

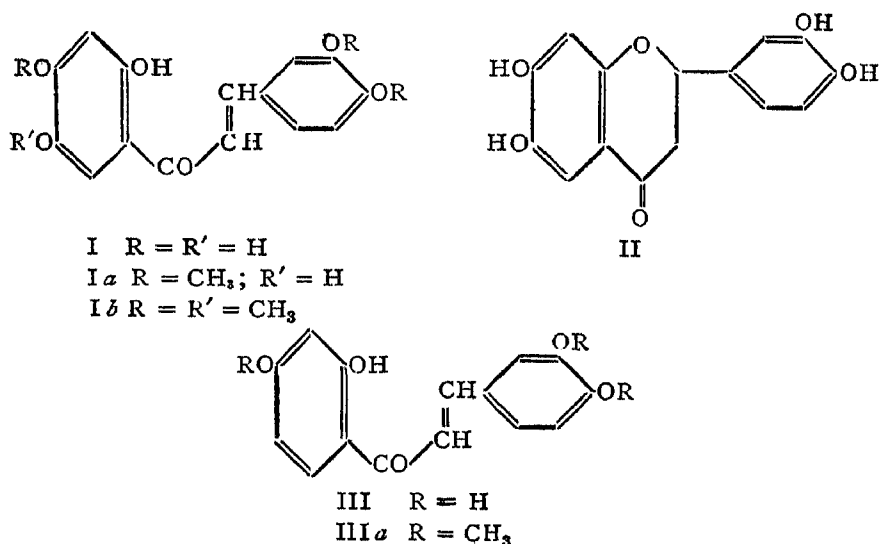
A SYNTHESIS OF STILLOPSIDIN AND ITS METHYL ETHERS*

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SEIKEL AND GEISSMAN¹ isolated a chalcone hexoside, stillopsin, from the flowers of *Coreopsis stillmanii*. They showed that it was a glucoside of 2:4:5:3':4'-pentahydroxychalcone (I, stillopsidin). Later, King *et al.*² obtained the same chalcone from the heartwood of *Plathymenia reticulata* in which it was accompanied by the corresponding flavanone which was called plathymenin (II). Obviously, partial flavanone conversion had taken place in the heartwood. In view of the fact that other *Coreopsis* species contain glycosides of butein (III), it could be suggested that the evolution of stillopsidin involves an extra stage of oxidation leading to the introduction of a hydroxyl group in the 5-position. Stillopsidin, therefore, is 5-hydroxybutein. Following this concept, it should be possible to oxidise butein to stillopsidin. Using butein trimethyl ether (III *a*), nuclear oxidation could now be conveniently carried out by means of alkaline persulphate to produce stillopsidin trimethyl ether (I *a*) which when partially methylated yields the known compound, stillopsidin tetramethyl ether (I *b*).

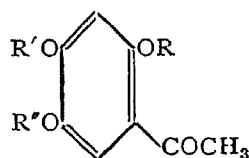


The free pentahydroxychalcone (stillopsidin) itself could not be obtained by demethylation of the above methyl ether because it was accompanied by

* The work discussed in this paper was completed in the 1954-55 session and was embodied in a thesis. In view of the publication of Seikel *et al.*,³ only matter not found in their paper is presented here.

complex changes. Hence, direct synthesis had to be carried out. Seikel *et al.*³ achieved this synthesis in rather poor yields by carrying out the chalcone condensation with 2:4:5-trihydroxyacetophenone and protocatechuic aldehyde in the presence of alkali. A more convenient method is to use the benzoates of the two components, effect the condensation in the presence of hydrogen chloride and finally remove the benzoyl groups. This gives rise to an easily purified product in a much better yield. Further conversion into the flavanone to obtain plathymenin has been already reported by Seikel *et al.*³

