NUCLEAR OXIDATION IN THE FLAVONE SERIES

Part XVIII. Oxidation of Acacetin and Related Flavones

By K. Visweswara Rao, T. R. Seshadri and N. Viswanadham

(From the Department of Chemistry, Andhra University, Waltair)

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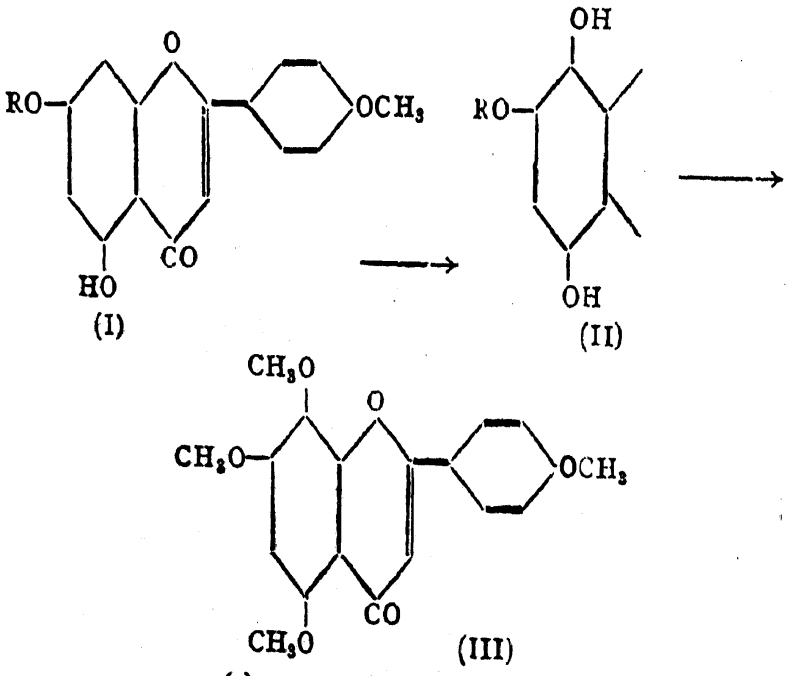
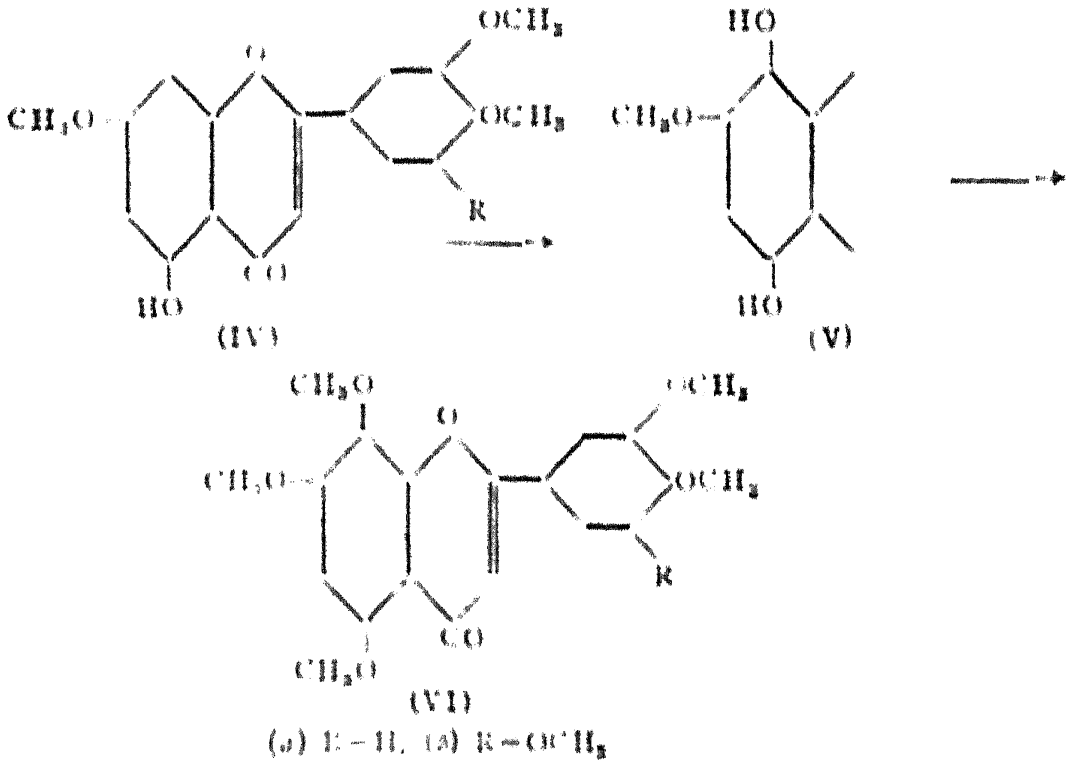
This paper is a continuation of Part II[1] wherein the oxidation of chrysin and tectochrysin to norwogonin and isowogonin was described. With the object of preparing directly 5:7:8:4′-tetrahydroxy flavone (isoscutellarein) which is the next higher member in the norwogonin series and which does not seem to have been obtained pure so far, oxidation of apigenin was carried out with alkaline persulphate. But the experiment was not successful. The yield of the product was extremely small and it could not be purified even after repeated trials. Hence the work was not pursued further with luteolin and tricetin. It is our experience that a free hydroxyl group in the 4′ and 3-positions are detrimental to smooth oxidation with persulphate.

