

NUCLEAR OXIDATION IN THE FLAVONE SERIES

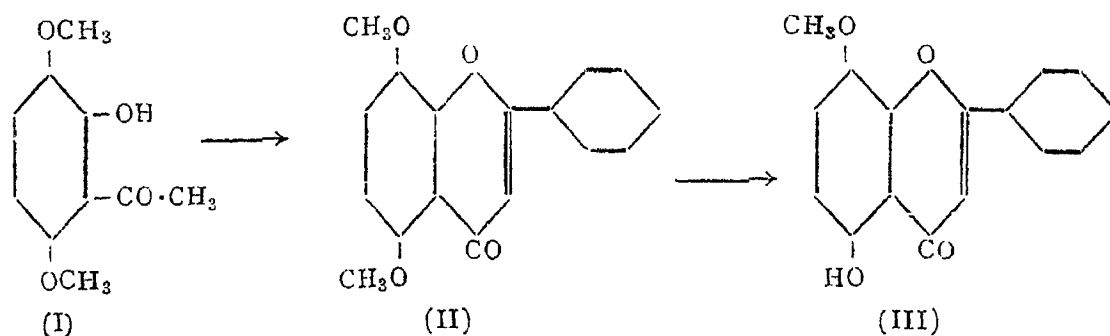
Part III. A New Synthesis of Primetin

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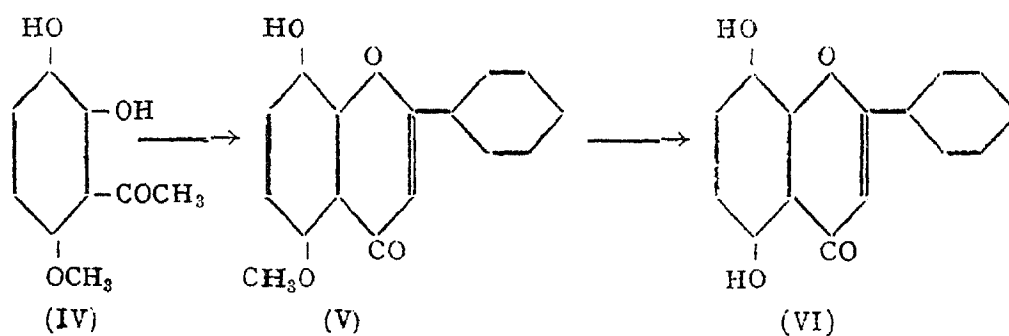
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PRIMETIN is an important member of the flavone group and is the only representative with the 5:8-arrangement of hydroxyl groups in the molecule, the hydroxyl in the 7-position being unusually absent. The dimethyl ether (II) and monomethyl ether (III) were synthesised by Baker *et al.*¹ as follows:



The dimethyl ether was the first product of flavone ring closure starting from the ketone (I). Partial demethylation with aluminium chloride in ether solution gave rise to the monomethyl ether (III). Complete demethylation using hydrobromic acid did not yield primetin since this reagent brought about rearrangement also producing 5:6-dihydroxy flavone. Other methods employed by the above workers were also unsuccessful. This difficulty was got over by Nakazawa² by employing 2:3-dihydroxy-6-methoxy acetophenone (IV) for the synthesis and finally demethylating the methoxyl in the 5-position with aluminium chloride giving rise to primetin (VI).



