NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXXV. Isomerisation of 5 : 7 : 8-Hydroxy Chromones into 5 : 6 : 7-Hydroxy Chromones

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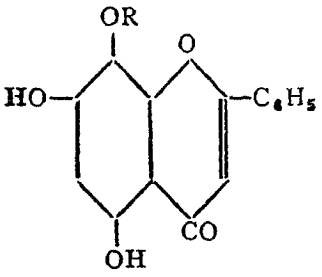
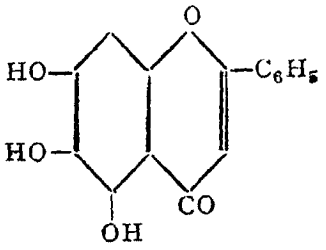
THE methods of nuclear oxidation have been successfully employed for the synthesis of flavonols, flavones and their partial methyl ethers which are otherwise more difficult to obtain (*vide* previous parts). These convenient methods have not been used for the preparations in the simpler group of chromones. Derivatives of chromones with the 5:7:8 and 5:6:7 arrangement of the hydroxyl groups were needed in connection with the study of possible isomeric changes in the chromone group and the application of the methods of nuclear oxidation for their preparation is described in this paper.

In the case of wogonin (I *b*) and primetin (II) derivatives treatment with hydriodic acid was found to bring about change into the isomeric structures with 5:6:7 (III) and 5:6 (IV) orientation of hydroxyl groups.[1] The change was not noticed in the corresponding flavonol derivatives. From the results of experiments recorded with flavone derivatives it could be concluded that the change is rather slow and requires heating for at least two hours for completion. It seems to be also clear that isomers with the 5:6:7 arrangement of hydroxyl groups (III) are more stable than those having the alternative 5:7:8 arrangement (I *a*); the former tend to be produced exclusively after treatment of the latter with hydriodic acid and the reverse change does not seem to be appreciable. Consequently this provides a convenient method of preparing the flavones with the 5:6:7 orientation.[2] Though it is obvious that in this isomerisation the pyrone ring opens out and closes again using a different hydroxyl,[3] no clear mechanism has so far been suggested and no comprehensive investigation made on the influence of the substituent groups. It is one of the objects of the present work to provide the necessary data.

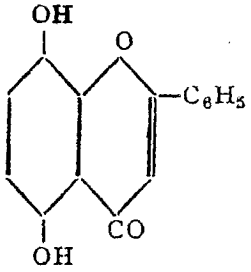


(I)



(III)

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



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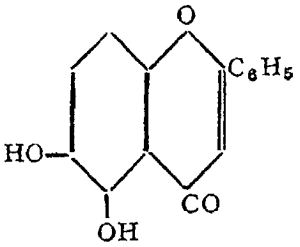
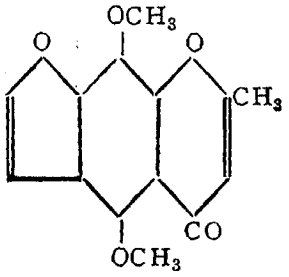
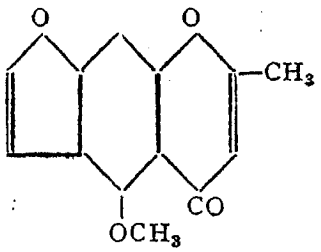


(IV)

The above-mentioned isomerisation met with in the flavone series and the influence of the substituents in the 3-position have not so far been studied in the case of the simpler chromones. Apart from the question of the extension of the field of study a new interest has arisen by the observations of Robertson and co-workers who have recorded that in the case of kellin (V) and visnagin (VI) action of hydriodic acid involves isomerisation of the furan ring and not of the pyrone ring.[4]



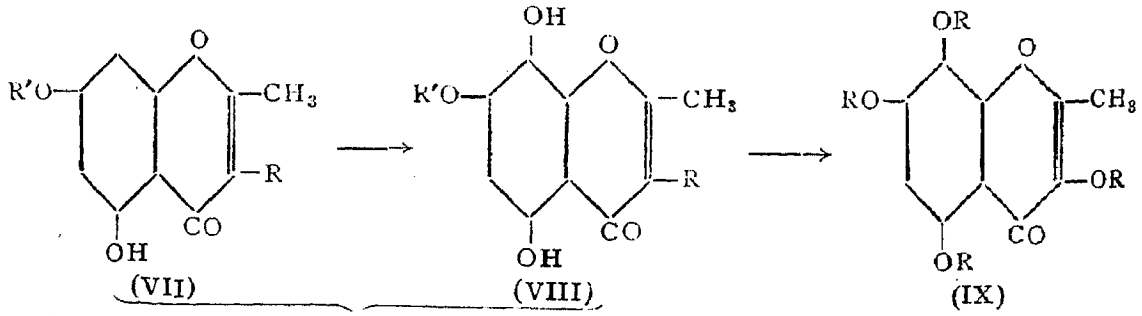
(V)



(VI)

