

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

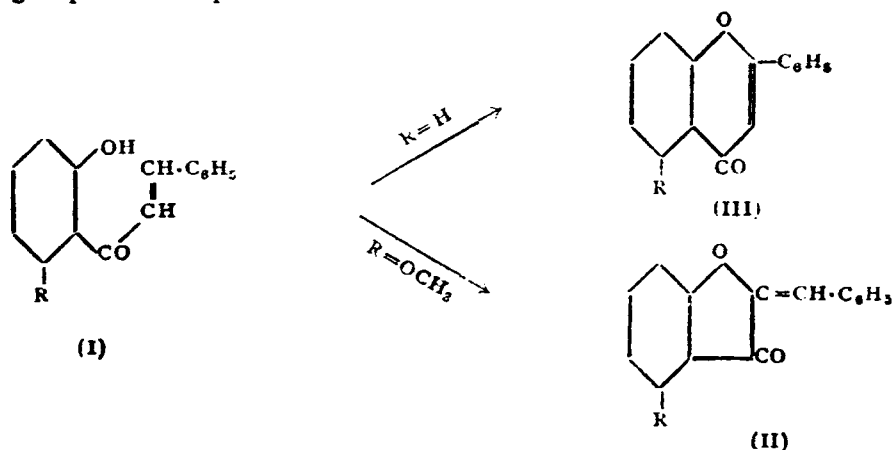
Part XX. Hydrogen Peroxide Oxidation of Some α -Methoxy Chalkones and Synthesis of Some Partial Methyl Ethers of Quercetin

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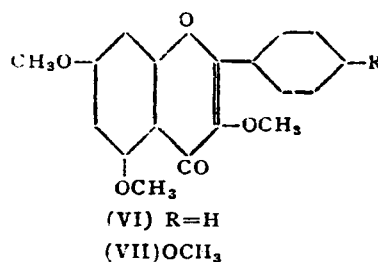
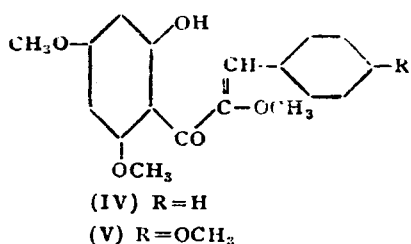
CHALKONES constitute important intermediates in the synthesis of flavanones, flavones and flavonols. The method originally adopted by Kostanecki¹ for obtaining flavonols from chalkones through the flavanones and their isonitroso derivatives has been largely replaced by the direct method employing alkaline hydrogen peroxide. This reaction discovered by Algar and Flynn² is influenced considerably by the presence of substituents particularly in the 6-position of the chalkone (I) and benzalcoumaranones (II) are formed in many cases instead of flavonols (III).^{3,4} However this difficulty has been reported⁵ to be counteracted by the presence of a hydroxyl group in the 4'-position.



The dual course of this reaction mentioned above can give rise to ambiguity in the nature of the product unless adequate precautions are taken. The formation of mixtures cannot be ruled out. It was expected that the presence of a methoxyl in the α -position of the chalkone would eliminate this difficulty and yield only flavonol derivatives even when the 6-position is substituted, since on any of the mechanisms advocated in the past,^{3,5} the

