

A NEW EFFECT OF HYDROGEN BOND FORMATION (CHELATION)

Part VI. Synthesis of 5-Hydroxy-2-methoxy Flavanone and 5:7-Dihydroxy-2-methoxy Flavanone

BY N. NARASIMHACHARI, D. RAJAGOPALAN AND I. R. SESHADRI, I.A.Sc.,

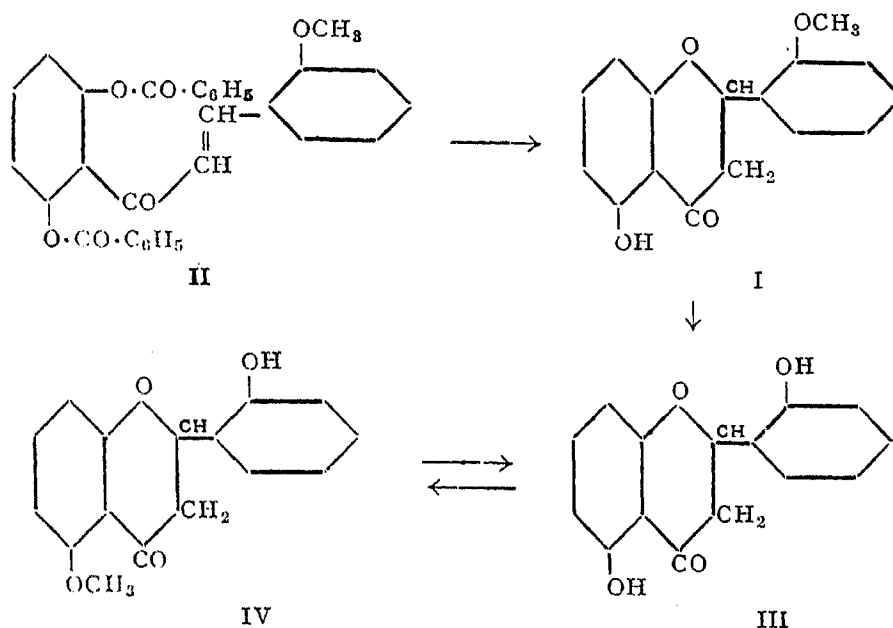
(From the Department of Chemistry, Delhi University)

Received December 6, 1952

In our earlier paper¹ in this series we recorded the extraordinary properties of 2-hydroxy flavanones. Attempts to get a 2-methoxy flavanone by initial chalcone condensation and subsequent ring closure failed in all the cases studied. The remarkable resistance to methylation of the 2-hydroxyl group makes it impossible to prepare a 2-methoxy flavanone by methylation. As citronetin² is claimed to be 5:7-dihydroxy-2-methoxy flavanone attempts have been made to work out methods for the preparation of 2-methoxy flavanones having free hydroxyl groups in the 5 and 7-position.

As the simplest example 5-hydroxy-2-methoxy flavanone (I) has been chosen and it has been prepared by the following procedure. The dibenzoate of γ -resacetophenone is condensed with *o*-methoxy benzaldehyde in dry ethyl acetate solution in presence of dry hydrogen chloride.³ The resulting dibenzoyloxy-2-methoxy chalcone (II) is hydrolysed with alcoholic potassium hydroxide. After removal of the alcohol and dilution with water a colourless product separates from the alkaline solution. The analytical values agree with the formula $C_{16}H_{14}O_4$ and its reaction and properties agree with the requirements of the structure of 5-hydroxy-2-methoxy flavanone. On demethylation with aluminum chloride in dry benzene solution it gives 5:2'-dihydroxy flavanone (III) which is identical with the compound of the same structure obtained earlier from the similar demethylation of 5-methoxy-2'-hydroxy flavanone (IV) and it forms the same 5-monomethyl ether with excess of dimethyl sulphate. This conversion of 5-hydroxy-2-methoxy flavanone (I) into the 5-methoxy-2'-hydroxy flavanone (IV) through the intermediate 5:2'-dihydroxy compound (III) provides further confirmation of the flavanone structure assigned earlier¹ to the products obtained by the direct condensation of 2-hydroxy ketone derivatives with salicylaldehyde.

