

NUCLEAR OXIDATION IN THE FLAVONE SERIES

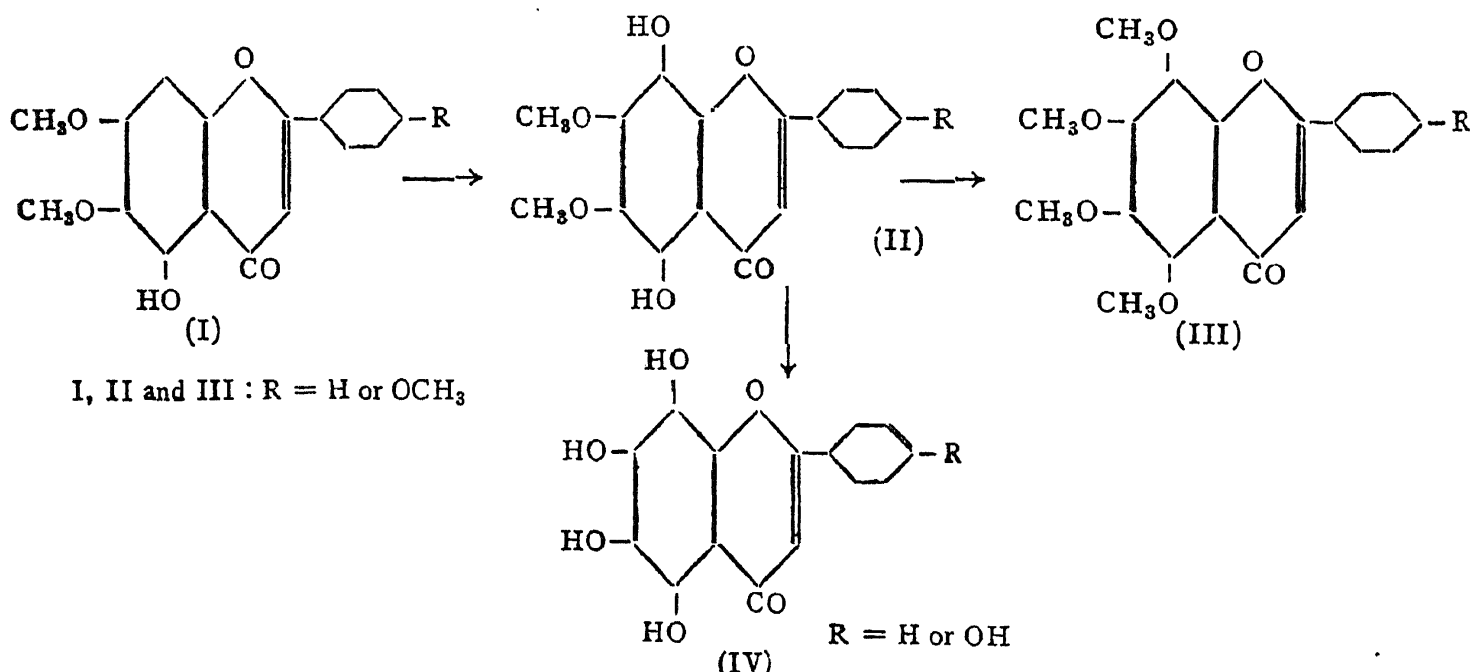
Part VII. Oxidation of Baicalein and Scutellarein

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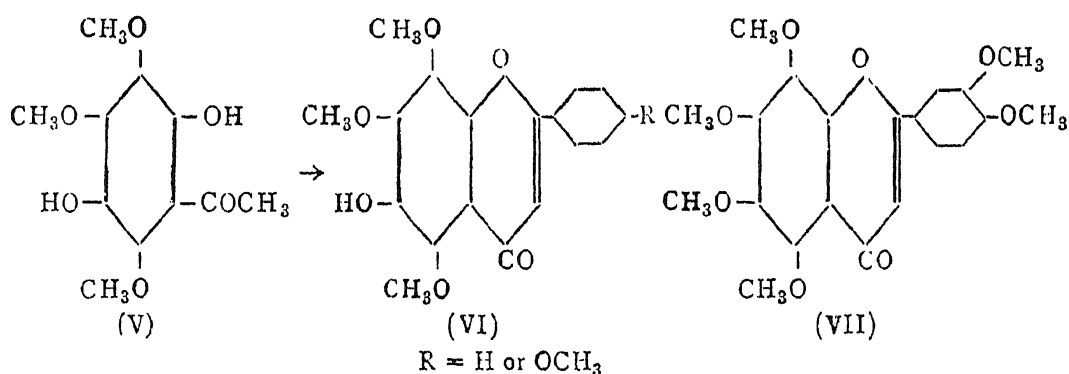
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A MARKED difference between anthoxanthins and anthocyanins is in the number of states of oxidation and of methylation in which they occur in nature. The former exhibits an enormously large range in this respect. One of the most interesting of these types is hydroxylated in all the 4 positions (5: 6: 7: 8) of the benzopyrone part. Calycopterin is a flavonol derivative and nobiletin a flavone derivative belonging to this category. In Part VI¹ of this series of papers it was pointed out that the calycopterin series is easily obtained by the nuclear oxidation of the corresponding members of the quercetagenin series of flavonols. The reaction has now been examined with regard to the analogous flavones and the nuclear oxidation of baicalein and scutellarein has been effected. The procedure adopted is the same as in similar cases. Partial methylation of baicalein and scutellarein has been carried out by means of dimethyl sulphate and potassium carbonate in dry acetone medium and the resulting 5-hydroxy-compounds (I) oxidised. The products are quinols (II) which on methylation yield the fully methylated ethers (III) and on demethylation the free hydroxy compounds (IV).



