SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP

Part XXIX. A Method for the Reduction of 5:7-Dihydroxyflavones to 5-Hydroxyflavones

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5-HYDROXYFLAVONE, which occurs together with flavone in the meal or dust of the leaves and stems of Primula imperialis, was first synthesized by Sugasawa by the Allan-Robinson reaction on 2-acetylresorcinol, and later by the transformation of 2:6-dibenzoyloxyacetophenone to the corresponding diketone, followed by cyclization. 5-Hydroxyflavonols have been prepared by Seshadri by the Kostanecki method from 2-hydroxy-6-methoxyacetophenone via the chalkone, flavanone and isonitrosoflavanone.

In the course of our work on Raney nickel reductions it was observed that an application of the method of Kenner and Murray for the cleavage of sulphonic esters with Raney nickel leads to a convenient method for the preparation of γ-resorcylic acid by the hydrogenolysis of the mono-O-p-toluenesulphonyl derivative of phloroglucinol carboxylic acid. Extending this procedure to the flavone series, we have converted chrysin (5:7-dihydroxyflavone) to 5-hydroxyflavone and galangin 3-methyl ether (5:7-dihydroxy-3-methoxyflavone) to 5-hydroxy-3-methoxyflavone. A general method has thus become available for the synthesis of 5-hydroxyflavones, which are of
interest because of their possible occurrence in nature and also as intermediates for the synthesis of naturally occurring 5:8-dihydroxyflavones by the Elbs-Seshadri persulphate oxidation.

Chrysin\(^7,8\) and galangin 3-methyl ether\(^9\) readily gave the 7-p-toluene-sulphonyl esters (I and II) on treatment with a molar proportion of p-toluene-sulphonyl chloride and excess of anhydrous potassium carbonate in boiling acetone. It was necessary to carry out the hydrogenolysis of the tosyl derivatives under controlled and mild conditions, leaving a part of the tosyl derivative unreacted to poison the nickel catalyst in order to avoid undesirable side reactions. The crude reaction mixture was treated with alcoholic caustic potash to hydrolyse the unreacted tosyl derivative and the mixture of hydroxyflavones separated by chromatography. Thus by the hydrogenolysis of the 7-tosyl ester (I) of chrysin, a mixture of 5-hydroxyflavone (III) and chrysin was obtained; when the mixed flavones were dissolved in benzene and chromatographed on Florex xxx (an extruded fuller's earth supplied by the Floridin Co., Inc.), development and elution with benzene yielded 5-hydroxyflavone (III) in a yield of about 25 per cent. calculated on the quantity of the tosyl derivative (I) consumed in the reaction. Elution with ethyl acetate then led to the recovery of the more strongly adsorbed chrysin. In the case of the 7-tosyl ester (II) of galangin 3-methyl ether Raney nickel treatment and hydrolysis of the product yielded galangin 3-methyl ether and 5-hydroxy-3-methoxyflavone (IV), readily separable by chromatography. It was found, however, that galangin 3-methyl ether and 5-hydroxy-3-methoxyflavone can be separated in a simpler manner by taking advantage of the sparing solubility of the former in benzene. Methylation of (IV) gave 3:5-dimethoxyflavone, m.p. 119-20°. The m.p. quoted by Seshadri\(^4\) for 3:5-dimethoxyflavone is 160-2°. The possibility of our compound (IV) and its methyl ether being flavanones was eliminated by Wilson's boric-citric acid test\(^10\) to which (IV) responded, and by treatment of the dimethyl ether with selenium dioxide in boiling xylene;\(^11\) most of the starting material was recovered unchanged, a small part undergoing oxidation to a brown oily substance. Further, the production of 5-hydroxyflavone by the reduction of the tosyl derivative of chrysin and the recovery of chrysin and of galangin 3-methyl ether in the two reduction experiments left little doubt that 5-hydroxy-3-methoxyflavone and 3:5-dimethoxyflavone obtained by us had the authentic structures assigned to them. It was also observed that quercetin and its pentamethyl ether were substantially unaffected by Raney nickel under the specified conditions. However, in view of the discrepancy in the melting points cited for 3:5-dimethoxyflavone, an alternative synthesis has been undertaken, based on the method reported by Karmarkar, Shah and one of
us for the preparation of 2-phenylacetlyresorcinol (2:6-dihydroxyphenyl benzyl ketone). 12

EXPERIMENTAL

5-Hydroxy-7-tosyloxyflavone (I)

Chrysin (2 g.) was dissolved in dry acetone (100 c.c.), p-toluenesulphonyl chloride (1.5 g., 1 mol.) and anhydrous potassium carbonate (10 g.) were added, and the mixture refluxed for 3 hours. The acetone was distilled off, the residue taken up in water and acidified. The precipitate was filtered, washed with water, dried and crystallized from alcohol; the yellow rectangular plates (2.88 g.) had m.p. 166° (Found: C, 64.7; H, 4.3. C_{29}H_{18}O_{7}S requires C, 64.7; H, 3.9%). The substance gives with dilute aqueous caustic soda a yellow sparingly soluble sodium salt, and with alcoholic ferric chloride a red-violet colour.