It was reported earlier that for the preparation of 2-hydroxy-6:2'-dimethoxy chalcone, the most convenient method was the use of sodium

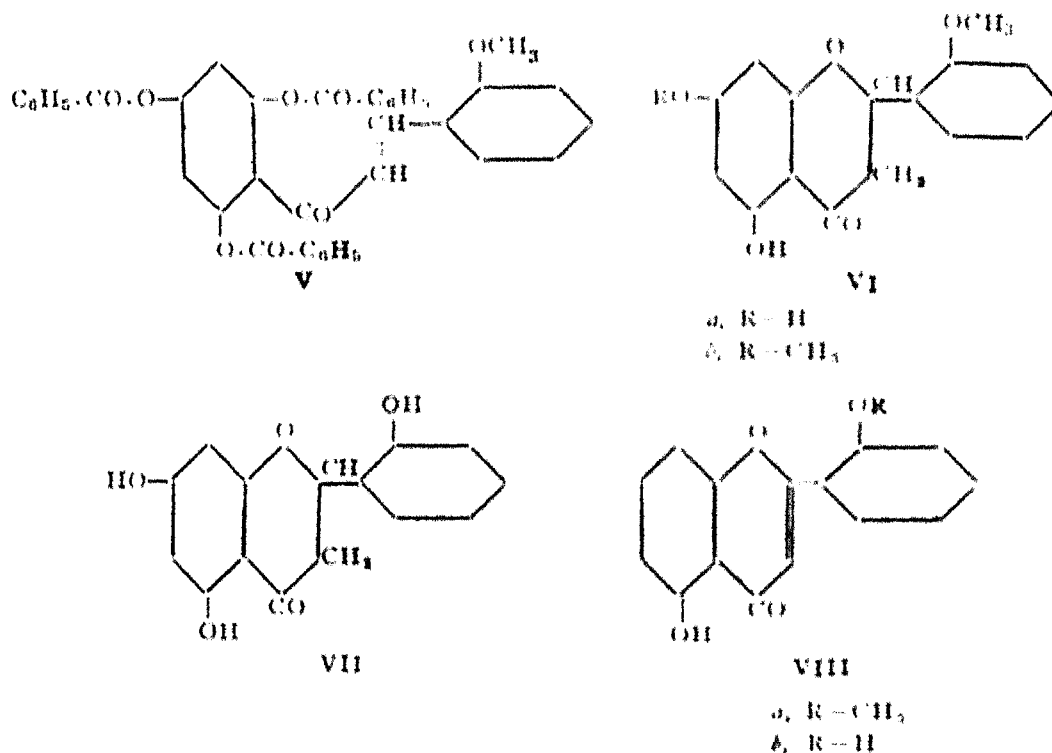


ethoxide as the condensing agent. The same chalkone has now been prepared by the acid condensation using the benzoate of γ -resacetophenone monomethyl ether and *o*-methoxy benzaldehyde followed by the alkaline hydrolysis of the 2-benzoyloxy chalkone. The conditions used for this condensation do not cause a demethylation of the 2'-methoxyl group of the chalkone.

In a previous communication¹ we pointed out the marked differences in regard to the properties of citronetin isolated from *Citrus limon ponderosa*² and the synthetic 5:7-dihydroxy-2'-methoxy flavanone. Shinoda and Sato⁴ synthesised the dihydroxy methoxy flavanone by condensing phloroglucinol with *o*-methoxy cinnamoyl chloride in the presence of anhydrous aluminium chloride. In our experience the use of hydroxy compounds in Friedel and Crafts synthesis leads to the formation of resinous by-products and it is difficult to obtain the pure compound. We have therefore examined alternative methods for the synthesis of this flavanone. The acid condensation procedure using the benzoate of the ketone given earlier in this paper gives successful results. Phloracetophenone is converted to the tribenzoate and is then condensed with *o*-methoxy benzaldehyde in dry ethyl acetate solution in the presence of dry hydrogen chloride gas.³ The tribenzoyloxy chalkone (V) on hydrolysis with alcoholic potassium hydroxide gives 5:7-dihydroxy-2'-methoxy flavanone (VI a). The yield of the flavanone is considerably lower than in the case of 5-hydroxy-2'-methoxy flavanone. The melting point of this compound agrees with that recorded by Shinoda and Sato⁴ and differs from that of citronetin.² The acetate has

