# NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

## Part XXXI. Synthesis of 3-Hydroxy Primetin and Its Nuclear Oxidation

BY T. R. SESHADRI, F.A.SC., S. VARADARAJAN AND V. VENKATESWARLU

*(From the Departments of Chemistry, Andhra and Delhi Universities)*

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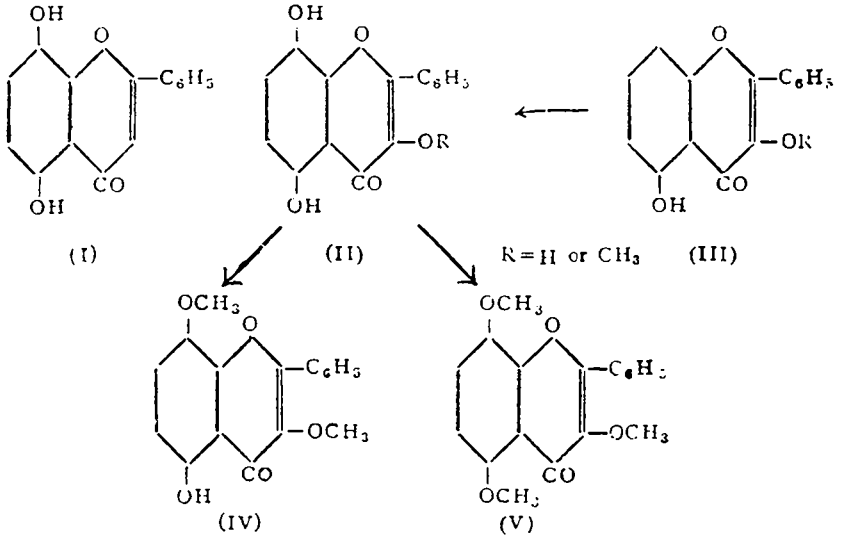
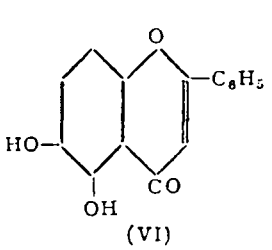
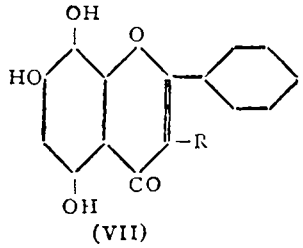
PRIMETIN (I) is one of the special compounds of the flavone group discovered in the plant genus Primula. Though the occurrence of the flavonol analogue, 3-hydroxy primetin (II, R = H) has not yet been recorded, it could also be expected to occur in nature. It has now been synthetically prepared from 3:5-dihydroxy flavone (III, R = H)[1] by a method similar to the one adopted earlier in the synthesis of primetin.[2] The first stage is partial methylation yielding 3-methoxy-5-hydroxy flavone (III, R = $CH_3$), the more resistant 5-hydroxyl being left out. Oxidation of this product with alkaline persulphate produces the quinol (II, R = $CH_3$) having all the expected properties. Partial methylation of (II, R = $CH_3$) using one mole of dimethyl sulphate yields 3:8-dimethoxy-5-hydroxy flavone (IV) and complete methylation using excess of the reagent gives rise to 3:5:8-trimethoxy flavone (V). By demethylation of the quinol (II, R = $CH_3$) with hydriodic acid, 3-hydroxy primetin (II, R = H) is obtained. These compounds are quite distinct from the isomeric 3:5:6-trihydroxy flavone and its derivatives.[3, 4]



