

NUCLEAR OXIDATION IN THE FLAVONE SERIES

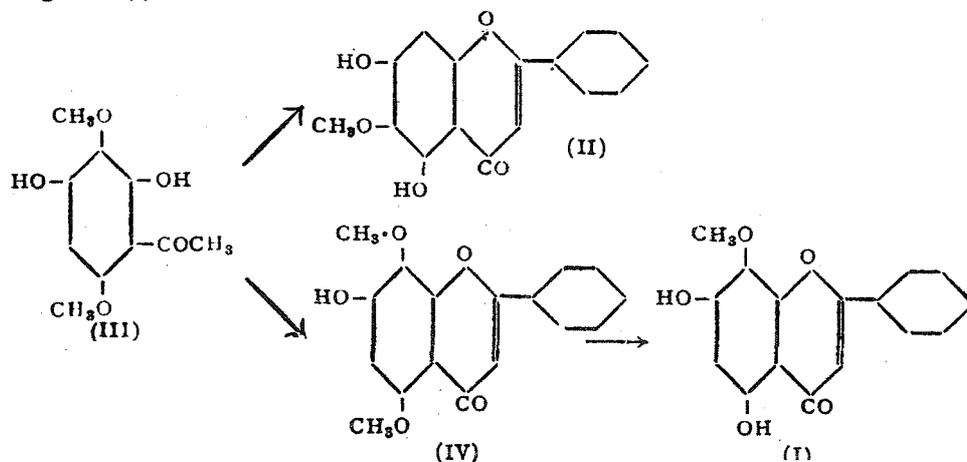
Part V. A New Synthesis of Wogonin

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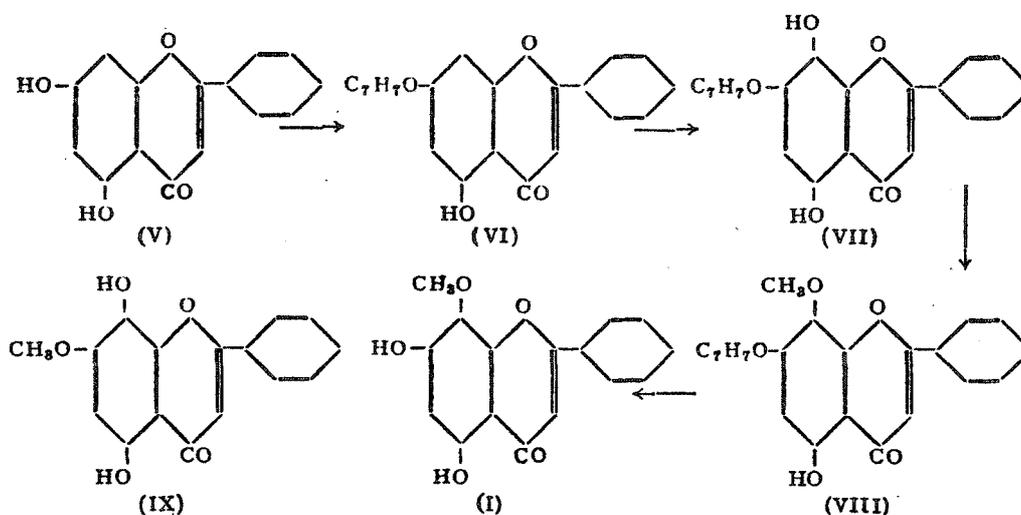
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IN Part II¹ was described the synthesis of norwogonin and isowogonin. Norwogonin has not so far been found to occur free in nature, but its mono-methyl ether is wogonin. This compound was first isolated by Takahashi² from the roots of *Scutellaria baicalensis* and named 'Scutellarin'. The name was subsequently changed to wogonin by Shibata³ in order to distinguish it from a different compound obtained by Molisch and Goldschmidt⁴ from the roots of *S. altissima*. Its constitution was established by Hattori as 5:7-dihydroxy-8-methoxyflavone⁵ (I). Its synthesis was effected by Shah, Mehta and Wheeler⁶ in the course of their attempt to synthesise oroxylin-A (II). The condensation of 2:4-dihydroxy-3:6-dimethoxy-acetophenone (III) with sodium benzoate and benzoic anhydride was expected to take the same course as the condensation of this ketone with anisic anhydride and sodium anisate⁷ with partial demethylation and subsequent ring closure to yield the 6-methyl-ether of baicalein (II). Unexpectedly the reaction proceeded in the normal way forming wogonin-monomethyl ether (IV). From this by partial demethylation with aluminium chloride wogonin (I) itself was obtained.