now been prepared using acetic anhydride and pyridine and it has a melting point 104–5°; its composition agrees with that of a triacetate. Shinoda and Sato give the melting point of the diacetate as 119°. On partial methylation with one mole of dimethyl sulphate 7:2'-dimethoxy-5-hydroxy flavanone (VI *b*) is obtained and it agrees with the sample of Shinoda and Sato.⁴ This methyl ether undergoes demethylation with anhydrous aluminium chloride in benzene solution and gives 5:7:2'-trihydroxy flavanone (VII) which when crystallised from alcohol melts at 195.6° agreeing with the sample described by us earlier¹ and a mixture of the two samples melted at 195.6°. However on recrystallisation from benzene the melting point rises up to 217–18°. In a repetition of the demethylation of 5:7-dimethoxy-2'-hydroxy flavanone¹ the same results are observed.

The above trihydroxy flavanone was prepared by Shinoda and Sato⁴ by the direct condensation of phloroglucinol with 2-carbethoxy cinnamoyl chloride and they reported a melting point of 185.7°.



In the course of attempts to convert 2'-methoxy flavanone derivatives into the corresponding flavones authentic samples of 2'-methoxy flavones were required for purposes of comparison. Further in view of the unusual resistance of the 2'-hydroxyl group of flavanones to methylation a study of the behaviour of the 2'-hydroxyl group in the corresponding flavones was also necessary. Hence 5-hydroxy-2'-methoxy flavone (VIII *a*) has now been

prepared by the Allan Robinson condensation using γ -resacetophenone, the anhydride and sodium salt of *o*-methoxy benzoic acid. This could be demethylated by means of hydriodic acid to yield 5:2'-dihydroxy flavone (VIII *b*).

No rearrangement of the flavone ring is noticed under the usual experimental conditions. This is shown by the formation of the same dihydroxy compound when aluminium chloride which is known to cause no isomeric change in many similar cases studied earlier,⁵ is employed for the demethylation (see also Gupta and Seshadri⁵). The experimental conditions under which ring isomeric change was noticed by Philbin and Wheeler⁶ in the case of 2'-methoxy flavones are however somewhat special. Partial methylation of 5:2'-dihydroxy flavone yielded the original 5-hydroxy-2'-methoxy flavone. This not only shows that in flavones the 2'-hydroxyl group is fairly readily methylated and that the 5-hydroxyl is as usual more resistant but also emphasises again the remarkable difference between flavanones and flavones in regard to the 2'-hydroxyl group (see also Jain *et al.*⁷). Further the above experimental result confirms the observation that there is no isomeric change during the demethylation of 5-hydroxy-2'-methoxy flavone with hydriodic acid under the usual conditions. Experiments for the oxidation of 2'-hydroxy flavanone derivatives using iodine and sodium acetate⁸ have not been successful as the reaction is complicated by the occurrence of iodination. Similar difficulties are encountered in the case of the corresponding 2'-methoxy flavanones, also.

EXPERIMENTAL

5-Hydroxy-2'-methoxy flavanone (I)

γ -Resacetophenone on benzylation using benzoyl chloride (2 moles) and pyridine yielded the dibenzoate (m.p. 108-10°). The dibenzoate (5 g.) and *o*-methoxy benzaldehyde (2 g.) were dissolved in dry ethyl acetate (70 c.c.) and a current of dry hydrogen chloride passed for 3 hours. The solution became yellow, orange, orange red and finally red. It was kept in an ice-bath overnight free from moisture. Ethyl acetate was then removed under reduced pressure and the dark semi-solid mass was taken in hot alcohol (40 c.c.). The alcoholic solution was refluxed with potassium hydroxide (2 g. in 2 c.c. of water) for 30 minutes after which alcohol was removed completely under reduced pressure. On adding water a pale yellow solid separated out which was filtered, washed with water and crystallised from alcohol. It separated from alcohol in which it was sparingly soluble as colourless rectangular tablets melting at 131-2°. Acidification of the alkaline solution gave some more of the same product. Total yield 1.0 g. 5-Hydroxy-2'-methoxy flavanone gave a reddish violet colour with ferric chloride and a

bright red colour with magnesium and hydrochloric acid in alcoholic solution (Found: C, 71.3; H, 5.6; $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%).