But acacetin (I*a*) and its 7-methyl ether (I*b*) underwent oxidation very satisfactorily and the products (II) could be methylated to yield 5:7:8:4′-tetramethoxy flavone (III), isoscutellarein-tetramethyl ether which was earlier obtained by a longer route.[2] The same reactions could be repeated with luteolin (IV*a*) and tricetin (IV*b*) partial methyl ethers with the 5-hydroxyl free and thus the partially and fully methylated ethers of all the flavones



(*a*) R=H; (*b*) R=CH_3



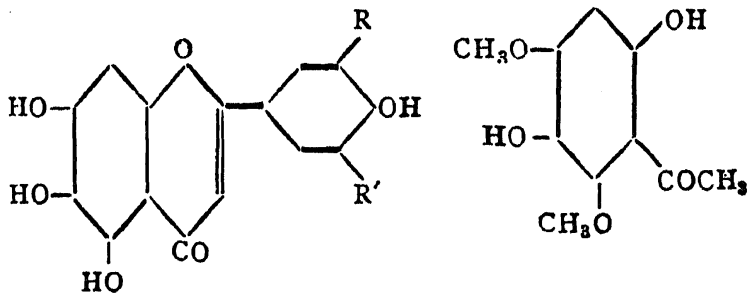
(IV) (V) (VI)

(a) R = H, (b) R = OCH_3

with the 5 : 7 : 8-arrangement of hydroxyl groups could be easily prepared. The higher members of this series were not described earlier. They could now serve as useful reference compounds in the case of new discoveries.

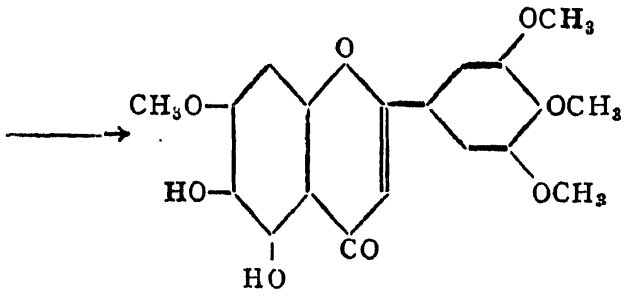
Demethylation of norwogonin methyl ethers with hydriodic acid definitely produces isomeric change into baicalein. Though the transformation may be slow and may not be considerable under mild conditions it cannot be altogether avoided (see Sastri and Seshadri[3] for discussion). Using aluminium chloride, however, for the demethylation, the successful preparation of norwogonin from its methyl ethers was reported.[3] This method has not succeeded with the higher members.