In the course of the abovementioned work, 2:5-dihydroxy-4-methoxyacetophenone (IV) and 2-hydroxy-4:5-dimethoxyacetophenone (V) were prepared as intermediates. The former was obtained from pæonol by oxidation with alkaline potassium persulphate⁴ and its properties agreed very closely with those of the substance prepared by Bargellini and Aureli⁵ by the demethylation of 2:4:5-trimethoxyacetophenone (VI). However, they considered this demethylation product to be 2:4-dihydroxy-5-methoxyacetophenone (VII). In view of the fact that a methoxyl group located para to a carbonyl is more resistant to demethylation than those in the meta and ortho positions, it appeared possible that the sample obtained by Bargellini and Aureli⁵ was really the 4-methyl ether. This has been confirmed by the demethylation of 2-hydroxy-4:5-dimethoxyacetophenone (V) with hydrobromic acid whereby the product was found to be identical with the one obtained by nuclear oxidation of pæonol. Further, the 5-methyl ether (VII) has also been prepared by employing the 4-benzyl ether of resacetophenone and subjecting it to nuclear oxidation, partial methylation and debenzylation.



IV $R = R'' = H; R' = CH_3$

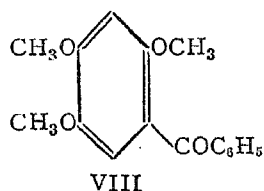
V $R = H; R' = R'' = CH_3$

VI $R = R' = R'' = CH_3$

VII $R = R' = H; R'' = CH_3$

A similar error seems to exist in the work of Bargellini and Martegiani⁶ when they considered that the partial demethylation of 2:4:5-trimethoxybenzophenone (VIII) yielded the corresponding 5-monomethyl ether. Here also, the substance is found to agree in its properties with the 4-methyl ether obtained by the nuclear oxidation of 2-hydroxy-4-methoxybenzophenone. As relevant to the above discussion, it may be mentioned that Gardner *et al.*⁷

have recently found that partial demethylation of 2:3:4-trimethoxyacetophenone yields the 4-monomethyl ether and not the 3-monomethyl ether as originally thought by Baker *et al.*⁸



EXPERIMENTAL

2:5-Dihydroxy-4:3':4'-trimethoxychalkone (Ia).—To a stirred solution of 2-hydroxy-4:3':4'-trimethoxychalkone⁹ (butein trimethyl ether) (2 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (2 g. in 16 c.c. of water) was added dropwise a solution of potassium persulphate (2 g. in 50 c.c. of water) in the course of 2 hours (18–20°). The mixture was allowed to stand for 24 hours, and neutralised with concentrated hydrochloric acid (Congo red). The precipitated unreacted chalkone was filtered off and the filtrate extracted with ether three times. The aqueous solution was treated with sodium sulphite (6 g.) and concentrated hydrochloric acid (40 c.c.) and heated on a boiling water-bath for $\frac{1}{2}$ hour, when an orange-yellow solid separated. After keeping overnight in the refrigerator, it was filtered and washed with a little cold water. On crystallisation from methyl alcohol, the dihydroxychalkone was obtained as deep orange-yellow prisms, m.p. 204–05°. Yield, 0.4 g. (Found: C, 65.5; H, 5.5; $C_{18}H_{18}O_6$ requires C, 65.5 and H, 5.5%). It gave an evanescent green colour with alcoholic ferric chloride and a pink colour with aqueous sodium hydroxide.