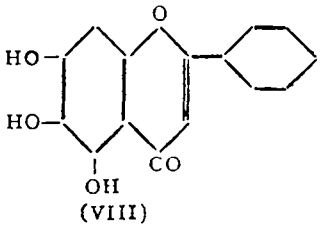
That there was no isomeric change during the above demethylation of (II, R = $CH_3$) and that the product had the expected constitution (3:5:8-trihydroxy flavone) (II, R = H) was evident from its properties. It was further confirmed by its remethylation to yield 3:8-dimethoxy-5-hydroxy flavone (IV). This is an important observation since the ethers of primetin (I) yield only 5:6-dihydroxy flavone (VI) by demethylation with hydriodic acid.[5] Earlier it was noted that derivatives of flavones with the 5:7:8-arrangement of hydroxyl groups (VII, R = H) underwent isomeric change into 5:6:7-hydroxy flavones (VIII) by this treatment (for a consolidated account, see Sastri and Seshadri[6]) but the corresponding flavonol derivatives (gossypetin group) (VII, R = OH) did not,[7] indicating thereby that the presence of a 3-hydroxyl group in the molecule prevents this rearrangement. Primetin (I) and 3-hydroxy primetin (II, R = H) are the simplest representatives of the flavone and flavonol series respectively having the minimum requirements for this study. Their behaviour confirms the importance of the 3-hydroxyl in preventing this isomeric change.



(VI)



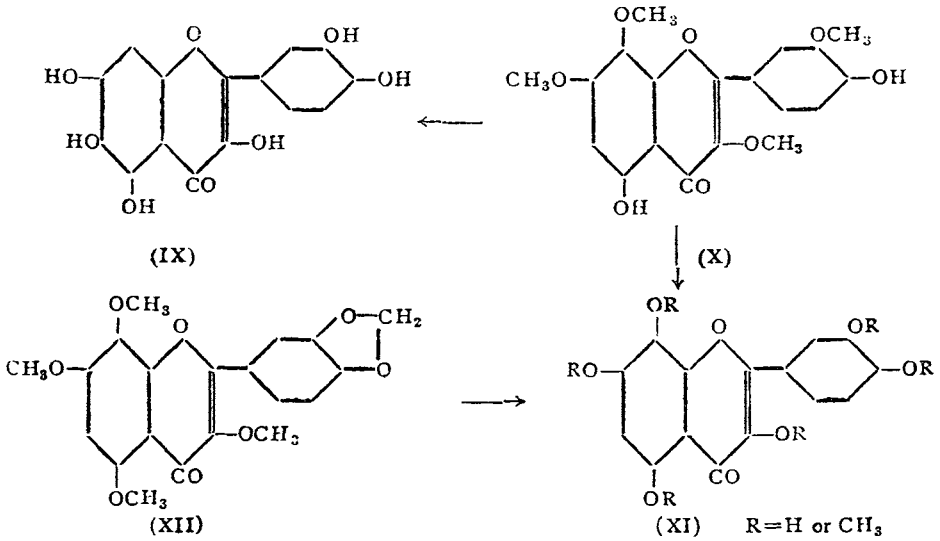
(VII)
R = H or OH



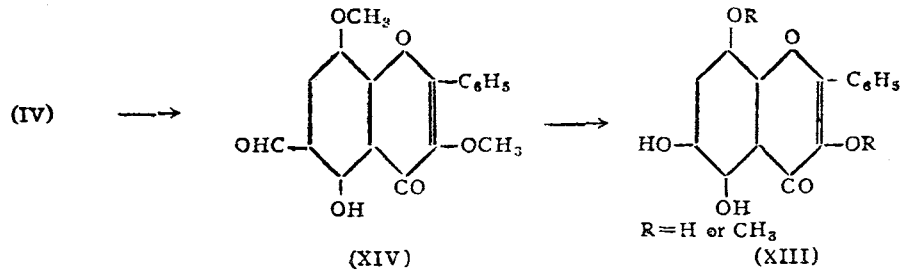
(VIII)

In view of these experimental observations and conclusions, the discussion of Briggs and Locker[8] regarding the constitution of meliternatin and ternatin seems to require careful reconsideration. They claim to have obtained quercetagetin (IX) by the dealkylation of the two compounds. On the analogy of the behaviour of the methyl ethers of the flavones, norwogonin (5:7:8-trihydroxy flavone) and isoscutellarein (5:7:8:4′-tetrahydroxy flavone), they consider that meliternatin and ternatin (X) may be gossypetin derivatives. In support of this contention, it is reported that ternatin (X) on methylation yields gossypetin hexamethyl ether (XI, R = $CH_3$). However, meliternin (XII) which is also a gossypetin derivative is found to yield only gossypetin (XI, R = H) under the same conditions of demethylation. Further work may be expected to clarify these discrepancies.