In view of the easy preparation of the partial methyl ethers (II and V) the possibility of their use in another direction suggested itself. By boiling them with hydriodic acid for over two hours the corresponding hydroxy flavones of the 5 : 6 : 7-hydroxy (baicalein) series could be obtained in satisfactory yields. This offers a simpler alternative method of preparing scutellarein[3] (VII*a*) and 6-hydroxyluteolin[4] (VII*b*) than those described before. Similarly can be obtained the highest member, 6-hydroxytricetin (VII *c*) which has not been described so far; hence its properties and those of its derivatives are given here in detail. For purposes of verification the older method of preparation has also been used. The condensation of 2 : 5-dihydroxy-4 : 6 dimethoxy acetophenone (VIII) with the anhydride and sodium salt of trimethyl gallic acid yields 5 : 6-dihydroxy-7 : 3′ : 4′ : 5′-tetramethoxy flavone (IX) owing to partial demethylation taking place during the reaction. Methylation of it produces the hexamethyl ether which is identical with the sample obtained by the newer method.



(VII)

(VIII)



(IX)

(*a*) R = R′ = H; (*b*) R = OH, R′ = H; (*c*) R = R′ = OH

Experimental

Acacetin.—The following is a modification of the original method of synthesis.[5] Phloracetophenone (5 g.) was condensed with anisic anhydride (35 g.) and sodium anisate (10 g.) under the conditions of Allan-Robinson reaction. After hydrolysis and working up, a yellowish brown solid (9 g.) was obtained which melted indefinitely between 140 and 160°. It was dissolved in 5% sodium carbonate (400 c.c.) and refluxed for 2 hours. After cooling, the solution was acidified when a yellowish brown solid was precipitated (5 g.). Crystallisation from alcohol yielded pure acacetin (3·5 g.) as pale straw yellow needles melting at 261–63°. The acid filtrate slowly deposited anisic acid.

5:7:8-*Trihydroxy-4′-methoxy-flavone* (II *a*).—A solution of acacetin (1 g.) in aqueous potassium hydroxide (1·5 g. in 30 c.c. of water) was treated dropwise while stirring with a solution of potassium persulphate (1·5 g. in 50 c.c.) in water during the course of two hours. The colour of the solution changed from yellow to dark greenish brown and finally brown red. After keeping for 24 hours it was acidified and the unchanged acacetin that separated out was filtered off and the filtrate extracted twice with ether. The clear brown aqueous solution was treated with sodium sulphite (3 g.) and concentrated hydrochloric acid (25 c.c.) and kept at 80–85° for 30 minutes with occasional stirring. The yellow solid that separated out on cooling was filtered and washed; from the filtrate some more was obtained by extraction with ether. Yield, 0·35 g. Crystallisation from a mixture of ethyl acetate and petroleum ether yielded yellow long rectangular plates

melting at 275–77°. (Found: C, 63·9; H, 3·7; $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%.) It was sparingly soluble in ethyl acetate and more soluble in alcohol. The alcoholic solution gave a greenish brown colour with a drop of ferric chloride and the colour changed to deep reddish brown with a few more drops. In 5% sodium hydroxide it readily dissolved to a deep brown red solution which quickly changed to pale blue on shaking with air.

The trihydroxy compound (0·1 g.) was methylated by boiling with dimethyl sulphate (0·3 c.c.) and potassium carbonate (3 g.) in dry acetone (20 c.c.) for 30 hours. The methyl ether crystallised from alcohol in the form of colourless needles melting at 209–10° alone or in admixture with an authentic sample of 5:7:8:4′-tetramethoxy flavone.[3] By boiling the trihydroxy compound with acetic anhydride and hydroiodic acid for over two hours complete conversion into scutellarein was effected.