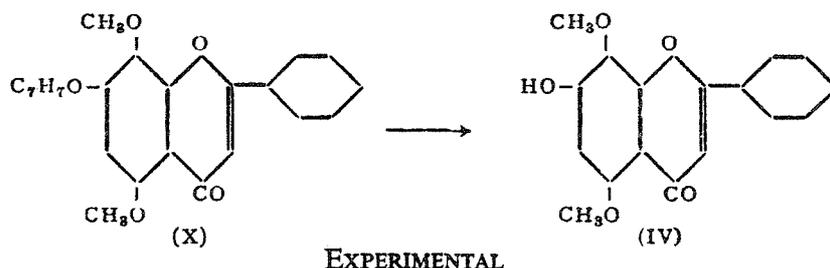


Though 8-methyl ethers of the type of wogonin are not well known, they do not seem to be so rare. Tambuletin⁸ which has recently been isolated from tambul seeds seems to belong to this category. In order to render the study of these new compounds more easy, the application of the recent discovery of facile nuclear oxidation in flavones has been made for the synthesis of wogonin. The method works quite satisfactorily and is capable of wide application. The scheme adopted is represented below:



The benzylation of chrysin (V) was carried out earlier by Gulati and Venkataraman⁹ using various conditions. They found that 7-O-benzyl-6-benzyl chrysin was the only product though in the parallel case of 5:7-dihydroxy-2-methyl-chromone the simple 7-benzyl-ether compound was obtained under those conditions. It has now been possible to prepare the required monobenzyl-ether (VI) of chrysin by using just over a molecular proportion of benzyl chloride and carrying out the reaction in anhydrous acetone medium in the presence of anhydrous potassium carbonate. The oxidation of the benzyl ether takes place easily though the yield of the quinol (VII) is not so good as in other cases. However, the unreacted ether could be recovered in an almost pure condition and could be reused. The next stage is partial methylation and this is effected conveniently with a molecular proportion of dimethyl sulphate, the more resistant 5-position being left out. Debenzylation of this partial methyl ether (VIII) takes place quite smoothly with acetic and hydrochloric acids yielding wogonin (I). The properties of this compound agree with the description in the literature.³ It differs from isowogonin¹ (IX) markedly in the reactions with alkali, ferric chloride and *p*-benzoquinone and resembles chrysin (V).

Complete methylation of (VII) with excess of dimethyl sulphate yields the dimethyl ether (X) which after debenzoylation forms wogonin-5-methyl ether (IV) readily. Further methylation of (I) and (IV) give rise to 5:7:8-trimethoxy flavone identical with the synthetic sample obtained by Sastri and Seshadri.¹⁰ All these transformations add further support to the constitution of the monobenzyl-ether of chrysin (VI).



7-Benzoyloxy-5-hydroxy-flavone (VI):

A solution of chrysin (V) (1 g.) in anhydrous acetone (100 c.c.) was treated with freshly distilled benzyl chloride (0.52 c.c.) and anhydrous potassium carbonate (5 g.). After refluxing the contents for 20 hours, the solvent was distilled off and the residue treated with water (200 c.c.). The undissolved yellowish brown solid was filtered, washed with petroleum ether followed by water and the aqueous filtrate preserved (F). The solid residue was the benzyl ether; yield 0.6 g. On crystallisation from acetone containing a few drops of glacial acetic acid it separated out in the form of glistening pale brown thin elongated rectangular plates melting at 173–75°. (Found: C, 76.8; H, 5.0; $C_{22}H_{18}O_4$ requires C, 76.7; H, 4.7%.) It was sparingly soluble in alcohol, acetone or ethyl acetate. In alcoholic solution it gave a deep reddish brown colour with ferric chloride. It was insoluble in aqueous sodium hydroxide and on boiling the mixture, the solid turned deep yellow.

On acidifying the brown aqueous filtrate (F) a cream-coloured solid separated out which was filtered and washed with water. When recrystallised from alcohol it yielded pure chrysin (0.3 g.).

5:8-Dihydroxy-7-benzyloxy-flavone (VII):