Recently the nuclear ortho-oxidation of primetin was carried out by Rajagopalan, Seshadri and Varadarajan[9] and 6-hydroxy primetin and its derivatives were obtained. A similar series of reactions starting with 3-




methoxy primetin (II, R $=CH_3$) would lead to the synthesis of 3:5:6:8-tetrahydroxy flavone (XIII, R = H) and its derivatives. The flavonol (XIII, R = H) is the lowest member of the gardenin series and was prepared earlier by Balakrishna and Seshadri[4] in two ways. The feasibility of a new method has now been explored by carrying out the essential stages, (1) partial methylation of 3-methoxy primetin to 3:8-dimethoxy-5-hydroxy flavone (IV), (2) preparation of the 6-aldehyde (XIV) and (3) oxidation with hydrogen peroxide to yield 3:8-dimethoxy-5:6-dihydroxy flavone (XIII, R $=CH_3$). The yields are satisfactory.




## Experimental

*3-Methoxy-5-hydroxy flavone (III, R $= CH_3$)*

3:5-Dihydroxy flavone (1·2 g.) was dissolved in dry acetone (150 c.c.) and dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (3 g.) were added and the mixture refluxed on a water-bath for 6 hours. The potassium salts were then filtered off and washed repeatedly with warm

acetone. The solvent was then distilled off from the filtrate and the residue crystallised twice from alcohol when it came out as pale yellow glistening rectangular plates and prisms melting at 115–16°. Yield 1 g. It gave a deep green colour with ferric chloride in alcoholic solution. It was easily soluble in alcohol and ethyl acetate and sparingly soluble in acetone (Found: C, 71·3; H, 4·8; $OCH_3$, 11·9; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5 and $OCH_3$, 11·6%).

3-*Methoxy*-5: 8-*dihydroxy flavone* (*II*, $R = CH_3$)

To a solution of 5-hydroxy-3-methoxy flavone (1 g.) in aqueous sodium hydroxide (10 c.c. of 3%) and pyridine (40 c.c.), maintained at 15–16°C., was added dropwise a solution of potassium persulphate (1·5 g. in 40 c.c.) during the course of four hours with continuous stirring. The stirring was continued for two hours more after the addition. The orange red solution along with some undissolved yellow sodium salt was left aside for 24 hours at the end of which time most of the salt had dissolved and the solution assumed a deep red colour. It was cooled in ice and acidified to congo red with concentrated hydrochloric acid. The precipitated yellow unchanged flavone (0·2 g.) was filtered off and the filtrate extracted repeatedly with ether to remove completely all the unreacted compound. To the clear deep red aqueous portion sodium sulphite (1·5 g.) and concentrated hydrochloric acid (25 c.c.) were added and the mixture kept in a boiling water-bath for half an hour. The solution was allowed to cool and the yellow crystalline solid that separated was filtered and washed with water. Ether extraction of the filtrate yielded some more of the dihydroxy compound. When crystallised twice from ethyl acetate it came out in the form of bright yellow rectangular plates melting at 210–12°. Yield 0·25 g. It was readily soluble in alcohol, acetone and ethyl acetate but sparingly in light petroleum. With ferric chloride in alcoholic solution it gave a reddish brown colour and dissolved readily in aqueous sodium hydroxide to give a deep red solution (Found: C, 67·2; H, 4·5; $OCH_3$, 11·0; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2 and $OCH_3$, 10·9%).

3: 8-*Dimethoxy-5-hydroxy flavone* (*IV*)

A solution of 3-methoxy-5: 8-dihydroxy flavone (II, $R = CH_3$) (1·2 g.) in dry acetone (150 c.c.) was refluxed for 6 hours with dimethyl sulphate (0·45 c.c.) and anhydrous potassium carbonate (2 g.). The acetone was filtered off and the potassium salts were washed several times with warm acetone. The pale red semi-solid left on distilling off acetone from the filtrate was crystallised twice from alcohol. It was obtained as pale yellow rectangular plates melting at 140–41°. It gave a green colour with alcoholic

ferric chloride (Found: C, 68·1; H, 4·7; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%).