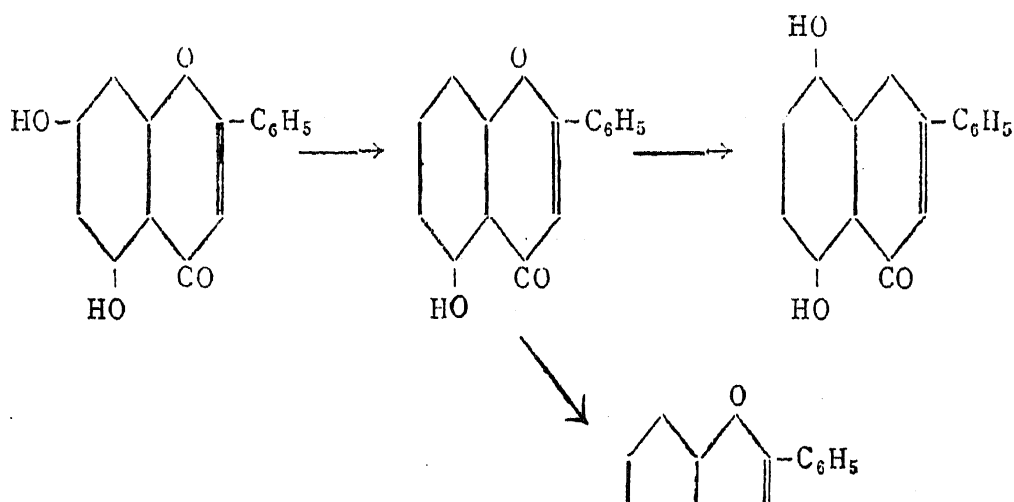
In a recent publication³ from this laboratory it was recorded that anhydrous aluminium chloride in dry benzene medium brings about smooth

demethylation of 5:7:8-trimethoxyflavone to norwogonin. This method has now been applied to primetin dimethyl ether with good success and pure samples of primetin obtained.

Plants belonging to the genus *Primula* appear to be as important in connection with the flavones as in the study of the anthocyanins. The occurrence of flavone, the fundamental compound of the group, as a characteristic dust, called 'meal' or 'farina' by gardeners, on the flower stalks, leaves and seed capsules of many species of the *Primula* was first recorded by Müller.⁴ Primetin was isolated by Nagai and Hattori⁵ from the leaves of the Japanese *P. modesta*; it was present along with flavone. More recently, from the deposit formed on the stalks and blossoms of *P. imperialis*, Karrer and Schwab⁶ isolated some 5-hydroxy flavone though flavone itself was the main component. These compounds are unique for these plants and have not been found elsewhere.

In the course of his study of the farina from twenty-one species of *Primula*, Blasdale⁶ found that all of them contained flavone as the main component. However, from *P. denticulata* he isolated in a very small yield an orange-yellow dihydroxy-flavone melting at 228° and forming an acetate with the melting point at 183–84° and from *P. verticillata* a yellow crystalline substance melting at 153° and having the molecular formula $C_{15}H_{10}O_3$. Though he did not identify them, it may here be pointed out that the properties of the dihydroxy-flavone agree with those of primetin and that the second compound resembles 5-hydroxy-flavone.

In an earlier paper by Rao and Seshadri⁷ was suggested the possibility of the formation of primetin in the plant from 5:7-dihydroxy-flavone through 5:7:8-trihydroxy flavone as an intermediate stage. The above mentioned discovery of 5-hydroxy-flavone seems to suggest the alternative course through



5-hydroxy-flavone as more probable. This is supported by the ready oxidation of 5-hydroxy-flavone directly into primetin by means of alkaline persulphate as described later in this paper and it constitutes the simplest and the most direct synthesis of this interesting flavone. The substance behaves like any other quinol and undergoes conversion into the corresponding quinone readily. Its dimethyl ether is identical with 5:8-dimethoxy-flavone prepared by the method of Baker *et al.*¹

