NUCLEAR OXIDATION IN THE FLAVONE SERIES

Part II. Synthesis of Norwogonin and Isowogonin

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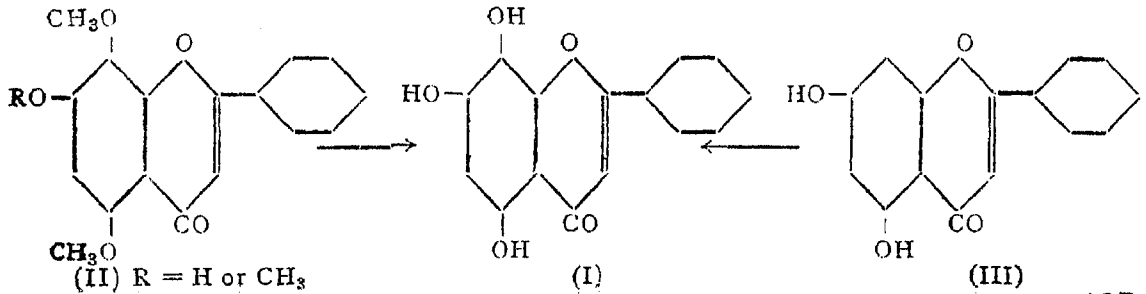
As already mentioned in Part I[1] attempts made by previous workers to effect nuclear oxidation of chrysin (III) were not successful. It is an important reaction since, apart from biogenetic interest, it will lead to an easy synthesis of norwogonin (I), a flavone having the 5:7:8-arrangement of hydroxyl groups. This compound was prepared in the past by methods involving the demethylation of its methyl ethers (II). Hydriodic acid could not be used for this purpose since it brings about re-arrangement in the molecule leading to the formation of 5:6:7-trihydroxy-flavone (baicalein). Aluminium chloride has been found to be free from this defect. Norwogonin was thus prepared by Shah *et al.*[2] by the demethylation of 5:8-dimethoxy-7-hydroxy-flavone (II, R = H) with aluminium chloride in nitrobenzene solution and by Sastri and Seshadri[3] by the demethylation of 5:7:8-trimethoxy-flavone (II, R = CH_3) using benzene solution. But it is our experience that this reagent does not always give consistent yields. Consequently a method of synthesis which does not involve demethylation will be the most satisfactory.

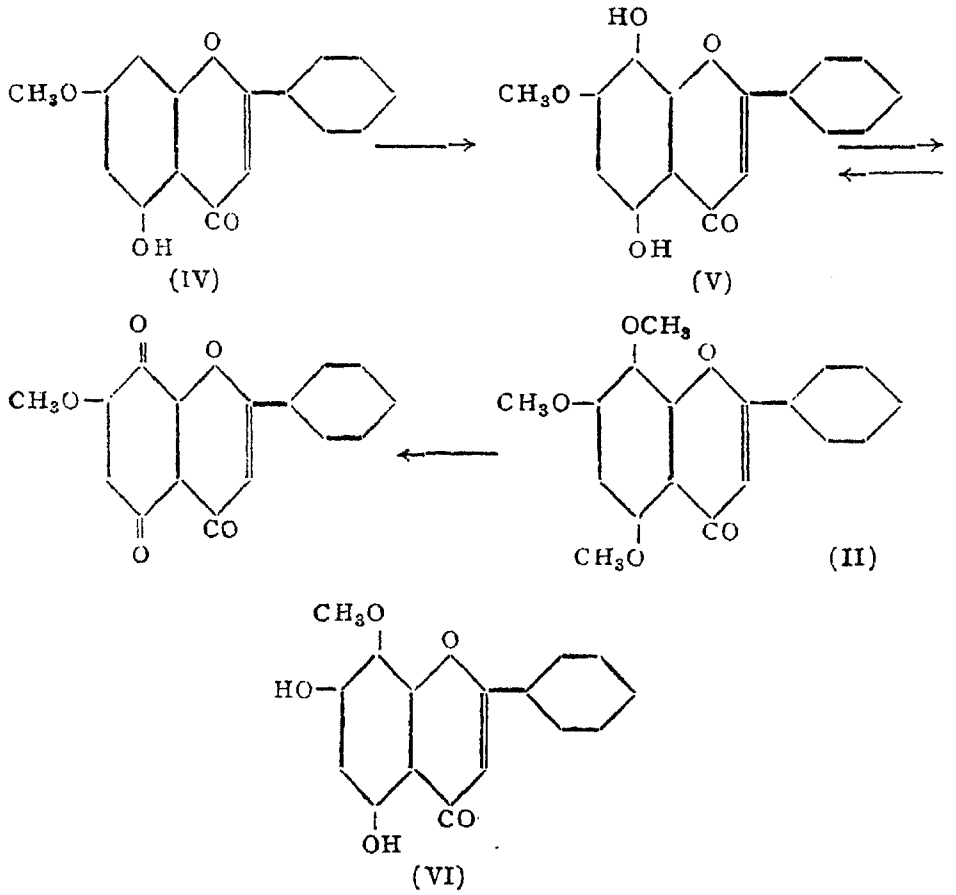
It has now been found that chrysin (III) could be oxidised smoothly by means of alkaline persulphate to norwogonin (I), the product agreeing in all respects with the synthetic sample of Sastri and Seshadri.[3] This result definitely confirms that aluminium chloride demethylation is free from the possibility of isomerisation. The properties of this compound are very different from those of hydroxy-chrysin reported by Nierenstein.[7]