3:5:8-*Trimethoxy flavone* (*V*)

3-Methoxy-5:8-dihydroxy flavone (II, R = $CH_3$) was methylated with excess of dimethyl sulphate and anhydrous potassium carbonate in dry acetone solution. 3:5:8-Trimethoxy flavone crystallised from dilute alcohol as colourless rectangular plates melting at 120–22° (Found: C, 69·3; H, 5·4; $OCH_3$, 30·0; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1 and $OCH_3$, 29·8%).

3:5:8-*Trihydroxy flavone* (3-*Hydroxy primetin*) (*II, R = H*)

3-Methoxy-5:8-dihydroxy flavone (0·45 g.) was dissolved in acetic anhydride (7 c.c.) and to the cooled solution was added cautiously hydriodic acid (10 c.c., d. 1·7). The mixture was heated in an oil-bath at 140° for 30 minutes, cooled and treated with a saturated solution of sodium bisulphite (60 c.c.). The yellow precipitate (0·35 g.) was filtered, washed with water and when dry, crystallised from ethyl acetate. It came out as short yellow needles melting at 196–98°. With ferric chloride in alcoholic solution, it gave a green colour which rapidly turned reddish brown and with aqueous sodium hydroxide a deep red colour. With *p*-benzo-quinone in alcoholic solution it developed a red colour, characteristic of the presence of hydroxyls in the 5:8-positions (Found: C, 66·4; H, 4·0; $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

*Methylation*

3:5:8-Trihydroxy flavone (0·3 g.) was dissolved in acetone (75 c.c.) and refluxed with dimethyl sulphate (0·2 c.c.) and anhydrous potassium carbonate (1 g.) for 6 hours and the product worked up as usual. The residue left after distillation of acetone crystallised from alcohol as pale yellow rectangular plates melting at 140–41° alone or in admixture with a sample of 5-hydroxy-3:8-dimethoxy flavone (IV) described above.

5-*Hydroxy*-3:8-*dimethoxy-flavone*-6-*aldehydé* (*XIV*)

5-Hydroxy-3:8-dimethoxy flavone (IV) (0·5 g.) and hexamine (2 g.) were heated with glacial acetic acid (15 c.c.) on a boiling water-bath for 6 hours. The solution which was orange red at the beginning turned slowly red. To the hot solution was added a boiling mixture of concentrated hydrochloric acid (10 c.c.) and water (15 c.c.). On cooling, bright yellow crystals of the aldehyde separated out. The mixture was diluted to 200 c.c. with water and left overnight. The yellow crystalline solid was filtered and washed with water. Yield 0·34 g. On crystallisation from alcohol containing a

few drops of acetic acid, it separated out as clusters of short yellow needles melting at 183–84°. It gave a green colour with alcoholic ferric chloride (Found: C, 66·1; H, 4·3; $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3%). The dinitrophenyl-hydrazone of the aldehyde, prepared in the usual manner, melted at 274–76°.

5 : 6-*Dihydroxy*-3 : 8-*dimethoxy flavone* (*XIII*, $R = CH_3$)

The above aldehyde (0·67 g.) was dissolved in pyridine (30 c.c.) and to the yellow solution was added aqueous sodium hydroxide (5·0 c.c., N/2). The colour of the solution changed to red. The solution was cooled to 0° and hydrogen peroxide (4·1 c.c. 5%) was added drop by drop with shaking in the course of ten minutes. The flask was corked and left at room temperature for two hours. The red colour changed slowly to yellow again. The solution was acidified with concentrated hydrochloric acid, the precipitated yellow solid filtered and washed with water. Yield 0·4 g. It crystallised from ethyl acetate as very fine yellow feathery needles melting at 267–68°. It was sparingly soluble in alcohol and acetone. With ferric chloride it gave a green colour and dissolved in dilute alkali to give a yellow solution (Found: C, 64·6; H, 4·5; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%).

## Summary

3-Hydroxy primetin has been synthesised starting with 3 : 5-dihydroxy flavone and using partial methylation, para nuclear oxidation and final demethylation. During the last stage no isomeric change is noticed. This is in conformity with the behaviour of similar cases of flavonol derivatives and is different from the behaviour of analogous flavone derivatives. Ortho-oxidation of 3-hydroxy primetin leading to the synthesis of the lowest member of the gardenin series is found to proceed satisfactorily.

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