5-Hydroxy-flavone was first prepared by Sugasawa⁸ by the fusion of γ -resacetophenone with benzoic anhydride and sodium benzoate at 180–90°. He reported that the use of a higher temperature gave a high percentage of the 3-benzoyl derivative. Later Baker⁹ reported that the yield of 5-hydroxy-flavone by the above method was unsatisfactory and sought an alternative route to the compound in the molecular rearrangement of 2:6-dibenzoyloxy acetophenone in toluene in presence of potassium carbonate. The reaction yielded directly the 3-benzoyl-5-hydroxy-flavone in poor yield and though this could be hydrolysed to 5-hydroxy-flavone conveniently by means of aluminium chloride in nitrobenzene solution the method was considered to be inferior to the first. More recently Trivedi, Sethna and Shah¹⁰ benzoylated 2-acetyl resorcinol using excess of sodium benzoate and benzoic anhydride and heating for 9 hours at 180–90°. They isolated 5-benzoyloxy-3-benzoyl flavone as the primary product and by effecting hydrolysis in stages obtained 5-hydroxy-3-benzoyl-flavone and 5-hydroxy-flavone. In our attempts to prepare this substance it was found that a good yield of 3-benzoyl-5-hydroxy-flavone could be obtained using the ordinary conditions of the Allan-Robinson reaction and this could be conveniently converted into 5-hydroxy-flavone by boiling with aqueous alcoholic sodium carbonate for 2 hours. As an independent check we have also prepared it by another method. Starting with the monomethyl-ether of γ -resacetophenone and adopting the Baker-Venkataraman procedure, 5-methoxy-flavone has been made and demethylated to yield 5-hydroxy-flavone. The samples obtained by the two methods are found to be identical.

EXPERIMENTAL

Demethylation of 5:8-dimethoxy-flavone to primetin.—

A solution of 5:8-dimethoxy-flavone¹ (0.15 g.) in dry benzene (10 c.c.) was treated with a suspension of finely powdered anhydrous aluminium chloride (0.5 g.) in benzene (10c.c.). The mixture was gently refluxed for 45 minutes on a water-bath. A dark red aluminium chloride complex separated out. The supernatant benzene solution was decanted off into

a porcelain basin and the residue in the flask washed again with a little more benzene. Crushed ice and hydrochloric acid were added to the reddish brown residue and stirred well. To complete the decomposition of the complex the mixture was heated in a boiling water-bath for 15 minutes. The yellow crystalline product was then filtered off and washed well with water. It was recrystallised from ethyl acetate from which it separated in the form of golden yellow rectangular plates melting at 230–32°. Yield 0.1 g. It was easily soluble in alcohol, acetone and ethyl acetate and sparingly in benzene and ether. In alcoholic solution it gave a green colour with a drop of ferric chloride and the colour changed to brown on the addition of more of the reagent. In aqueous sodium hydroxide it readily dissolved giving a red colour. With *p*-benzoquinone in alcoholic solution it developed a red colour. Mixed melting point with 5:8-dihydroxy-flavone obtained by the direct oxidation of 5-hydroxy-flavone was undepressed.

5-Methoxy-flavone.—

2-Hydroxy-6-methoxy acetophenone (2 g.) was dissolved in anhydrous pyridine (8 c.c.) and treated with benzoyl chloride (2.1 c.c.) and the solution heated in a boiling water-bath for one hour. It was then cooled, poured into dilute hydrochloric acid and the product extracted twice with ether. The ether extract was washed successively with hydrochloric acid, aqueous sodium carbonate, aqueous sodium hydroxide and water. When it was finally dried over calcium chloride and the solvent distilled off, the benzoate was obtained as a pale yellow viscous oil; yield 2.5 g.

A solution of the 2-benzoyloxy-6-methoxy acetophenone (2 g.) in anhydrous toluene (15 c.c.) was treated with finely powdered sodamide (6 g.) and the mixture kept at 100° for 4 hours. The solid as well as the supernatant solution assumed a deep yellow colour and in the initial stages vigorous evolution of ammonia was noticed. The contents were then filtered under suction, and washed well with dry benzene. The dry residue was then dropped into ice-water (60 c.c.) in small lots with vigorous stirring and the yellowish brown solution saturated with carbon dioxide when a yellow semi-solid mass separated. It was extracted with ether, the ether solution dried over sodium sulphate and the solvent distilled off when a bright red viscous oil was left behind. The toluene filtrate provided some more of the same substance when extracted with alkali and the alkali solution saturated with carbon dioxide followed by ether extraction. The diketone dissolved in aqueous sodium hydroxide to a yellow solution and a yellow sodium salt separated out soon. In alcoholic solution a reddish brown colour was obtained with ferric chloride.