(II) R = H or CH_3 (I) (III)

. The oxidation of tecto-chrysin (7-monomethyl-ether of chrysin, IV) has also been carried out with persulphate. It gives rise to the 7-methyl-ether (V) of norwogonin. This is different in its properties from wogonin and hence offers further support to the accepted constitution of wogonin as the 8-mono-methyl-ether (VI). The new compound is therefore named iso-wogonin (V).

In connection with the constitution of gossypin[4] it has recently been shown that gossypetin-hexamethyl-ether undergoes smooth conversion into gossypetone tetramethyl ether by treatment with nitric acid, and reduction of the quinone yields the 5:8-dihydroxy-compound. This process of oxidative demethylation has also been employed now for the preparation of isowogonin (V) from 5:7:8-trimethoxy-flavone[3] (II, $R = CH_3$). The samples obtained by the two methods are found to be identical.



In preparing chrysin for the above experiments the procedure of Robinson and Venkataraman[5] frequently yields a product with a low melting point and it is obviously a mixture. Ordinary crystallisation from alcohol does not effect a separation. By using a mixture of ethyl acetate and petroleum ether the less soluble fraction is found to be chrysin but the

yield is poor. The remaining portion which seems to be mainly 3-benzoyl-chrysin[6] could be converted into chrysin by boiling with 5% aqueous sodium carbonate for 2 hours. Giving this treatment to the crude mixture itself a yield of about three grams of almost pure chrysin could be obtained from 5 grams of phloroacetophenone. Partial methylation of chrysin leading to the formation of tectochrysin is readily effected by using the correct amount of dimethyl sulphate and potassium carbonate in anhydrous acetone medium.

Experimental

Oxidation of chrysin to norwogonin.—A stirred solution of chrysin (0·9 g.) in aqueous potassium hydroxide (1·2 g. in 25 c.c.) was gradually treated with potassium persulphate solution (1·2 g. in 50 c.c.) during the course of two hours. The deep brown solution was left for 24 hours and then rendered slightly acidic to Congo Red. The brown solid that separated out was filtered off and the filtrate extracted twice with ether. The aqueous layer was treated with sodium sulphite (3 g.) and concentrated hydrochloric acid (25 c.c.) and kept at 90° for 30 minutes. A yellow solid began to separate out. After cooling, it was filtered and washed well with water. On extracting the filtrate with ether some more of the substance could be obtained. Yield 0·4 g. On crystallisation from a mixture of ethyl acetate and petroleum ether the product separated out in the form of golden yellow rectangular plates and prisms melting at 258–60° alone or in admixture with an authentic sample of norwogonin.[3] It was soluble in acetone. In aqueous sodium carbonate (5%) it readily dissolved to a brown coloured solution while in aqueous sodium hydroxide it gave a deep reddish brown colour changing to pale blue. In alcoholic solution it gave with ferric chloride a pale green colour which changed to deep reddish brown.

The oxidation product (0·1 g.) was acetylated by boiling with acetic anhydride (2 c.c.) and a few drops of pyridine for 1 hour. After distilling off the reagents under reduced pressure the residual white solid was crystallised from ethyl acetate when it separated out as colourless narrow rectangular plates melting at 225–27°. Mixed melting point with the triacetate of norwogonin was not depressed.