5:2'-Dihydroxy flavanone (III)

A benzene solution of 5-hydroxy-2'-methoxy flavanone (1 g. in 20 c.c.) was heated for 2 hours with freshly powdered anhydrous aluminium chloride (4 g.). Benzene was then completely removed by distillation and the complex decomposed with ice and hydrochloric acid. The colourless solid thus obtained was filtered, washed with water and after drying crystallised from a mixture of ethyl acetate and petrol from which it separated as colourless rectangular tablets melting at 154.5°. It gave a deep reddish violet colour with ferric chloride. It was identical in its reactions with 5:2'-dihydroxy flavanone obtained by the similar demethylation of 5-methoxy-2'-hydroxy flavanone¹ and a mixed melting point of the two samples was undepressed.

5-Methoxy-2'-hydroxy flavanone (IV)

The dihydroxy flavanone (0.4 g.) obtained above was methylated by refluxing in acetone solution for 16 hours with excess of dimethyl sulphate (0.4 c.c.) and anhydrous potassium carbonate (1 g.). On working up the methylated product it separated as a sticky mass. It was directly taken up in ether, the ether solution dried over anhydrous sodium sulphate and finally the ether removed by distillation. The residue was then sublimed in vacuum in a hot water-bath when it was obtained as colourless long needles. It gave a green colour with concentrated nitric acid, a reddish violet colour with ferric chloride and melted at 55.6°. Thus it agreed in all its properties with 5-methoxy-2'-hydroxy flavanone and a mixed melting point with the sample described earlier¹ was undepressed.

2-Hydroxy-6:2'-dimethoxy chalcone

2-Benzoyloxy-6-methoxy acetophenone was prepared by the benzylation of 2-hydroxy-6-methoxy acetophenone with benzoyl chloride and pyridine. Rajagopalan *et al.*⁹ originally obtained it as a viscous oil. In the present work it was washed with petroleum ether when it solidified. It then crystallised from alcohol as colourless stout prisms melting at 63.4° (Found: C, 69.0; H, 5.2; $C_{16}H_{14}O_4, \frac{1}{2} H_2O$ requires C, 68.8; H, 5.4%). The above benzoate (2.7 g.) was condensed with benzaldehyde (1.4 g., 1 mole) in dry ethyl acetate solution at 0° by passing a current of dry hydrogen chloride gas for 4 hours and leaving the mixture at 0° for 24 hours. The product (monobenzoyloxy chalcone) was worked up as in a similar experiment described earlier. The alkaline solution on acidification gave a bright yellow solid. It was filtered, washed with aqueous sodium bicarbonate and

water. On crystallising from alcohol the product separated as bright yellow stout rhombic prisms melting at 96–7°. Yield 0.8 g. It gave a reddish brown colour with ferric chloride, no colour with magnesium and hydrochloric acid and only a red colour with nitric acid. It agreed in its reactions with 2-hydroxy-6:2'-dimethoxy chalcone¹ and the mixed melting point with that compound was undepressed.

Phloracetophenone tribenzoate

This was originally made by Canter *et al.*¹⁰ The following slightly modified procedure has now been employed. Phloracetophenone (5 g.) was dissolved in pyridine (9 c.c.), the cooled solution treated with benzoyl chloride (10 c.c.) and the mixture kept aside for 2 hours. Pieces of ice were added and the semi-solid mass that was obtained was directly taken up in ether. The ether solution was successively washed with ice-cold dilute hydrochloric acid, aqueous alkali (5%) and finally with water. It was then dried over anhydrous sodium sulphate. On distilling off ether the tribenzoate was obtained as a semi-solid mass which gave no colour with ferric chloride in alcoholic solution. It was directly used for the chalcone condensation since it was pure enough and there was considerable loss on crystallisation.