7:4′-*Dimethoxy-5-hydroxy-flavone* (*I b*).—A solution of acacetin (1·5 g.) in dry acetone (50 c.c.) was treated with dimethyl sulphate (0·55 c.c.) and potassium carbonate (5 g.). After refluxing for 6 hours the solvent was distilled off and the residue treated with water; the brownish yellow solid left behind was filtered off, washed and purified by crystallisation from ethyl acetate from which it separated as pale brown rectangular plates melting at 171–72° (*cf.* Perkin[6]). Yield, 1·3 g.

5:8-*Dihydroxy*-7:4′-*dimethoxy-flavone* (*II b*).—The above dimethyl ether of apigenin (1 g.) was dissolved in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (1·5 g. in 25 c.c.). The clear bright yellow solution was treated dropwise with a solution of potassium persulphate (1·5 g. in 50 c.c.) with continuous stirring. The deep greenish brown solution after allowing to stand for 24 hours, was worked up as described in an earlier experiment. The bright yellow crystalline solid which separated out during the hydrolysis was filtered and some more obtained from the filtrate on extraction with ether. Yield 0·3 g. It crystallised from excess of ethyl acetate in the form of yellow flat needles melting at 265–67°. (Found: C, 65·0; H, 4·2; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%.) It was sparingly soluble in alcohol, ethyl acetate and acetone and moderately in glacial acetic acid. In alcoholic solution it gave with ferric chloride a green colour which rapidly changed to deep brown. In 5% aqueous sodium hydroxide it readily dissolved to a deep reddish brown solution.

The above dihydroxy flavone (0·2 g.) was methylated using dimethyl sulphate (0·2 c.c.) and potassium carbonate (2 g.). The tetramethyl ether crystallised from alcohol in the fo m of colourless needles melting at 209–10° and was identical with the sample already described.

3′: 4′-*O-Dimethyl luteolin*.—Phloracetophenone (5 g.) was intimately mixed with veratric anhydride (35 g.) and sodium veratrate (12 g.) and heated at 180–90° under reduced pressure for 5 hours. The reaction product was refluxed with 10% alcoholic potash (150 c.c.) for 30 minutes and the solvent distilled off under reduced pressure. The residue was dissolved in water (500 c.c.) and the clear solution saturated with carbon dioxide when the crude 3-veratroyl derivative separated out. Yield, 7 g. It was filtered, washed with water and refluxed with 5% sodium carbonate (300 c.c.) for 2 hours and the solution acidified. The precipitated flavone was filtered and washed twice with hot water and crystallised from alcohol. It formed pale yellow flat needles melting at 283–85°. (Found: C, 64·6; H, 4·8; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%.) Yield, 3 g. It was sparingly soluble in alcohol and the solution gave a deep violet brown colour with ferric chloride.

Luteolin-7: 3′: 4′-*trimethyl ether* (*IV a*).—A mixture of dimethyl luteolin (3 g.), dimethyl sulphate (1 c.c.), potassium carbonate (5 g.) and acetone (100 c.c.) was refluxed for 6 hours. The product was isolated by distilling off the solvent and adding water (150 c.c.). It crystallised from alcohol as pale yellow needles melting at 169–70°. Yield, 2·4 g. Purification through the potassium salt[7] did not change the melting point. Perkin and Horsfall[8] who obtained it along with a related nuclear methylated product and experienced considerable difficulty in purification, recorded its melting point as 161–63°.