A solution of norwogonin (0·1 g.) in dry acetone (20 c.c.) was methylated using dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (5 g.). The methyl ether crystallised from a mixture of benzene and petroleum ether in the form of colourless needles melting at 167–68°. Mixed melting point with an authentic sample of 5:7:8-trimethoxy-flavone was undepressed.

Nierenstein's description[7] of hydroxy-chrysin is as follows: m.p. of the substance, 304–5°; does not dissolve in acetone and gives a yellow colour with cold alkali; m.p. of acetate 214–17°.

Tectochrysin.—A solution of chrysin (1·3 g.) in anhydrous acetone (100 c.c.) was refluxed with dimethyl sulphate (0·55 c.c.) and anhydrous potassium carbonate (5 g.) for 6 hours. After distilling off the solvent the residue was treated with water. The undissolved solid was filtered, washed and crystallised from alcohol from which it separated out as pale brown needles melting at 165–66°. Yield 1 g.

Oxidation of tectochrysin to isowogonin.—To a stirred solution of tectochrysin (1 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (1 g. in 25 c.c.) was added a solution of potassium persulphate (1·5 g. in 50 c.c.) during the course of two hours. The deep greenish brown solution, after keeping for 24 hours, was neutralised with hydrochloric acid and the pale brown precipitate was removed by filtration. This was found to be almost pure tectochrysin and some more of it was obtained by ether extracting the filtrate twice. The clear brown filtrate was then treated with sodium sulphite (3 g.) and concentrated hydrochloric acid (25 c.c.) and heated on a boiling water-bath for 30 minutes. The yellow solid that separated out was filtered and the filtrate extracted with ether; the ether extract gave some more of the yellow substance. Total yield was 0·45 g. After crystallisation from ethyl acetate it came out as bright yellow soft needles melting at 234–35°. (Found: C, 67·4; H, 4·0; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%.)

It was sparingly soluble in alcohol, ether and benzene. In alcoholic solution, with a drop of ferric chloride it gave a green colour which rapidly turned brown particularly with excess of the reagent. In aqueous sodium hydroxide it readily dissolved to a deep reddish brown solution. When treated with *p*-benzoquinone in alcoholic solution an orange coloured flavoquinone slowly crystallised out; after recrystallisation from ethyl acetate it came out as rectangular plates and melted at 245–47°.

Isowogonin (0·1 g.) was acetylated by boiling with acetic anhydride (3 c.c.) and a few drops of pyridine for 1 hour. The acetate crystallised from ethyl acetate in the form of colourless narrow rectangular plates melting at 230–32°.

Isowogonin (0·1 g.) when methylated in dry acetone medium (20 c.c.) with dimethyl sulphate (0·5 c.c.) and potassium carbonate (5 g.) yielded the dimethyl ether which crystallised from a mixture of benzene and petroleum ether as colourless needles melting at 167–68°; the mixed melting point with 5:7:8-trimethoxy flavone was undepressed.

Oxidative demethylation of 5:7:8-*trimethoxy-flavone.*—5:7:8-Trimethoxy-flavone (0.2 g.) was treated with nitric acid (5 c.c.; d. 1·25) followed by vigorous stirring. The solid slowly went into solution giving a yellow colour and soon an orange coloured solid crystallised out. After keeping for 30 minutes, it was filtered, washed well with nitric acid (d. 1·25) followed by water. Crystallisation from acetone yielded the flavo-quinone in the form of orange coloured rectangular plates melting at 245–47°. It was very sparingly soluble in alcohol and acetone. It readily dissolved in aqueous sodium hydroxide to a bluish violet solution.

A solution of the quinone (0·1 g.) in glacial acetic acid (1 c.c.) was treated with sodium sulphite (0·5 g.). The mixture was heated for a minute and diluted with water. The bright yellow solid was filtered, washed and crystallised from ethyl acetate when it separated out as golden yellow soft needles melting at 235–36° alone or in admixture with a sample of isowogonin prepared by the direct oxidation of tectochrysin.

In some experiments the flavoquinone was accompanied by some impurity which was difficult to remove by crystallisation and the product sintered markedly below the melting point. But after reduction the sample of isowogonin could be more easily purified by crystallisation.

Summary

The nuclear oxidation of chrysin and tectochrysin has been successfully effected using potassium persulphate. The first yields norwogonin and the second the 7-methyl-ether now named isowogonin. The method of oxidative demethylation of the 5- and 8-positions has also been employed for the preparation of isowogonin from 5:7:8-trimethoxy-flavone.

References

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7. Nierenstein .. *Ber.*, 1912, **45**, 499.