A mixture of the above diketone (2 g.), glacial acetic acid (15 c.c.) and freshly fused sodium acetate (2 g.) was kept gently refluxing for 4 hours. It was then cooled and diluted with water (100 c.c.). The white crystalline solid that separated out was filtered off and washed with water. Crystallisation of the substance from a mixture of benzene and petroleum-ether gave colourless rectangular prisms and plates melting at 130–31° (Found: C, 75.9; H, 4.5; $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8%). Yield 1.5 g.

5-Hydroxy-flavone.—

(a) 5-Methoxy-flavone (1.5 g.) was dissolved in acetic anhydride (10 c.c.) and the solution cautiously treated with hydriodic acid (20 c.c.). After gently refluxing the resulting deep brown solution for one hour it was cooled, poured into water (100 c.c.) and treated with sufficient sodium sulphite to remove iodine. The yellow product was filtered, washed with water and crystallised from ethyl acetate when it separated out as pale yellow lustrous needles melting at 158–60°. It gave a purple colour with ferric chloride and was very sparingly soluble in aqueous sodium hydroxide. Yield 1 g.

(b) An intimate mixture of 2-acetyl resorcinol (2 g.) benzoic anhydride (10 g.) and sodium benzoate (3 g.) was heated under reduced pressure at 180–90° for 4 hours. The product when worked up as usual and crystallised from alcohol, came out as pale yellow needles melting at 177–78°. Yield 2 g.

The above 3-benzoyl derivative (1 g.) was gently refluxed with (1 : 1) aqueous alcoholic sodium carbonate (5%, 50 c.c.) for 2 hours. The alcohol was removed under reduced pressure, the alkaline solution acidified and the brown solid filtered and crystallised from alcohol-ethyl acetate mixture. It separated out as pale yellow needles melting at 158–60°. Yield 0.45 g.

5:8-Dihydroxy-flavone: Primetin.—

A stirred solution of 5-hydroxy-flavone (1 g.) in a mixture of pyridine (20 c.c.) and aqueous potassium hydroxide (1.2 g. in 20 c.c.) was slowly treated with aqueous potassium persulphate (1.7 g. in 50 c.c.) in the course of 2 hours. The greenish brown solution was allowed to stand for 24 hours and acidified when unchanged 5-hydroxy-flavone separated out; it was filtered and washed, quantity recovered being 0.3 g. The filtrate was extracted twice with ether and the clear brown aqueous layer treated with sodium sulphite (3 g.) and concentrated hydrochloric acid (25 c.c.) and kept in a boiling water-bath for 30 minutes. The yellow crystalline solid which separated out was filtered and washed with water. The filtrate on

ether extraction provided some more of the substance. Total yield was 0.45 g. When recrystallised from ethyl acetate it separated out in the form of golden yellow rectangular plates and prisms melting at 230–32° (Found: C, 70.5; H, 4.2; $C_{15}H_{10}O_4$ requires C, 70.9; H, 3.9%). In all its properties and reactions it was identical with the sample obtained by the demethylation of 5:8-dimethoxy flavone reported earlier.

The dihydroxy compound (0.3 g.) was methylated in anhydrous acetone medium (25 c.c.) with dimethyl sulphate (0.5 c.c.) and potassium carbonate (5 g.) by refluxing for 6 hours. The solvent was distilled off and the residue treated with water when a pale brown solid was left behind which was filtered and washed with water. It crystallised out from a mixture of benzene and petroleum ether in the form of colourless rectangular plates melting at 144–45°. Mixed melting point with an authentic sample of 5:8-dimethoxy flavone prepared according to the method of Baker, Brown and Scott¹ was undepressed. It was insoluble in aqueous alkali and did not give any colour with ferric chloride in alcoholic solution.

SUMMARY

The difficulty of the demethylation of synthetic primetin dimethyl ether into primetin has been solved by the use of anhydrous aluminium chloride in benzene medium. The possibility of the formation of primetin in the *Primula* through the intermediate stage of 5-hydroxy-flavone is suggested. This is supported by a new synthesis of primetin in which the nuclear oxidation of 5-hydroxy-flavone is effected by means of persulphate. 5-Hydroxy-flavone required for these experiments has been prepared by independent methods.

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