5: 8-*Dihydroxy*-7: 3′: 4′-*trimethoxy flavone* (*V a*).—The above trimethyl luteolin (2 g.) was oxidised in a mixture of pyridine (30 c.c.) and potassium hydroxide (2 g. in 20 c.c.) with aqueous potassium persulphate (2·5 g. in 100 c.c.) added during the course of two hours. The product was isolated after hydrolysis with concentrated hydrochloric acid (40 c.c.) at 100° for 30 minutes. It was crystallised first from a mixture of acetone and ethyl acetate and subsequently from pyridine from which it came out in the form of yellow feathery plates melting at 254–55°. (Found: C, 62·5; H, 5·0; $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%.) Yield, 0·8 g. It was very sparingly soluble in alcohol, acetone and ethyl acetate and moderately so in pyridine. In alcoholic solution it gave a greenish brown colour with a drop of ferric chloride solution and with more turned deep brown red. In 5% alkali it dissolved to a deep brown red solution.

The diacetate prepared by boiling with acetic anhydride and pyridine crystallised from alcohol as colourless needles melting at 216–17°.

5: 7: 8: 3′: 4′-*Pentamethoxy flavone* (*VI a*).—The dihydroxy compound (0·2 g.) was methylated in acetone solution (25 c.c.) with dimethyl sulphate

(0·5 c.c.) and potassium carbonate (3 g.) by refluxing for 30 hours. The methyl ether crystallised from a mixture of benzene and ligroin in the form of colourless needles melting at 206–7°. (Found: C, 64·2; H, 5·7; $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4%.) It was insoluble in aqueous sodium hydroxide and did not give any colour with ferric chloride.

5:6:7:3′:4′-*Pentahydroxy flavone* (*VII b*).—The dihydroxy compound (0·5 g.) was demethylated in acetic anhydride solution (6 c.c.) with hydriodic acid (10 c.c.) by refluxing for 2½ hours. The pentahydroxy compound crystallised from a mixture of ethyl acetate and benzene in the form of yellow short prisms melting with decomposition at 315°, yield 0·25 g. In all its properties and reactions it agreed with 5:6:7:3′:4′-pentahydroxy flavone already described by Murti and Seshadri.[4]

The penta-acetate prepared by the reaction of acetic anhydride and pyridine crystallised from alcohol as colourless narrow rectangular plates melting at 225–26°.

5:7-*Dihydroxy*-3′:4′:5′-*trimethoxy flavone*.[9]—This compound was made by the condensation of phloracetophenone (5 g.) with O-trimethyl gallic anhydride (40 g.) and sodium O-trimethyl gallate (12 g.). In a number of experiments the product was invariably the corresponding 3-acyl derivative and it was therefore subjected to hydrolysis by refluxing with 5% sodium carbonate for 2 hours. The dihydroxy compound crystallised from alcohol in the form of pale yellow needles melting at 269–70°. Yield, 1·2 g.

Tricetin tetramethyl ether (*IV b*).—This has not been reported earlier and is now made by the partial methylation of the above 5:7-dihydroxy compound.

A mixture of 5:7-dihydroxy-3′:4′:5′-trimethoxy flavone (3·4 g.), dimethyl sulphate (1 c.c.), potassium carbonate (10 g.) and anhydrous acetone (100 c.c.) was refluxed for 6 hours. The solvent was distilled off, the residue treated with water and the solid filtered. It crystallised from alcohol in the form of colourless rectangular plates melting at 195–96°. Yield, 3·2 g. (Found: C, 63·8; H, 5·4; $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%.) In contrast with other 5-hydroxy compounds of this series, this tetramethyl tricetin is quite colourless. It gave a deep reddish brown colour with alcoholic ferric chloride and on heating with aqueous sodium hydroxide, the solid turned yellow in colour.

5:8-*Dihydroxy*-7:3′:4′:5′-*tetramethoxy flavone* (*V b*).—The above tricetin tetramethyl ether (2 g.) was oxidised in a mixture of pyridine (40 c.c.) and aqueous potash (2 g. in 40 c.c.) with a solution of potassium persulphate

2·2 g. in 100 c.c.). The product was worked up as usual by removing the unchanged compound and hydrolysing with concentrated hydrochloric acid (40 c.c.). The resulting yellow solid was crystallised from ethyl acetate. It formed bright yellow elongated rectangular prisms melting at 227–29°. (Found: C, 60·7; H, 5·0; $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%.) Yield, 0·8 g. It was sparingly soluble in alcohol and the solution gave a brown red colour with ferric chloride deepening with excess. It readily dissolved in aqueous sodium hydroxide to a deep reddish brown solution.