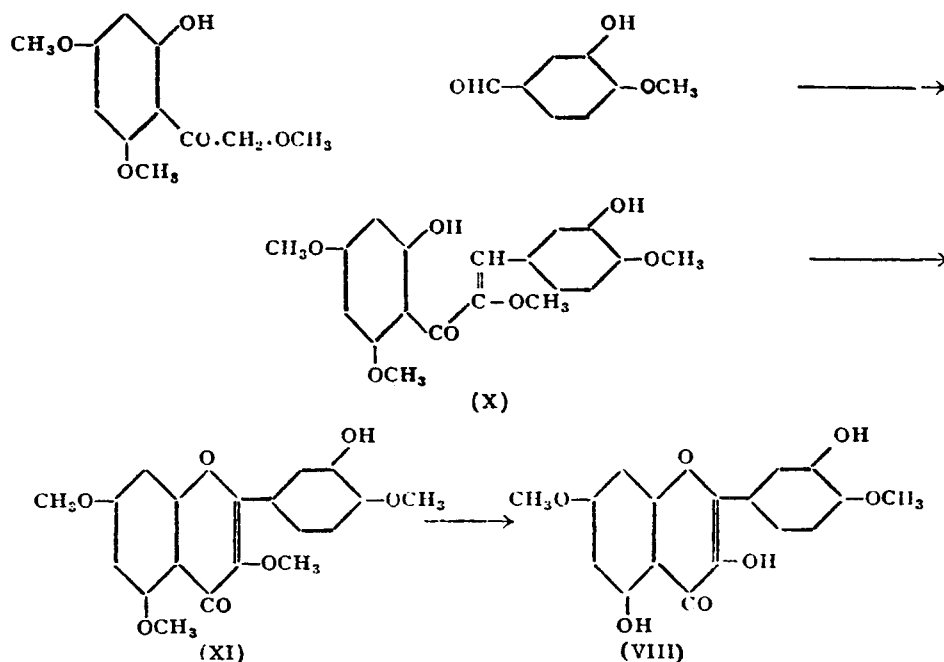
presence of a free hydrogen atom in this position is necessary for the formation of benzalcoumaranones. Such α -methoxy chalcones have now been obtained in good yields. They undergo smooth oxidation with alkaline hydrogen peroxide to yield the corresponding flavonol methyl ethers. Besides removing the ambiguity in the nature of the product this procedure provides a good preparative method.

ω -Methoxy phloracetophenone dimethyl ether is condensed with benzaldehyde and anisaldehyde to yield 2-hydroxy- α :4:6-trimethoxy and 2-hydroxy- α :4:6:4'-tetramethoxy chalcones (IV and V).⁶ On treating these chalcones with alkaline hydrogen peroxide good yields of galangin trimethyl ether (VI) and kempferol tetramethyl ether (VII) identical with authentic samples are obtained. One of the main advantages of this method is the absence of a free hydroxyl group in the 3-position of the product, thus adding greatly to its stability to further oxidation by alkaline hydrogen peroxide and producing good yields.



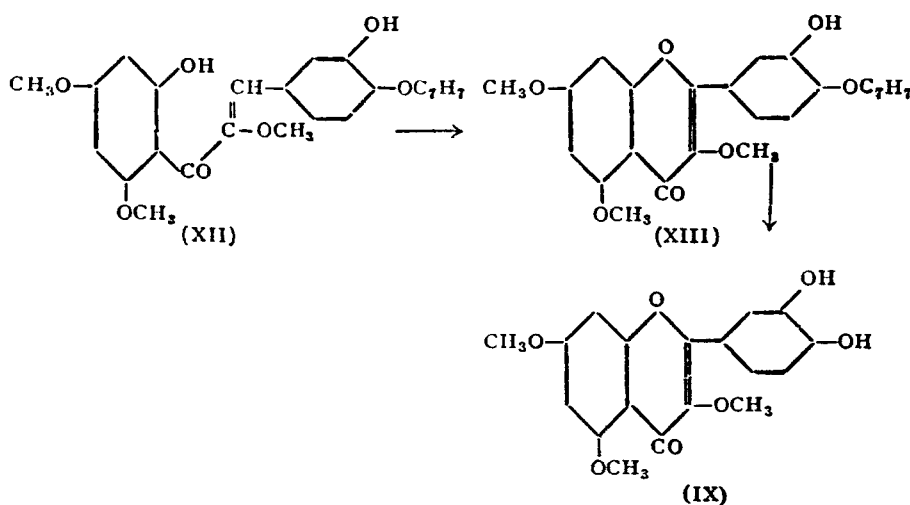
The abovementioned method could be employed in conjunction with partial demethylation for the preparation of partial methyl ethers of flavonols many of which are important naturally occurring compounds. As typical examples the syntheses of 7:4'-dimethyl ether of quercetin (now named isorhamnazin, VIII) and 3:5:7-trimethyl ether of quercetin (IX) have now been carried out. 2-Hydroxy- ω :4:6-trimethoxy acetophenone is condensed with isovanillin in the presence of alcoholic potassium hydroxide. The resulting 2:3'-dihydroxy- α :4:6:4'-tetramethoxy chalcone (X) is oxidised with alkaline hydrogen peroxide at 0°. The product obtained on acidification is almost colourless, gives no colour with ferric chloride, but produces a red colour with magnesium and hydrochloric acid thus agreeing with the requirements of a flavonol structure. It resembles in all its properties 3'-hydroxy-5:7:3:4'-tetramethoxy flavone (XI) recently reported by King, *et al.*,⁷ in the course of their work on the synthesis of ayanin. They adopted the Allan-Robinson condensation using ω -methoxy phloracetophenone and the anhydride and sodium salt of benzyl isovanillic acid, methylated the product and finally removed the benzyl group. The present

method is simpler to carry out and consists of less number of stages giving better yields.