2-Hydroxy-4:5:3':4'-tetramethoxychalkone (stillopsidin tetramethyl ether) (Ib).—A solution of the above chalkone (Ia) (1 g.) in dry benzene (40 c.c.) and dry acetone (40 c.c.) was refluxed with dimethyl sulphate (0.35 c.c., 1.1 mole) and anhydrous potassium carbonate (2 g.) for 6 hours, and filtered. The chalkone, obtained after distilling off the solvent from the filtrate, crystallised from alcohol as orange-yellow plates, m.p. 173–74°. Yield, 0.7 g. It gave a brown colour with alcoholic ferric chloride (*see* Seikel and Geissman¹ and King *et al.*²). For comparison, this tetramethyl ether was prepared by the condensation of 2-hydroxy-4:5-dimethoxyacetophenone and varatraldehyde in the presence of caustic alkali in the cold (48 hours) whereby good yields were obtained and the substance was identical with the compound prepared by Seikel and Geissman.¹

2:4:5-Trihydroxyacetophenone.—Seikel *et al.*³ reported that the nuclear oxidation of resacetophenone does not proceed satisfactorily. By adopting

the conditions mentioned below, fairly good yields of 2:4:5-trihydroxyacetophenone could be obtained.

To a stirred solution of resacetophenone (15 g.) in potassium hydroxide (30 g. in 100 c.c. of water) was added dropwise a saturated aqueous solution of potassium persulphate (30 g.) during 5 hours and the mixture was left at room temperature for 48 hours. It was worked up as usual and the aqueous solution after hydrolysis was thoroughly extracted with ether (10 × 300 c.c.). The ether extract was evaporated to dryness and the solid washed with a small quantity of ether. It was crystallised from ether; m.p. 202–04°. Yield, 5 g.

The tribenzoate of the above acetophenone was prepared using benzoyl chloride and pyridine; m.p. 138–39°.

2:4:5:3':4'-*Pentahydroxychalkone (stillopsidin) (I)*.—A solution of 2:4:5-tribenzoyloxyacetophenone (4.8 g.) and protocatechuic aldehyde dibenzoate (3.4 g.) in dry ethyl acetate (60 c.c.) was saturated with dry hydrogen chloride for 4 hours, and left overnight. The solvent was removed under reduced pressure and the clear red syrup was boiled with alcohol (50 c.c.), cooled and decanted off. The crude chalkone benzoate was dissolved in boiling alcohol (150 c.c.) and potassium hydroxide (14 g. in 100 c.c. of water) added dropwise along with a small amount of sodium sulphite. After keeping for 4 hours, it was just acidified and the alcohol distilled off. The dark red solution was cooled in ice and the solid product collected. Extraction of the filtrate, after saturation with sodium chloride, yielded a further quantity of the hydroxychalkone. It was freed from benzoic acid by repeatedly washing with hot benzene and finally crystallised from aqueous methyl alcohol yielding orange plates; m.p. 226–28°. Yield, 0.7 g. (Found: C, 62.1; H, 4.1; $C_{15}H_{12}O_6$ requires C, 62.5 and H, 4.2%). It gave a dark brown colour with alcoholic ferric chloride (*see* Seikel and Geissman¹ and King *et al.*²).

Partial demethylation of 2-hydroxy-4:5-dimethoxyacetophenone.—2-Hydroxy-4:5-dimethoxyacetophenone (0.5 g.) was dissolved in acetic acid (10 c.c.) and hydrobromic acid (constant boiling; 10 c.c.) added. The solution was refluxed gently for 2 hours, and then diluted with water. Most of the acid was neutralised by the addition of sodium bicarbonate and the mixture extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and distilled when a brown oil was obtained which solidified on keeping in the refrigerator. It crystallised from water as pale brown, elongated rods; m.p. 164–65°. It gave an evanescent green colour with alcoholic ferric chloride. It was identical with 2:5-dihydroxy-4-methoxyaceto-

phenone, obtained by the persulphate oxidation of pæonol;⁴ the mixed melting point was also undepressed.