To a stirred solution of 5-hydroxy-7-benzyloxy-flavone (VI) (1 g.) in a mixture of pyridine (35 c.c.) and aqueous potassium hydroxide (0.9 g. in 20 c.c.) was added dropwise a solution of potassium persulphate (1.5 g. in 50 c.c. of water) during the course of 2 hours. After keeping the deep brown solution for 24 hours it was slightly acidified when a pale brown precipitate was thrown down. It was filtered and washed with water. It

was found to be almost pure 7-benzyloxy-5-hydroxy-flavone; recovery 0.6 g. The filtrate was twice extracted with ether and the clear aqueous layer was treated with sodium sulphite (3 g.) and concentrated hydrochloric acid (25 c.c.) and heated in a boiling water-bath for 30 minutes. A yellow crystalline solid separated out in the course of the heating. After cooling it was filtered and washed with water; by extracting the filtrate with ether some more of the substance was obtained. Yield 0.2 g. On crystallisation from a mixture of ethyl acetate and benzene it separated out in the form of bright golden yellow narrow rectangular plates melting at 220–21°. (Found: C, 72.9; H, 4.3; $C_{22}H_{18}O_5$ requires C, 73.3; H, 4.4%.) It was sparingly soluble in alcohol, ethyl acetate and ether. In alcoholic solution it gave with ferric chloride a pale green colour which quickly changed to deep brown. It dissolved in aqueous sodium hydroxide to a deep reddish brown solution.

8-Methoxy-7-benzyloxy-5-hydroxy-flavone (VIII):

A solution of 5:8-dihydroxy-7-benzyloxy flavone (VII) (0.4 g.) in anhydrous acetone (25 c.c.) was treated with dimethyl sulphate (0.1 c.c.) and potassium carbonate (2 g.). After refluxing for 6 hours the solvent was distilled off and the residue treated with water (50 c.c.). The undissolved solid was filtered and washed with water. After crystallisation from acetone it separated out in the form of pale yellow soft woolly needles melting at 208–10°. (Found: C, 73.9; H, 5.0; $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.8%.) It was very sparingly soluble in alcohol and acetone but more easily in benzene. In alcoholic solution it gave a stable green colour with ferric chloride. It was insoluble in alkali even on heating.

8-Methoxy-5:7-dihydroxy flavone: Wogonin (I):

Concentrated hydrochloric acid (3 c.c.) was added to a solution of 8-methoxy-7-benzyloxy-5-hydroxy-flavone (VIII) (0.15 g.) in glacial acetic acid (10 c.c.) and the solution kept in a boiling water-bath for 1 hour. Water (100 c.c.) was then added and the yellow solid that separated out was filtered off and washed with water. Crystallisation from a mixture of ethyl acetate and benzene yielded bright yellow glistening stout spear-shaped crystals melting at 200–02°. (Found: C, 67.7; H, 4.5; $C_{18}H_{12}O_5$ requires C, 67.6; H, 4.2%.) It was easily soluble in alcohol, ethyl acetate and acetone but sparingly in benzene. In aqueous sodium carbonate and sodium hydroxide it readily dissolved to a bright golden yellow solution. In alcoholic solution it gave a greenish brown colour with ferric chloride and it was unchanged on adding excess of the reagent. It did not react with *p*-benzoquinone.

5: 8-Dimethoxy-7-benzyloxy-flavone (X):

A solution of 7-benzyloxy-5: 8-dihydroxy-flavone (VII) (0.15 g.) in anhydrous acetone (20 c.c.) was refluxed with dimethyl sulphate (0.2 c.c.) and potassium carbonate (2 g.) for 6 hours. The solvent was distilled off, the residue treated with water and the pale brown solid that remained behind was filtered off and washed with water. Crystallisation from a mixture of benzene and petroleum-ether furnished the compound in the form of colourless prismatic needles melting at 160–61°. (Found: C, 73.9; H, 5.1; $C_{24}H_{20}O_5$ requires C, 74.2; H, 5.2%) It was insoluble in aqueous alkali and did not give any colour with ferric chloride.

5: 8-Dimethoxy-7-hydroxy-flavone (IV):

Concentrated hydrochloric acid (2 c.c.) was added to a solution of 5: 8-dimethoxy-7-benzyloxy flavone (X) (0.1 g.) in glacial acetic acid (5 c.c.). After keeping the mixture in a boiling water-bath for 1 hour and finally heating it to boiling, it was cooled and diluted with water (50 c.c.). The light brown solid product was filtered, washed with water, dried and crystallised from absolute alcohol from which it separated in the form of almost colourless rhombohedral plates and needles melting at 285–87°. It was sparingly soluble in alcohol and other common organic solvents and readily dissolved in aqueous sodium hydroxide to a yellow solution. It was found to be identical with the sample obtained by Sastri and Seshadri¹⁰ from 2: 4-dihydroxy-3: 6-dimethoxy-acetophenone by adopting the Baker Venkataraman procedure; the mixed melting point was undepressed.

SUMMARY

Using the new discovery of facile nuclear oxidation in hydroxy-flavones, (1) wogonin and (2) its 5-methyl ether have been synthesised. Starting with 7-O-benzyl-chrysin, oxidation followed by partial methylation and debenylation yields (1) and by complete methylation and debenylation yields (2).

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