The tetramethoxy monohydroxy flavonol (XI) yields on methylation the well-known pentamethyl quercetin. The tetramethyl ether (XI) has been subjected to partial demethylation with anhydrous aluminium chloride in nitrobenzene solution. This method is known to bring about demethylation in the 3- and 5-positions. The product is a dimethyl ether giving greenish yellow fluorescence in conc. sulphuric acid and a deep olive brown colour with ferric chloride in alcohol. Its m.p. is 201-03°. Based on these properties and on the established course of the reaction it is given the constitution of 7:4'-O-dimethyl quercetin (VIII) and the trivial name of isorhamnazin since it could also be expected to occur in nature.

ω -Methoxy phloracetophenone dimethyl ether is condensed with the 4'-benzyl ether of protocatechuic aldehyde and the resulting 2:3'-dihydroxy-4'-benzyloxy- α :4:6-trimethoxy chalcone (XII) oxidised with alkaline hydrogen peroxide. The product gives all the reactions of a flavonol derivative (XIII). When debenzylated with conc. hydrochloric acid in acetic acid solution the 3:5:7-trimethyl ether of quercetin (IX) is obtained. This partial methyl ether of quercetin has not so far been reported in the literature and should serve as a useful intermediate for the preparation of rhamnetin.



The flavonol methyl ethers could also be obtained from α -methoxy chalcones by direct dehydrogenation with selenium dioxide. In this case the course of the reaction is obvious. It should first undergo change to the corresponding 3-methoxy flavanone under the conditions of heating and then suffer dehydrogenation. A similar mechanism could be suggested for the oxidation with alkaline hydrogen peroxide also. It is not unusual for flavanones to be produced to some extent in alkaline media. Actually in many condensations using alkali the chalcones are produced along with the corresponding flavanones.⁸ The removal of the flavanone by dehydrogenation with hydrogen peroxide may be expected to accelerate the production of more flavanone from the chalcone leading to the eventual production of flavonol methyl ether in good yield.

The simplest of the *o*-hydroxy chalcones containing a substituent in the 6-position is 2-hydroxy-6-methoxy chalcone. Oliverio and Schiavello⁹ claimed to have obtained 5-methoxy flavonol by oxidising it with hydrogen peroxide. Repetition of this oxidation in this laboratory has yielded only 4-methoxy benzalcoumaranone as the sole product. In view of this and other contradictory results the Algar-Flynn reaction seems to require more detailed investigation.

EXPERIMENTAL

Oxidation of 2-hydroxy- α :4:6-trimethoxy chalcone to galangin trimethyl ether:

(i) *With hydrogen peroxide.*—2-Hydroxy- α :4:6-trimethoxy chalcone⁶ (1 g.) was dissolved in a mixture of aqueous sodium hydroxide (6.4 c.c.,

1 N.) and pyridine (5 c.c.) and the solution cooled well with crushed ice. Aqueous hydrogen peroxide (5.5 c.c., 5%) was added to it dropwise and the solution left in the refrigerator overnight. A colourless product separated and more was obtained on diluting the solution with water (60 c.c.). It was filtered and washed with water. It crystallised from alcohol as colourless needles melting at 195–97°. The mixed melting point with an authentic sample of galangin trimethyl ether¹⁰ was not depressed. Yield 0.65 g. The alkaline filtrate on acidification gave a little of the original chalkone (m.p. and mixed m.p. 118°).

(ii) *With selenium dioxide.*—The chalkone (1 g.) was mixed with dry selenium dioxide (1 g.) and the mixture heated under reflux with amyl alcohol (20 c.c.) at 140° for 12 hours. After cooling it was filtered and the black selenium on the filter washed with hot rectified spirits. Amyl alcohol was removed by distillation under reduced pressure, the last traces being removed by passing in a current of steam. The residue was twice crystallised from alcohol when it was obtained as colourless needles melting at 195–97°; a mixed melting point with the sample obtained in experiment (i) was undepressed. Yield 0.4 g.