5:7-Dihydroxy-2'-methoxy flavanone (VI a)

The tribenzoate (5 g.) and *o*-methoxy benzaldehyde (1.5 g. 1 mole) were dissolved in dry ethyl acetate and a current of dry hydrogen chloride passed at 0° for 4 hours. On working up the product as already described earlier in a similar case using alcoholic potassium hydroxide (2 g. in 40 c.c.) and acidifying the alkaline solution a coloured product was obtained. It was filtered, washed with aqueous sodium bicarbonate and water and dried. The dry solid repeatedly extracted with a mixture of benzene and petroleum ether (1:2 in 100 c.c. lots) by refluxing on a hot water-bath. By extracting five or six times the pure colourless product could be completely extracted leaving behind a coloured resinous by-product. The combined benzene-petroleum ether solution was distilled to remove the solvent and it yielded an almost colourless residue. By crystallising twice from methanol 5:7-dihydroxy-2'-methoxy flavanone was obtained as colourless stellar aggregates of prisms melting at 220.2°. Further crystallisation did not improve the melting point. It gave a pink colour with magnesium and hydrochloric acid and a reddish violet colour with ferric chloride. It readily dissolved in aqueous sodium carbonate (Found: C, 66.9; H, 5.2; C₁₆H₁₄O₅ requires C, 67.1; H, 4.9%).

Triacetate

The above flavanone (0.1 g.) was refluxed with acetic anhydride (2 c.c.) and 3 drops of pyridine at 140° for 2 hours. On pouring the solution into

ice water (20 c.c.) a colourless solid separated. It was filtered, washed with water and crystallised from absolute alcohol when it came out as colourless small prismatic needles melting at 104.5° (Found: C, 64.1; H, 5.2; $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.9%).

5-Hydroxy-7:2'-dimethoxy flavanone (VIb)

(i) 5:7-Dihydroxy-2'-methoxy flavanone (0.3 g.) was boiled for 4 hours with 1 mole of dimethyl sulphate (0.1 c.c.) in acetone solution (20 c.c.) in presence of anhydrous potassium carbonate. The monomethyl ether crystallised from alcohol-benzene mixture as colourless long rectangular tablets melting at 91.2°. It gave a blue colour with concentrated nitric acid and wine red colour with ferric chloride. It was insoluble in aqueous sodium carbonate and sparingly soluble in aqueous alkali. With magnesium and hydrochloric acid it developed a pink colour. It agreed in its properties with 7:2'-dimethoxy-5-hydroxy flavanone described by Shinoda and Sato¹ who gave the melting point as 91.2° (Found: 68.0; H, 5.4; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

(ii) On methylating the dihydroxy flavanone (0.2 g.) using methyl iodide (0.5 c.c.) and potassium carbonate in acetone the same partial methyl ether was obtained (m.p. and mixed m.p. 91.92°).

5:7:2'-Trihydroxy flavanone (VII)

5-Hydroxy-7:2'-dimethoxy flavanone (0.2 g.) was refluxed in benzene solution (10 c.c.) with anhydrous aluminium chloride (0.5 g.) for 2 hours. Benzene was then distilled off and the complex decomposed with ice and concentrated hydrochloric acid (4 c.c.). On leaving overnight a colourless crystalline solid separated which was filtered, washed with water. It crystallised from alcohol as colourless thin plates melting at 195.6°. A mixed melting point with our earlier sample of 5:7:2'-trihydroxy flavanone was undepressed. This product on recrystallising from dry benzene separated as colourless thin plates melting at 217.18°. Further crystallisation did not raise the melting point. In a repetition of the demethylation of 5:7-dimethoxy-2'-hydroxy flavanone¹ with aluminium chloride in benzene solution it was found that the product when once crystallised from alcohol melted at 195.6°, but a recrystallisation from benzene raised the melting point to 217.18°. A mixture of the two samples also melted at 216.18°.

5-Hydroxy-2'-methoxy flavone (VIIIa)

An intimate mixture of γ -resacetophenone (3 g.), *o*-methoxy benzoic anhydride (20 g.) and sodium salt of *o*-methoxy benzoic acid (4 g.) was heated under reduced pressure at 175–85° for 5 hours. At the end of the reaction

the solid crust was broken up and refluxed with alcohol (40 c.c.) for 10 minutes. It was then treated with alcoholic potash (5.5 g. in 30 c.c.) and refluxed for 15 minutes more. As much alcohol as possible was removed under reduced pressure and excess of water (150 c.c.) added to the residue. A stream of carbon dioxide was passed when a brownish yellow mass separated. The precipitate was filtered and a portion crystallised from alcohol. The 3-acyl derivative of the flavone melted at 180–2°. The bulk of the precipitate was deacylated by refluxing with sodium carbonate solution (5%) for 2 hours. It was then filtered and washed with water. The alkaline filtrate was acidified and the acid recrystallised from dilute alcohol. It then melted at 100° and was identical with *o*-methoxy benzoic acid thus clearly indicating that the 3-acyl derivative was obtained in the condensation. The crude flavone on crystallisation from ethyl acetate gave pale yellow rhombohedral and rhombic prisms melting at 190–1°. It has a deep red colour with ferric chloride and was sparingly soluble in aqueous alkali. Yield 2.5 g. (Found: C, 71.9; H, 4.2; $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%).