5 : 7-Dihydroxy-3-methoxy-2-methyl chromone (VII *a*) undergoes oxidation with alkaline persulphate to give a good yield of the corresponding 5 : 7 : 8-trihydroxy compound (VIII *a*). Oxidation of the 3 : 7-dimethyl ether (VII *b*) is also found to proceed smoothly but the yield of the product is not better and hence there is no particular advantage in employing this partial methyl ether. Methylation of these compounds yields the 3 : 5 : 7 : 8-tetramethyl ether (IX *a*) and demethylation gives rise to 3 : 5 : 7 : 8-tetrahydroxy-2-methyl chromone (IX *b*). The properties of the demethylated product agree in every respect with the expectations for the 5 : 7 : 8 arrangement of hydroxyl groups. That there is no isomeric change during

this demethylation is confirmed by methylation of the tetrahydroxy compound whereby 3 : 5 : 7 : 8-tetramethyl ether identical with (IX *a*) is obtained.

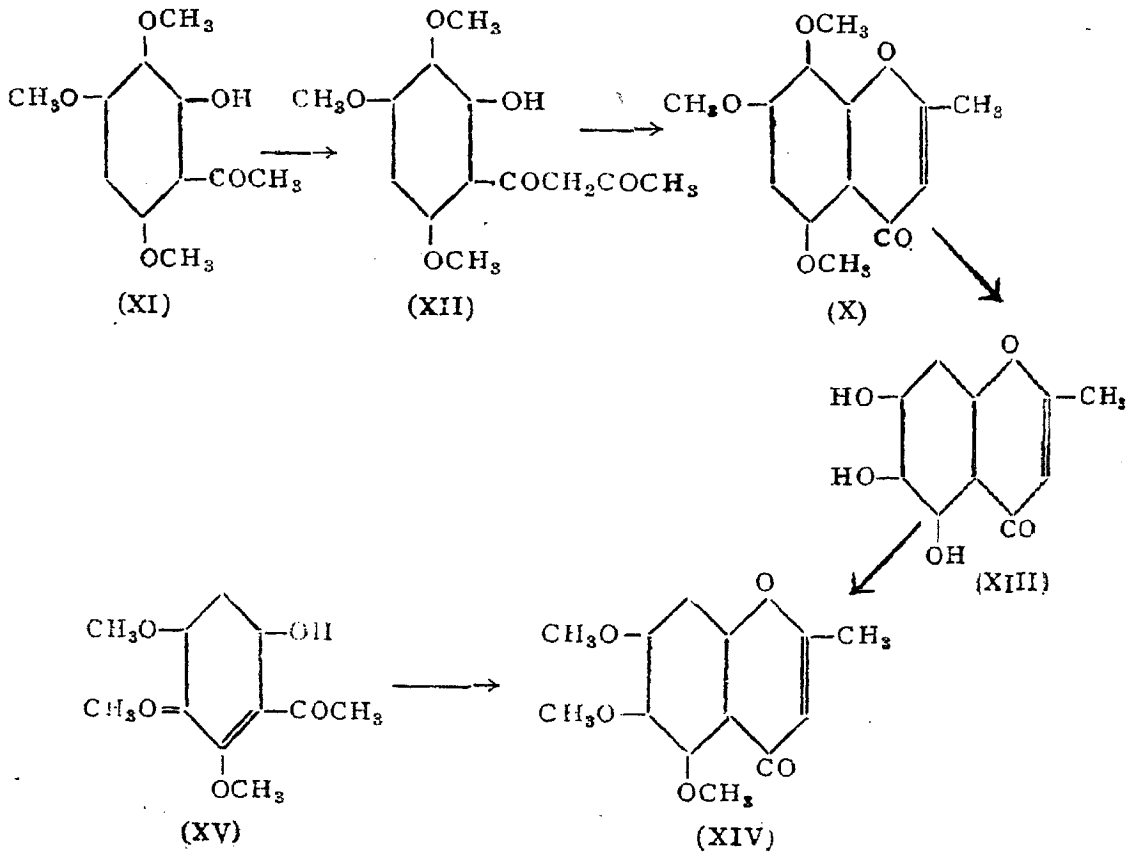


(VII) (VIII) (IX)

(*a*) R = OCH_3 ; R′ = H
(*b*) R = OCH_3 · R′ = CH_3
(*c*) R = R′ = H

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

For the preparation of 5 : 7 : 8-trihydroxy-2-methyl chromone (VIII *c*) and its methyl ether, alkaline persulphate oxidation of the corresponding 5 : 7-dihydroxy compound (VII *c*) was first used but the yield of the product was not satisfactory. 5 : 7 : 8-Trimethoxy-2-methyl chromone (X) could, however, be prepared more easily starting from 2-hydroxy-3 : 4 : 6-trimethoxy acetophenone (XI). Of the methods examined for the chromone ring closure the most convenient one involves conversion of it into the corresponding diketone (XII) by condensation with ethyl acetate in the presence