Oxidation of 2-hydroxy- α :4:6:4'-tetramethoxy chalkone to k mpferol tetramethyl ether

(i) *With hydrogen peroxide.*—To a cooled solution of 2-hydroxy- α :4:6:4'-tetramethoxy chalkone (0.5 g.) in aqueous sodium hydroxide (0.12 g. in 3 c.c. of water) hydrogen peroxide (2 c.c. of 5%) was added slowly when a solid separated. Pyridine (2 c.c.) was added to get a clear solution which was left in the refrigerator overnight. The product, on working up as in the previous experiment, crystallised from alcohol as colourless needles melting at 165–66°. It was identical with k mpferol tetramethyl ether¹¹ (mixed m.p. 165–66°). Yield 0.3 g.

(ii) *With selenium dioxide.*—The chalkone (0.42 g.) was mixed with selenium dioxide (0.42 g.) and amyl alcohol (20 c.c.). After refluxing for 12 hours it was treated in exactly the same manner as described in the earlier case. The product on crystallising twice from alcohol melted at 165–66° and the mixed melting point with the above sample of k mpferol tetramethyl ether was undepressed. Yield 0.2 g.

2:3'-Dihydroxy- α :4:6:4'-tetramethoxy chalkone (X)

ω -Methoxy phloracetophenone dimethyl ether (1 g.) and *iso*-vanillin (0.7 g.) were dissolved in alcohol (10 c.c.) and the solution treated with a strong solution of potassium hydroxide (2.5 g. in 2.5 c.c. of water). More

alcohol (25 c.c.) was added and the solution kept for 24 hours. A bright yellow solid separated which was brought into solution by heating and the solution refluxed on a water-bath for one hour and again left at room temperature overnight. On diluting with water a white turbidity appeared which cleared on extracting with ether. The clear aqueous solution when acidified gave a sticky mass which turned a definite solid on being kept in the refrigerator. It was filtered, washed with saturated sodium bicarbonate solution and finally with water. Crystallisation once from alcohol and again from ethyl acetate yielded the chalkone as golden yellow prisms and prismatic needles melting at 193–94°. It gave a brown colour with ferric chloride in alcoholic solution. Yield 0.8 g. (Found: C, 63.0; H, 5.6; $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6%).

3:5:7:4'-Tetramethoxy-3'-hydroxy flavone (XI)

The above chalkone (1 g.) was dissolved in aqueous sodium hydroxide (4 g. in 20 c.c. of water) and the solution diluted with water (50 c.c.). It was cooled well in ice and aqueous hydrogen peroxide (5 c.c. of 16%) was added to it slowly and left in the refrigerator for 12 hours. A pale yellow solid (A) separated which was filtered and the filtrate acidified with hydrochloric acid when a crystalline solid was obtained; this was collected, washed with aqueous bicarbonate (in which it was insoluble) and water. It crystallised from alcohol as lens-shaped and rhombic plates melting at 223–24°. The original solid (A) that separated from the alkaline solution also melted at 223–24° on crystallisation and the two fractions were identical. Recrystallisation from glacial acetic acid did not alter the melting point. It gave no colour with ferric chloride and with magnesium and hydrochloric acid its alcoholic solution developed a magenta colour. It agreed closely in its properties and reactions with 3:5:7:4'-tetramethoxy-3'-hydroxy flavone described by King, *et al.*, who reported the m.p. as 220–22° (Found: C, 58.3; H, 5.5; $C_{19}H_{18}O_7 \cdot 2H_2O$ requires C, 57.9; H, 5.6%).

The acetate crystallised from alcohol as aggregates of small rectangular prisms melting at 147–48° (Found: C, 62.5; H, 5.0; $C_{21}H_{20}O_8$ requires C, 63.0; H, 5.0%).

On refluxing the above 3'-hydroxy compound with dimethyl sulphate and anhydrous potassium carbonate in acetone solution and crystallising the product from dilute alcohol quercetin pentamethyl ether was obtained; m.p. and mixed m.p. 143–44°.

