cit.*), it is essential to introduce the PhCOCl slowly with vigorous stirring below 15° and to use an excess of KCN so as to preserve an alkaline reaction. 40% CH_2O aq. (60 c.c.), KCN (28 g.), and PhCOCl (35·7 c.c.)

gave 23·5 g., b. p. 150—160°/13 mm., which solidified completely, m. p. 26° (lit., 27°). By the method of Heap and Robinson (*loc. cit.*) 10 g. of $PhCO{\cdot}O{\cdot}CH_2{\cdot}CN$, on condensation with phloroglucinol, furnished 20 g. of ketimine hydrochloride and 16 g. of pure ω-benzoyloxyphloracetophenone. The substance, m. p. 235°, is readily sol. in most org. solvents but sparingly sol. even in hot H_2O. PhCOCl (10 c.c.) was added drop-wise to ω-benzoyloxyphloracetophenone (5 g.) in dry C_5H_5N (40 c.c.) kept at − 5°. After 3 hr. in the freezing mixture the product was added to very dil. H_2SO_4, and the solid isolated, dried, and washed with Et_2O in order to remove $PhCO_2H$ (yield, 10 g. or 96%). It crystallised from EtOH (forming about a 1% solution in the boiling solvent) in fine colourless needles, m. p. 142·5° (Found : C, 71·8; H, 4·1; *M*, in C_6H_6, 610. $C_{36}H_{24}O_9$ requires C, 72·0; H, 4·0%; *M*, 600). This *derivative* is very sparingly sol. in most solvents and it gives no colour reaction with ferric salts.

An attempt to prepare a monobenzoyl derivative of ω-benzoyloxyphloracetophenone by limiting the amount of PhCOCl employed led to the formation of the fully benzoylated ketone only.

Galangin (II).—A mixture of the tetrabenzoate (1 g.), dry KOAc (5 g.), and EtOH (25 c.c.) was refluxed for 10 hr. (and in other expts. for shorter periods) and examination of the fluorescent properties of H_2SO_4 solutions showed that galangin derivatives were produced. The isolation of O-*tribenzoylgalangin* involved a tedious fractional crystn. from EtOH in order to separate it from unchanged material. The pure substance (yield, 0·1 g. from 5·0 g.) formed nearly colourless needles, m. p. 177° (Found : C, 74·1; H, 4·0. $C_{36}H_{22}O_8$ requires C, 74·2; H, 3·8%). The solution in conc. H_2SO_4 fluoresces bright blue.

A better method is the following and it appears that an aroyl group will not be displaced by acetoxyl if it is already joined to oxygen atoms in positions 2 and 6 of the phloracetophenone molecule. The danger is indicated by the observation of Kalff and Robinson (J., 1925, **127**, 1972), who obtained a 2-methylchromone derivative in the attempted *o*-acetoxybenzoylation of ω-methoxyphloracetophenone.

A mixture of ω : 2 : 4 : 6-tetrabenzoyloxyacetophenone (5 g.), KOAc (5 g.), and Ac_2O (50 c.c.) was refluxed for 6 hr. The product was worked up as usual, ultimately by hydrolysis with NaOH and pptn. by CO_2, but this gave a sodium salt, which was dissolved in hot H_2O and decomposed by dil. HCl. The substance separated from MeOH in greenish-yellow crystals (0·4 g.), m. p. 214° alone or mixed with an authentic specimen. Addition of H_2O to the solution in MeOH pptd. the colourless hydrate characteristic of galangin (Found : C, 62·4; H, 4·3. Calc. for $C_{15}H_{10}O_5,H_2O$: C, 62·5; H, 4·2%). The triacetate was also prepared in the usual manner (Found : C, 63·5; H, 4·2. Calc. for $C_{21}H_{16}O_8$: C, 63·6; H, 4·1%), m. p. 142° alone or mixed with an authentic specimen.

Acetoxyacetonitrile.—A solution of KCN (112 g. techn.) in H_2O (220 c.c.) was placed in a 3-litre flask provided with a *long* condenser, and 40% CH_2O aq. (120 c.c.) was slowly added with cooling in ice to keep the mixture below 15°. A mixture of Ac_2O (264 g.) and Et_2O (400 c.c.) was gradually introduced through the condenser with very vigorous shaking. The Et_2O refluxed and the success of the operation depended on the efficiency of the agitation. The ethereal solution was separated, and the aq. layer extracted several times with more Et_2O, the nitrile being readily sol. in H_2O. The combined Et_2O solutions were dried with Na_2SO_4. The fraction, b. p. 170—180°, was collected and on a second distillation had b. p. 175°/767 mm.; yield, 50 g. of very pure material.

ω-Hydroxyphloracetophenone.—The condensation of acetoxyacetonitrile and phloroglucinol in a Hoesch synthesis does not yield the desired ω-acetoxy-derivative. Again the attempted benzoylation of the ketimine in the hope of obtaining ultimately ω-hydroxy-2 : 4 : 6-tribenzoyloxyacetophenone was unsuccessful.

A solution of $AcO{\cdot}CH_2{\cdot}CN$ (10 g.) and $C_6H_6O_3$ (13·5 g.) in Et_2O (100 c.c.) was sat. at 0° with HCl for 3 hr.; the solvent was then decanted from the cryst. crust, which was washed with fresh Et_2O and exposed to a vac. over KOH. Hydrolysis was effected by boiling in EtOH (100 c.c.) and H_2O (80 c.c.) solution for 8 hr.; the EtOH was then evaporated and, on cooling, the ketone crystallised (12 g., and 3 g. from the mother-liquor). After many crystns. from H_2O (charcoal) the *substance* was obtained in very pale rose-coloured, slender needles, m. p. 224° (Found : C, 52·4, 52·2; H, 4·5, 4·4. $C_8H_8O_5$ requires C, 52·2; H, 4·3%). On benzoylation with PhCOCl and C_5H_5N at − 5°, a nearly quantitative yield of ω : 2 : 4 : 6-tetrabenzoyloxyacetophenone, m. p. and mixed m. p. 142·5°, was obtained (Found : C, 72·0; H, 4·1%). This proves that the acetoxyl group suffered hydrolysis in the prepn. of the ketone.

ω : 2 : 4 : 6-*Tetra-acetoxyacetophenone*, obtained by acetylating the tetrahydroxyacetophenone by boiling with Ac_2O and a little C_5H_5N for 1 hr., crystallised from EtOH in well-shaped prisms,

m. p. 106·5° (Found : C, 54·7; H, 4·7; *M*, in C_6H_6, 351. $C_{16}H_{16}O_9$ requires C, 54·5; H, 4·5%; *M*, 352). The partial acetylation of the tetrahydroxyacetophenone has been attempted under a variety of conditions, especially involving the use of Ac_2O in various solvents (Et_2O, C_6H_6) and aqueous alkaline solutions of the phenolic ketone. The only product isolated was the tetra-acetate.

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