For purposes of comparison, synthesis of compounds (III) and (IV) has also been effected independently starting from the ketone² (V) and adopting the Allan-Robinson method. This direct condensation seems to be more convenient for getting these compounds than the Baker-Venkataraman procedure adopted by Horii³ for the synthesis of nobiletin (VII). The 6-hydroxy compounds (VI) first formed yield (III) when subjected to methylation and (IV) when demethylated. The samples of (III) and (IV) obtained by the two methods are found to be identical.



Dihydroxy compounds of type (II) are yellow crystalline solids giving the characteristic reactions of similarly constituted quinols. With sodium hydroxide they form brown red solutions. When a drop of ferric chloride is added to an alcoholic solution a deep greenish blue colour is obtained and this is fairly stable. On long standing or adding excess of the reagent it turns deep brownish red. The 6-hydroxy-compounds (VI) are also yellow substances dissolving in alkali to form yellow solutions. They do not give colour with ferric chloride. The fully methylated flavones (III) are colourless solids which crystallise best when free from moisture; anhydrous solvents should therefore be used for this purpose. They dissolve in strong mineral acids forming yellow solutions; no fluorescence is found in sulphuric acid solutions. They are characterised by the readiness with which they give bright red colour with magnesium and hydrochloric acid in alcoholic solution. The corresponding free polyhydroxy flavones (IV) give only orange red colours in this reaction. They are bright yellow substances which dissolve in sulphuric acid with a red colour and no fluorescence. The two described in this paper do not yield prominent colour changes in buffer solutions. The tetrahydroxy-compound prepared from baicalein resembles it in giving a stable greenish blue precipitate in alkali, whereas with the higher member the initial blue precipitate subsequently dissolves.

EXPERIMENTAL

Baicalein-dimethyl-ether (I, R = H)

This was prepared by the partial methylation of baicalein using dimethyl sulphate and anhydrous potassium carbonate in dry acetone medium. A

more convenient procedure is to use the mixture of baicalein and oroxylin—A that can be obtained from the bark of *Oroxylum indicum* as described below.

A solution of the mixture (2 g.) in anhydrous acetone (50 c.c.) was treated with dimethyl sulphate (1.2 c.c.) and anhydrous potassium carbonate (10 g.). After refluxing for 6 hours the solvent was distilled off and the residue treated with water. The yellow solid left behind was filtered, washed well with water and dried. Crystallisation from alcohol (with a few drops of glacial acetic acid) yielded pale yellow rectangular plates melting at 156–57°. Yield 1.5 g. (Bargellini⁴ gave the m.p. 155–56°). When in some experiments appreciable quantities of the trimethyl ether were also formed the mixture was dissolved in absolute alcohol, treated with just enough potash, and evaporated. The solid residue was washed well with hot benzene to remove the trimethyl ether. The remaining potassium salt was decomposed with dilute hydrochloric acid and the product crystallised.

5:8-Dihydroxy-6:7-dimethoxy-flavone (II, R = H)

A stirred solution of the above dimethyl ether (1 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (1.5 g. in 25 c.c.) was treated dropwise with a solution of potassium persulphate in water (1.5 g. in 50 c.c.) in two hours. The greenish brown solution was allowed to stand for 24 hours, just acidified with hydrochloric acid and the precipitated solid filtered off. The filtrate was extracted twice with ether to recover completely the unchanged dimethyl ether of baicalein, treated with sodium sulphite (2 g.) and concentrated hydrochloric acid (25 c.c.) and kept in a boiling water-bath for 30 minutes. The glistening yellowish brown crystalline solid that separated out was filtered after cooling, washed and purified by recrystallising from a mixture of ethyl acetate and petroleum ether when it appeared as golden yellow broad rectangular plates melting at 181–82°. (Found: C, 64.9; H, 4.2; $C_{17}H_{14}O_6$ requires C, 65.0; H, 4.5%.) Yield 0.35 g. It was sparingly soluble in alcohol and the solution gave an intense bluish green colour with a drop of ferric chloride and with a few more drops the colour changed to dark brown. In aqueous sodium hydroxide it readily dissolved to a dark red solution.