5:7:8:3′:4′:5′-*Hexamethoxy flavone* (*VI b*).—The above dihydroxy compound (0·2 g.) was boiled for 30 hours in acetone solution (20 c.c.) with dimethyl sulphate (0·5 c.c.) and potassium carbonate (5 g.). The methyl ether crystallised from alcohol in the form of colourless narrow rectangular plates melting at 196–98°. (Found: C, 62·7; H, 5·8; $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·5%.) It was insoluble in aqueous alkali and did not give any colour with ferric chloride.

5:6:7:3′:4′:5′-*Hexahydroxy flavone* (*VII c*).—The hydroxy compound (V *b*) described above (0·5 g.) was demethylated with acetic anhydride (6 c.c.) and hydriodic acid (10 c.c.) by refluxing for 2½ hours. The reaction mixture was cooled and poured into water containing sulphur dioxide. The yellowish solid was filtered, washed well and crystallised from a mixture of ethyl acetate and acetone. It formed yellow prisms which did not melt below 340° but darkened at about 320°. (Found: C, 56·2; H, 3·3; $C_{15}H_{10}O_8$ requires C, 56·6; H, 3·1%.) Yield, 0·25 g.

5:6:7:3′:4′:5′-*Hexamethoxy flavone*.—The hexamethoxy flavone (0·2 g.) was methylated in acetone medium (30 c.c.) with dimethyl sulphate (0·1 c.c.) and potassium carbonate (5 g.) by boiling for 30 hours. The methyl ether crystallised from benzene-ligroin mixture in the form of colourless rectangular plates melting at 151–52°. (Found: C, 63·0; H, 5·8; $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·5%.)

5:6-*Dihydroxy*-7:3′:4′:5′-*tetramethoxy flavone*.—An intimate mixture of 4:6-dimethoxy-2:5-dihydroxy-acetophenone (Sastri and Seshadri[3]) (2 g.), O-trimethyl gallic anhydride (10 g.) and sodium O-trimethyl gallate (4 g.) was heated under reduced pressure at 180–90° for 5 hours. The product was worked up as usual and the crude flavone derivative precipitated by passing carbon dioxide. It was directly hydrolysed by refluxing with 5% sodium carbonate (100 c.c.) and alcohol (20 c.c.) for 2 hours. The alkaline solution was acidified, the brown solid filtered and washed well with hot water. Crystallisation from ethyl acetate yielded pale yellow glistening rectangular prisms melting at 265–68°. (Found: C, 61·0; H, 5·2;

$C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%.) It was sparingly soluble in alcohol and the solution gave a deep green colour with ferric chloride. In 5% aqueous sodium hydroxide it formed a yellowish brown solution with a bluish green precipitate.

On boiling with excess of dimethyl sulphate and potassium carbonate in acetone medium, this dihydroxy compound yielded the methyl ether which crystallised from benzene-ligroin mixture in the form of colourless rectangular plates melting at 151–52°. The mixed melting point with the 5:6:7:3′:4′:5′-hexamethoxy flavone already described was not depressed.

Summary

Apigenin does not undergo persulphate oxidation satisfactorily. But acacetin, its monomethyl ether and analogous higher members do so. By the methylation of the products (quinols) the fully methylated ethers of iso-scutellarein, 8-hydroxyluteolin and 8-hydroxytricetin could be readily obtained. Demethylation of the quinols or their methyl ethers with aluminium chloride is not successful. Boiling with hydriodic acid produces isomeric change yielding conveniently scutellarein and the higher members. 6-Hydroxy-tricetin and its derivatives are newly described.

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