7:4'-Dimethoxy-3:5:3'-trihydroxy flavone (Isorhamnazin) (VIII)

The above tetramethyl ether of quercetin (XI) (0.6 g.) was mixed with anhydrous aluminium chloride (2 g.) and dry nitrobenzene (10 c.c.) and the

mixture refluxed over a water-bath for 2 hours. After allowing it to cool, petroleum ether was added to precipitate the complex. The supernatant liquid was decanted and the residue washed with petroleum ether repeatedly to remove nitrobenzene. The aluminium chloride complex was treated with ice and hydrochloric acid (20 c.c.). The last traces of nitrobenzene were removed by passing in steam. The pale brown solid that separated was filtered and washed with water. The product was acetylated after drying by refluxing with acetic anhydride and pyridine at 140° for 2 hours. On pouring the mixture into crushed ice a pale brown solid was obtained. After a crystallisation from alcohol the product was still coloured. It was therefore taken in boiling ethyl acetate, treated with animal charcoal and filtered. The clear filtrate was treated with petroleum ether till there was turbidity which on allowing to stand cleared up depositing a sticky mass. The clear solution was decanted off, treated with more petrol and warmed to get a clear solution. On cooling it colourless stout prisms separated out; m.p. $198-200^\circ$ (Found: C, 60.4; H, 4.5; $C_{23}H_{20}O_{10}$ requires C, 60.5; H, 4.4%).

The above acetate was dissolved in boiling alcohol (2 c.c.) and refluxed for 15 minutes with conc. hydrochloric acid (2 c.c.). A pale brown powder separated on cooling which crystallised from alcohol as yellow aggregates of small prisms melting at $201-03^\circ$ (Found: in air-dried sample: C, 58.6; H, 4.6; loss on drying 2.5; $C_{17}H_{14}O_7$, H_2O requires C, 58.6; H, 4.6; loss of $\frac{1}{2} H_2O$ 2.6%. Found in a sample dried *in vacuo* at 140° for 2 hours: C, 59.8; H, 4.5; $C_{17}H_{14}O_7$, $\frac{1}{2} H_2O$ requires C, 60.1; H, 4.4%). The product gave an olive brown colour with ferric chloride in alcohol; with concentrated sulphuric acid it gave a solution exhibiting greenish yellow fluorescence and with aqueous alkali a bright yellow solution.

4-Benzyl protocatechuic aldehyde

The preparation of this is reported only in patent literature.¹² It is formed along with the 3-benzyl compound by heating protocatechuic aldehyde with benzyl chloride in alcoholic potassium hydroxide. It has now been prepared by two methods; the easier method uses benzyl chloride and anhydrous potassium carbonate in dry acetone medium.

(i) Protocatechuic aldehyde (4 g.) and benzyl chloride (3.5 c.c., 1 mole) were refluxed in acetone solution (150 c.c.) with anhydrous potassium carbonate (15 g.) for 20 hours. The potassium salts were filtered, washed with hot acetone and acetone distilled off from the filtrate. Steam was passed through the residue to remove the last traces of unreacted benzyl chloride; after cooling the mixture water was decanted off leaving a semisolid mass. On adding a little alcohol and scratching, the whole mass solidified and was

separated into alkali-soluble and alkali-insoluble fractions as follows. The product was first treated with aqueous sodium carbonate (5%) in which it was found to be completely insoluble. On treatment with sodium hydroxide most of it went into the solution leaving a little residue which was separated by filtration. Acidification of the alkaline solution gave a colourless solid which crystallised from alcohol as colourless rectangular rods melting at 121–22° (reported¹² m.p. of the 4-benzyl ether 122°); yield 3.2 g. The alkali-insoluble residue (dibenzyl ether, not reported earlier) crystallised from alcohol as stout rectangular prisms and rods melting at 93–94° (Found: C, 78.7; H, 5.7; $C_{21}H_{18}O_3$ requires C, 79.2; H, 5.7%).

(ii) Protocatechuic aldehyde (4 g.) and benzyl chloride (4.25 c.c.) were refluxed in alcoholic solution (60 c.c.) with sodium bicarbonate (10 g.) for 10 hours. The mixture was then filtered and alcohol was distilled off from the filtrate. The oily residue was well digested with sodium carbonate in which the 3-benzyl ether was soluble (solution A). The carbonate-insoluble residue was next treated with sodium hydroxide (5%) solution which dissolved the 4-benzyl ether (solution B) and the final residue (C) consisted of the dibenzyl ether.

The product obtained on acidifying the carbonate solution (A) crystallised from alcohol as colourless needles melting at 113–14° (reported m.p. for the 3-benzyl ether 113°)¹²; yield 0.5 g. The sodium hydroxide solution (B) on acidification gave the 4-benzyl ether (m.p. 121–22° from alcohol); yield 2.1 g. The dibenzyl ether (alkali-insoluble residue C) crystallised from alcohol as colourless stout rectangular prisms melting at 93–94° (identical with the sample described in experiment (i). Yield 1.8 g.