The dihydroxy compound (0.1 g.) was acetylated using acetic anhydride (3 c.c.) and a drop of pyridine. The acetate crystallised from alcohol in the form of colourless needles melting at 172–73°.

5:6:7:8-Tetramethoxy-flavone (III, R = H)

A solution of the dihydroxy compound (II) (0.2 g.) in anhydrous acetone (25 c.c.) was treated with dimethyl sulphate (0.5 c.c.) and potassium carbo-

nate (5 g.). After refluxing for 6 hours the potassium salts were filtered off and the residue washed with hot acetone. The filtrate was distilled to recover the solvent and treated with water when a colourless solid separated out. It was filtered, washed with aqueous sodium hydroxide followed by water, dried and purified by crystallisation from ligroin. It came out in the form of colourless narrow rectangular plates melting at 117–18° (Found: C, 66.9; H, 5.4; $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%). It was readily soluble in common organic solvents, insoluble in aqueous sodium hydroxide and did not give any colour with alcoholic ferric chloride. It gave a deep red colour with magnesium and hydrochloric acid in alcoholic solution. It was identical with the sample obtained by the Allan-Robinson method described later and the mixed melting point was undepressed.

5:6:7:8-Tetrahydroxy-flavone: (6:8-dihydroxy chrysin) (IV, R = H)

The above dihydroxy-compound (II, R = H) (0.3 g.) was dissolved in acetic anhydride (5 c.c.) and the solution cautiously treated with hydriodic acid (8 c.c.). The mixture was gently refluxed for 1 hour, cooled and poured into water (100 c.c.). Sufficient sodium sulphite was added to remove the iodine present. The orange yellow solid product was filtered and washed well with water. It crystallised from ethyl acetate in the form of glistening orange yellow stout rectangular prisms melting with decomposition at 275–77°. (Found: C, 62.7; H, 3.2; $C_{15}H_{10}O_6$ requires C, 62.9; H, 3.5%.) It was sparingly soluble in acetone and ethyl acetate but more easily in alcohol. In alcoholic solution it gave an intense blue colour with a drop of ferric chloride and this changed to brown red with excess of the reagent. With *p*-benzoquinone the solution in absolute alcohol became deep red and soon faded to yellow. With 5% sodium hydroxide a deep brown red solution was obtained along with a blue precipitate; on shaking with air the colour of the solution changed to greenish yellow and then pale green. In 5% sodium carbonate the solid substance turned first red and then formed a deep brown solution with a blue precipitate; the colour of the solution changed to pale green the precipitate being unchanged. In 5% sodium bicarbonate the solid slowly dissolved to a yellow solution with a blue precipitate and the colour of the solution changed to pale greenish brown. In alcoholic solution a bright orange coloured precipitate was obtained with lead acetate.

The tetrahydroxy flavone (0.1 g.) was acetylated using acetic anhydride (5 c.c.) and a drop of pyridine. The acetate crystallised out from absolute alcohol in the form of colourless rectangular plates melting at 215–17°.

Scutellarein-trimethyl-ether (I, $R = OCH_3$) was made by the partial methylation of scutellarein adopting the procedure described for baicalein-dimethyl-ether. It was dull yellow in colour and melted at 189–90°.

5:8-Dihydroxy-6:7:4'-trimethoxy-flavone (II, $R = OCH_3$)

A solution of the above trimethyl-ether of scutellarein (1 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (2 g. in 25 c.c.) was gradually treated with stirring with a solution of potassium persulphate (2 g. in 50 c.c.) during the course of two hours. The dark brown solution was kept for 24 hours and the product worked up as described already for the similar case. On crystallisation from alcohol it separated out as bright yellow short needles melting at 250–51° with decomposition (Found: C, 59.3; H, 5.0; $C_{18}H_{16}O_7$, H_2O requires C, 59.7; H, 5.0%). It gave the same reactions as the corresponding compound obtained from baicalein dimethyl ether; yield 0.3 g.

5:6:7:8:4'-Pentamethoxy-flavone (III, $R = OCH_3$)

The above dihydroxy compound (0.1 g.) was methylated in anhydrous acetone solution (20 c.c.) with dimethyl sulphate (0.5 c.c.) and anhydrous potassium carbonate (5 g.). The methyl ether crystallised out from dry ethyl acetate as colourless long rectangular prisms and rods melting at 150–51° alone or in admixture with the sample obtained by the Allan-Robinson method. (Found: C, 64.2; H, 5.5; $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%.) Its reactions were quite similar to those of the tetramethoxy-compound (III, $R = H$) described earlier.