The above flavone (0.2 g.) was refluxed with acetic anhydride (3 c.c.) and a few drops of dry pyridine for 2 hours at 140°. The product was poured into ice-water (50 c.c.) when a colourless solid separated out. On recrystallisation from absolute alcohol the acetate was obtained as stout rectangular prisms melting at 180–1° (Found: C, 69.2; H, 4.0; $C_{18}H_{14}O_5$ requires C, 69.7; H, 4.5%).

5:2'-Dimethoxy flavone

5-Hydroxy-2'-methoxy flavone (0.2 g.), dimethyl sulphate (0.15 c.c.) and potassium carbonate (1 g.) were refluxed in dry acetone (50 c.c.) for 20 hours. On crystallisation from ethyl acetate, 5:2'-dimethoxy flavone was obtained in the form of stout prisms melting at 134–5° (Found: C, 71.9; H, 4.7; $C_{17}H_{14}O_4$ requires C, 72.4; H, 5.0%).

5:2'-Dihydroxy flavone (VIII b)

(i) *Demethylation with hydriodic acid.*—5-Hydroxy-2'-methoxy flavone (0.4 g.) was dissolved in acetic anhydride (3 c.c.), hydriodic acid (10 c.c.) added and the solution refluxed at 140° for 1 hour. The mixture was cooled and poured into sulphur dioxide water when a pale yellow solid separated which was collected and washed with water. It crystallised from ethyl alcohol as pale yellow prisms melting at 175–6°. It gave a deep red colour with ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 70.8; H, 4.0; $C_{15}H_{10}O_4$ requires C, 70.9; H, 3.9%).

(ii) *Demethylation with aluminium chloride.*—5-Hydroxy-2'-methoxy flavone (0.5 g.) was dissolved in dry benzene (20 c.c.) and the solution refluxed with

anhydrous aluminium chloride (2 g.). On working up the product as in similar cases 5: 2'-dihydroxy flavone was obtained as a pale yellow solid. It crystallised from alcohol as pale yellow prisms and was identical with the dihydroxy flavone described in the above experiment (m.p. and mixed m.p. 175-6°).

Partial methylation.—The above dihydroxy flavone (0.5 g.) was refluxed in acetone solution (100 c.c.) with dimethyl sulphate (0.2 c.c. 1 mole) and anhydrous potassium carbonate (1 g.) for 12 hours. The mixture was then filtered and the potassium salts washed with hot acetone. On removing acetone from the filtrate a solid was obtained which crystallised from alcohol as pale yellow rhombohedral and rhombic prisms melting at 190-1° and was identical with 5-hydroxy-2'-methoxy flavone described earlier (mixed m.p. 190-1°). On acetylation it gave an acetate which was identical with 5-acetoxy-2'-methoxy flavone (m.p. and mixed m.p. 180-1°).

SUMMARY

For the preparation of flavanones having a 2'-methoxy group the acid method of chalcone condensation employing benzoates of hydroxy ketones is convenient. 5-Hydroxy-2'-methoxy flavanone and 5: 7-dihydroxy-2'-methoxy flavanone have thus been prepared. By demethylating the former with aluminium chloride 5: 2'-dihydroxy flavanone is obtained which undergoes only partial methylation in the 5-position even with excess of the reagent confirming that the 2'-hydroxyl is highly resistant. Synthetic 5: 7-hydroxy-2'-methoxy flavanone and its derivatives made by us and by Shinoda and Sato agree, but they do not agree in their properties with natural citronetin and its derivatives.

5-Hydroxy-2'-methoxy flavone does not undergo isomeric change under ordinary conditions of demethylation. 5: 2'-dihydroxy flavone undergoes partial methylation smoothly in the 2'-position thus showing the existence of marked difference between flavanones and flavones.

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