2:4-Dihydroxy-5-methoxyacetophenone (VII): (a) 2:5-Dihydroxy-4-benzyloxyacetophenone.—2-Hydroxy-4-benzyloxyacetophenone, required for this preparation, was obtained in improved yields by a modification of the method of Gulati *et al.*¹⁰ using 1 mole of benzyl chloride and potassium iodide. It (4.8 g.) was dissolved in a mixture of potassium hydroxide (6 g. in 50 c.c. of water) and pyridine (25 c.c.). To this solution was added dropwise a solution of potassium persulphate (6 g. in 200 c.c. of water) in the course of 4 hours, keeping the temperature of the reaction mixture below 15°. The product was worked up as usual and it crystallised from alcohol as yellow plates and prisms; m.p. 160–62°. Yield, 1.2 g. (Found: C, 69.2; H, 5.4; $C_{15}H_{14}O_4$ requires C, 69.7 and H, 5.5%). It gave a green colour with alcoholic ferric chloride.

(b) 2-Hydroxy-4-benzyloxy-5-methoxyacetophenone.—The above compound (4.2 g.) was partially methylated with dimethyl sulphate (1.8 c.c.) and potassium carbonate (4 g.) in acetone (100 c.c.) by refluxing for 6 hours. The methyl ether crystallised from alcohol as stout needles; m.p. 126° (Found: C, 70.2; H, 6.2; $C_{16}H_{16}O_4$ requires C, 70.6 and H, 5.9%). It gave a dark green colour with alcoholic ferric chloride.

(c) Debenzylation.—2-Hydroxy-4-benzyloxy-5-methoxyacetophenone (1 g.) was boiled with a mixture of concentrated hydrochloric acid (10 c.c.) and glacial acetic acid (10 c.c.) for 1 hour. On cooling the mixture, a dark product separated which was filtered and dried. It crystallised from ether (charcoal) as colourless plates and prisms; m.p. 174° (Found: C, 59.0; H, 5.6; $C_9H_{10}O_4$ requires C, 59.3 and H, 5.5%). It gave a brownish green colour with alcoholic ferric chloride.

2:5-Dihydroxy-4-methoxybenzophenone.—2-Hydroxy-4-methoxybenzophenone, required for this synthesis, was earlier prepared by the partial methylation of 2:4-dihydroxybenzophenone by Kostanecki and Tambor¹¹ as well as by the partial demethylation of 2:4-dimethoxybenzophenone by Kaufmann *et al.*¹² Now this has been prepared by Friedel and Crafts' reaction between resorcinol dimethyl ether and benzoyl chloride in dry ether solution. It (3 g.) was dissolved in potassium hydroxide (4 g. in 30 c.c. of water) and treated with potassium persulphate (4 g. in 100 c.c. of water) during the course of 3 hours, and worked up as usual. The product crystallised from alcohol as deep yellow, thin plates; m.p. 188°. Yield, 0.7 g. (Found: C, 68.4; H, 5.3; $C_{14}H_{12}O_4$ requires C, 68.8 and H, 5.0%). It gave a green colour with alcoholic ferric chloride. (Bargellini and Martegiani⁶ reported

a melting point of 183-85° for the compound obtained by the partial demethylation of 2:4:5-trimethoxybenzophenone).

The above quinol derivative on partial methylation with dimethyl sulphate (1.1 mole) and potassium carbonate in acetone solution gave 2-hydroxy-4:5-dimethoxybenzophenone, m.p. 109-10°.—Bargellini and Martegiani⁶ reported a melting point of 106-07° for this compound.

SUMMARY

On the consideration that stillopsidin is 5-hydroxybutein, butein trimethyl ether has been subjected to nuclear oxidation and final methylation to yield stillopsidin tetramethyl ether. Stillopsidin has now been prepared in better yields by an improved method. The product obtained by the partial demethylation of 2:4:5-trimethoxyacetophenone is shown to be 2:5-dihydroxy-4-methoxyacetophenone which has been prepared by an unequivocal method from pæonol. Similarly an authentic sample of 2:5-dihydroxy-4-methoxybenzophenone has been prepared and shown to be the same as that obtained by the partial demethylation of 2:4:5-trimethoxybenzophenone. A synthesis of 2:4-dihydroxy-5-methoxyacetophenone has also been carried out.

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