5:6:7:8:4'-Pentahydroxy-flavone (6:8-dihydroxy-apigenin) (IV, $R = OH$)

The dihydroxy compound (II, $R = OCH_3$) (0.1 g.) was demethylated using acetic anhydride and hydriodic acid. The penta-hydroxy-flavone (6:8-dihydroxy-apigenin) crystallised from ethyl acetate in the form of yellow plates melting at 318° with decomposition. (Found: C, 59.6; H, 3.3; $C_{15}H_{10}O_7$ requires C, 59.6; H, 3.3%.) With ferric chloride in alcoholic solution an intense blue colour was obtained which rapidly changed to brown with a little excess of the reagent. With *p*-benzoquinone in alcoholic solution a deep red colour was obtained which changed to yellowish brown. In 5% sodium carbonate the flavone quickly dissolved to a brown red solution with a small amount of a blue precipitate which however dissolved slowly and the solution changed its colour to pale brownish yellow. In 5% sodium hydroxide it quickly dissolved to deep brown red solution rapidly going to pale greenish brown and finally pale yellow.

5:7:8-Trimethoxy-6-hydroxy-flavone (VI, R = H)

An intimate mixture of the ketone² (V) (1.2 g.), benzoic anhydride (9 g.) and sodium benzoate (5 g.) was heated under reduced pressure at 180–85° for 4 hours. The product was refluxed with 10% alcoholic potash (60 c.c.) for 30 minutes. The solvent was distilled off under reduced pressure, the residue dissolved in water and the clear brown solution saturated with carbon dioxide. It was then extracted with ether, the extract dried over sodium sulphate and distilled. The yellow crystalline solid left behind was crystallised from alcohol when it separated out as golden yellow rectangular plates melting at 178–79°. (Found: C, 65.8; H, 5.1; C₁₈H₁₆O₆ requires C, 65.9; H, 4.9%). Yield 0.2 g. It dissolved in sodium hydroxide to a bright yellow solution and did not give any colour with ferric chloride in alcoholic solution.

Methylation of the above flavone (0.1 g.) in anhydrous acetone (20 c.c.) with dimethyl sulphate (0.2 c.c.) and potassium carbonate (2 g.) yielded the methyl ether which crystallised from ligroin in the form of colourless narrow rectangular plates melting at 117–18°. Mixed melting point with the sample obtained by the nuclear oxidation followed by methylation of baicalein dimethyl ether was not depressed.

Demethylation of the 6-hydroxy compound (VI) in the usual manner with hydriodic acid yielded the tetrahydroxy-flavone (6:8-dihydroxy-chrysin) which crystallised from dry ethyl acetate in the form of golden yellow stout rectangular prisms melting at 275–77° with decomposition. It was identical with the sample prepared by the method of nuclear oxidation from baicalein in all its properties and reactions.

6-Hydroxy-5:7:8:4'-tetramethoxy-flavone (VI, R = OCH₃)

The ketone (1.5 g.) (V) was condensed with anisic anhydride (10 g.) and sodium anisate (3 g.) under the conditions already described. The flavone crystallised from alcohol as golden yellow triangular plates melting at 199–200°. Yield 0.3 g. (Found: C, 64.2; H, 4.8; C₁₉H₁₈O₇ requires C, 63.7; H, 5.0%). It dissolved to a yellow solution in aqueous sodium hydroxide and in alcoholic solution it did not give any colour with ferric chloride.

Methylation of the above flavone (0.3 g.) was done in dry acetone (20 c.c.) with dimethyl sulphate (0.5 c.c.) and anhydrous potassium carbonate (5 g.). When crystallised from dry ethyl acetate, the pentamethyl ether separated out in the form of colourless needles and prismatic rods melting at 150–51°. Mixed melting point with the sample prepared by the

nuclear oxidation of scutellarein was not depressed. Yield 0.2 g. (Found: C, 64.8; H, 5.6; $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%). The pentamethoxy flavone was insoluble in aqueous sodium hydroxide and did not give colour with ferric chloride. In alcoholic solution it readily gave a deep red colour with magnesium and hydrochloric acid.

Demethylation of the 6-hydroxy flavone (VI) in acetic anhydride solution with hydriodic acid yielded the pentahydroxy flavone (6:8-dihydroxy apigenin) which crystallised out from ethyl acetate in the form of bright yellow plates melting with decomposition at 318° identical with the sample prepared by the nuclear oxidation of scutellarein described before.

SUMMARY

Nuclear oxidation of baicalein and scutellarein takes place readily in the 8-position, the partial methyl ethers being employed. Further methylation yields fully methylated ethers of the nobiletin series and demethylation the corresponding nor-compounds. For purposes of comparison these substances have also been prepared from 2:5-dihydroxy-3:4:6-trimethoxy acetophenone by the Allan-Robinson method. The characteristic properties and reactions of these compounds are described.

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