Reduction of 5-hydroxy-7-tosyloxyflavone

5-Hydroxy-7-tosyloxyflavone (1:1 g.) was dissolved in alcohol (500 c.c.) Raney nickel (7 g.) was added, and the mixture agitated at room temperature for one hour while a steady stream of hydrogen was led in. The mixture was then filtered. The alcoholic filtrate was concentrated to 20 c.c. The nickel residue was deactivated under hydrochloric acid, filtered and the residue was extracted with ether. The product obtained after the removal of ether was added to the alcohol concentrate, caustic potash (0.5 g.) dissolved in a few drops of water was added, and the mixture refluxed for one hour. On removal of the alcohol the residue was taken up in water and acidified. The precipitate (0.32 g.) was dissolved in benzene and chromatographed on Florex xxx. Elution with benzene and evaporation of the yellow percolate gave yellow needles, which were recrystallized from alcohol (yield 0.12 g.). The m.p. was 157°, undepressed when mixed with 5-hydroxyflavone prepared from 2-acetylresorcinol dibenzoate. 3 Further elution with ethyl acetate yielded chrysin (0.11 g.).

5-Hydroxy-3-methoxy-7-tosyloxyflavone (II)

Galangin 3-methyl ether (3.5 g.), p-toluenesulphonyl chloride (2.4 g.; 1 mol.), anhydrous potassium carbonate (15 g.), and acetone (250 c.c.) were refluxed for 3 hours. The acetone was then removed, the residue taken up in water and acidified. The yellow precipitate was collected, washed and dried, and it crystallized from alcohol in yellow needles (4.5 g.), m.p. 156–57° (Found: C, 63.4; H, 4.4. C_{29}H_{18}O_{7}S requires C, 63.0; H, 4.1%). The substance gives with aqueous caustic soda a sparingly soluble yellow sodium salt, and with alcoholic ferric chloride a red-violet colour.
Reduction of 5-hydroxy-3-methoxy-7-tosyloxyflavone

The tosyl ester (II; 3 g.) was dissolved in alcohol (1,500 c.c.), Raney nickel (21 g.) added, and the mixture agitated for one hour while a steady stream of hydrogen was led in. The mixture was then filtered and concentrated to 40 c.c. The nickel residue was deactivated under hydrochloric acid, filtered and the residue extracted with hot alcohol. The extract was added to the above concentrate, potassium hydroxide (1.5 g.) dissolved in a small amount of water added, and the solution refluxed for one hour. The alcohol was distilled off, the residue taken up in water and acidified. The precipitate (1.62 g.) was extracted with cold benzene, and the benzene extract chromatographed on Florex. The yellow percolate on evaporation gave a yellow substance, which crystallized from methanol in yellow elongated prisms (0.82 g.), m.p. 115° (Found: C, 71.5; H, 4.9. C_{17}H_{19}O_{4} requires C, 71.7; H, 4.5. The m.p. quoted by Seshadri is 115-16). 13 5-Hydroxy-3-methoxyflavone (IV) gives a difficultly soluble yellow sodium salt with aqueous caustic soda, and with alcoholic ferric chloride a violet colour which develops a slightly greenish tinge. On treatment with magnesium and hydrochloric acid the substance gives an orange-red colour. With Wilson’s boric-citric acid-acetone reagent it gives a yellow colour like 5-hydroxyflavone and quercetin.

The residue unextracted by benzene (0.62 g.), after crystallization from ethyl acetate was identified as galangin 3-methyl ether by m.p. and mixed m.p.

3: 5-Dimethoxyflavone

5-Hydroxy-3-methoxyflavone (0.3 g.) was treated with dimethyl sulphate (1 c.c.) and anhydrous potassium carbonate (3 g.) in boiling acetone (20 c.c.) for 12 hours. The mixture was filtered and the residue washed with acetone. Evaporation of the solvent gave a colourless substance which crystallized from aqueous methanol in long colourless plates, m.p. 119-20° (Found: C, 72.1; H, 5.1. C_{17}H_{14}O_{4} requires C, 72.3; H, 5.0%). The substance is insoluble in dilute caustic soda solution and gives no colour with alcoholic ferric chloride.

The substance (0.3 g.) was dissolved in xylene (10 c.c.) selenium dioxide (0.3 g.), added and the mixture refluxed for 12 hours. On cooling, selenium was filtered off and washed with ether. The xylene and ether were removed by steam distillation and the brown residue was dissolved in benzene and chromatographed on alumina. The pale yellow eluent gave a minute amount of a brown oil. On further elution with alcohol, a yellow percolate was
obtained which on concentration gave an oil. The oil solidified on con-
tact with methanol, and crystallized from aqueous methanol in colourless
elongated plates (0.25 g.), m.p. 119-20°, undepressed when mixed with the
starting material.

SUMMARY

A general method for the preparation of 5-hydroxyflavone and its
derivatives from the corresponding 5:7-dihydroxyflavones by the action of
Raney nickel on the 7-tosyloxy derivatives is described. Thus chrysin has
been converted into 5-hydroxyflavone, and galangin 3-methyl ether to 5-
hydroxy-3-methoxyflavone.

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REFERENCES


See also Rajagopalan, Rao and Sheshadri