2: 3'-Dihydroxy- α : 4: 6-trimethoxy-4'-benzyloxy chalkone (XII)

ω -Methoxy phloracetophenone dimethyl ether (0.6 g.) and 4-benzyl protocatechuic aldehyde (0.6 g.) were dissolved in alcohol (20 c.c.) by warming and a solution of potassium hydroxide (1.8 g. in 2 c.c. of water) was added. The solution was refluxed for two hours when all the solid dissolved and a deep red solution was obtained. It was kept corked for 48 hours; the solution was diluted when some turbidity appeared which was cleared by ether extraction. On acidification and cooling in ice an oily product was obtained. The aqueous layer was decanted, the oily product taken in ether and washed with aqueous sodium bicarbonate solution. Attempts to crystallise the chalkone were not successful and hence it was directly used for oxidation.

3'-Hydroxy-3:5:7-trimethoxy-4'-benzyloxy flavone (XIII)

The above chalcone (1 g.) was dissolved in a mixture of sodium hydroxide (5 g. in 60 c.c. of water) and pyridine (5 c.c.). The clear solution was cooled and hydrogen peroxide (6 c.c., 16%) was added slowly. After the addition was complete the solution was left in the refrigerator for 12 hours. A pale yellow solid separated which was filtered and washed with water. It crystallised from alcohol as colourless tiny prisms melting at 201–03°. Acidification of the alkaline solution and crystallisation gave the same product (m.p. and mixed m.p. 201–03°. It gave no colour with ferric chloride but gave a red colour with magnesium and hydrochloric acid in alcoholic solution (Found: C, 68·8; H, 4·8; $C_{25}H_{22}O_7$ requires C, 69·1; H, 5·1%).

3:5:7-Trimethoxy-3':4'-dihydroxy flavone (IX)

The above 4'-benzyloxy flavonol (0·2 g.) was dissolved in minimum quantity of glacial acetic acid (4 c.c.) and the solution heated with conc. hydrochloric acid (4 c.c.) for 30 minutes on a water-bath. It was then cooled, diluted with water and the acids neutralised by adding carefully solid sodium bicarbonate. The solid which separated was crystallised from alcohol when it was obtained as tiny prisms melting at 282–84° (decomp.). It gave a green colour with ferric chloride in alcoholic solution and magenta colour with magnesium and hydrochloric acid (Found: C, 63·1; H, 5·1; $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%).

Oxidation of 2-hydroxy-6-methoxy chalcone

The chalcone (2 g.) was dissolved in a solution of sodium hydroxide (4 g. in 70 c.c. of water) and treated with aqueous hydrogen peroxide (5 c.c., 16%) under the usual conditions. A bright yellow solid slowly separated. After leaving overnight it was filtered, washed with water and crystallised from excess of alcohol. It melted at 189–90° and further crystallisations did not raise the melting point. It gave a red colour with conc. sulphuric acid, no colour with alcoholic ferric chloride and was insoluble in aqueous alkali (Found: C, 70·7; H, 5·0; $C_{16}H_{12}O_3$, H_2O requires C, 71·1; H, 5·2%). Thus it possessed the properties expected of 4-methoxy benzalcoumaranone. The alkali filtrate on acidification and extraction with ether gave no product. Yield 0·8 g.

SUMMARY

A new method of synthesis of flavonols is described. It involves the oxidation of α -methoxy chalcones with alkaline hydrogen peroxide. The special advantages are (1) it avoids the formation of benzal coumaranones and (2) it gives good yields owing to the stability to further oxidation

conferred by the 3-methoxyl group. The same products are obtained using selenium dioxide as the oxidising agent. Complete methyl ethers of galangin and kempferol have been prepared. The method is also useful for the preparation of partial methyl ethers of flavonols. 3:5:7:4'-Tetramethyl ether of quercetin and 3:5:7-trimethyl ether of quercetin are prepared. The former has been subjected to partial demethylation to yield the new 7:4'-dimethyl ether of quercetin which is now named isorhamnazin.

Under ordinary conditions 2-hydroxy-6-methoxy chalcone yields with alkaline hydrogen-peroxide only 4-methoxy benzalcoumaranone and not 5-methoxy flavonol as claimed by Oliverio and Schiavello.

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