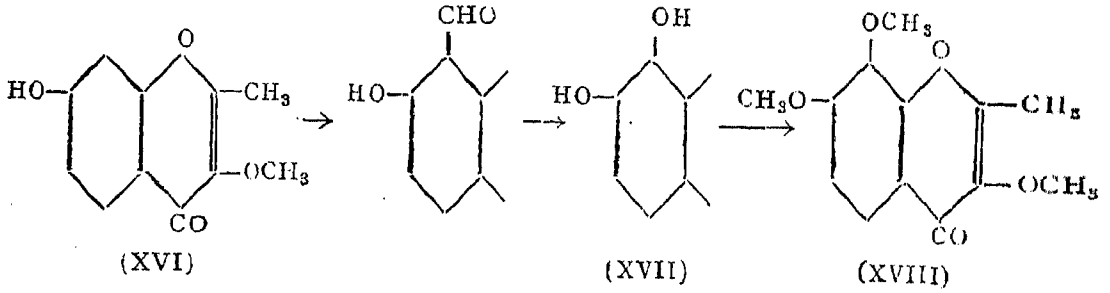


(XI) (XII) (X) (XIII) (XV) (XIV)

of sodium and subsequent closing up of the pyrone ring by means of alcoholic sulphuric acid. Demethylation of the trimethoxy chromone involves also isomeric change because the properties of the product are different from those of the 5:7:8-trihydroxy-2-methyl chromone (VIII *c*) prepared by direct nuclear oxidation but correspond with those expected for the 5:6:7 arrangement (XIII). This conclusion is also confirmed by the fact that the trimethyl ether obtained by remethylation of the demethylated product differs from 5:7:8-trimethoxy-2-methyl chromone (X). For purposes of confirmation the 5:6:7-trimethoxy-2-methyl chromone (XIV) has been synthesised by an unequivocal method starting from 2-hydroxy-4:5:6-trimethoxy acetophenone (XV)[5] and using the same method of chromone ring formation as described above.

It is thus clear that the isomeric change in the simpler chromones follows the same lines as in the case of the flavones and is obviously controlled by the same factors: chromonol derivatives (3-hydroxy) do not undergo the isomeric change whereas chromones without this substitution in the 3-position do. It may be mentioned here that for the preparation of the 5:6:7-trihydroxy-2-methyl chromone and its methyl ether the method involving isomerisation of the 5:7:8 isomer seems to be more convenient than the method of direct synthesis.

The two-stage process of nuclear oxidation[6] has now been applied to 7-hydroxy-3-methoxy-2-methyl chromone (XVI) and thereby the corresponding 7:8-dihydroxy-3-methoxy-2-methyl chromone (XVII) is obtained. Since there is no convenient method for preparing ω-methoxy gallacetophenone the above method is the only satisfactory one for the preparation of this particular chromone.



(XVI) (XVII) (XVIII)

Experimental

5:7:8-*Trihydroxy-3-methoxy-2-methyl chromone* (*VIII a*)

5:7-Dihydroxy-3-methoxy-2-methyl chromone (1 g.) was dissolved in a solution of sodium hydroxide (0·75 g.) in water (15 c.c.). The brownish-red solution was mechanically stirred while keeping the flask in a water-bath at 10–15° C. and to it was added dropwise a saturated solution of

potassium persulphate (2 g.). During this addition the colour of the solution became deeper. After the addition was complete (3 hours) the contents were stirred for two hours more and then left overnight at room temperature. The solution was then made just acidic to congo red with concentrated hydrochloric acid and the unconverted chromone extracted with ether. The aqueous layer was made strongly acidic with concentrated hydrochloric acid (15 c.c.), sodium sulphite (about 4 g.) was added and the mixture heated in a boiling water-bath for 20 minutes to hydrolyse the intermediate sulphate. On cooling the solution in ice for an hour the trihydroxy compound separated as brown shining crystals. This was filtered and the mother-liquor repeatedly extracted with ether. On evaporating ether extract an yellowish-brown solid was obtained. This was combined with the product that was filtered off and crystallised from ethyl acetate-benzene mixture when the trihydroxy chromone was obtained as yellow rectangular needles which turn brown at 195° and melt with decomposition at 242–44°. The substance is sparingly soluble in ether and benzene but highly soluble in acetone, alcohol and ethyl acetate. Yield, 0·4 g. The recovery of the original chromone was 0·12 g. (Found: C, 48·4; H, 4·8; $C_{11}H_{11}O_6$, $2H_2O$ requires C, 48·2; H, 5·1).

The compound gives a green colour with ferric chloride in alcoholic solution which changes to brown with excess. It does not dissolve in cold aqueous sodium bicarbonate solution; on warming it dissolves to a pink solution which changes to yellow on boiling. With aqueous sodium carbonate a bright yellow solution is obtained which becomes colourless on shaking with air. It dissolves in aqueous sodium hydroxide to a brownish-yellow solution which quickly fades and then turns violet. With benzoquinone in alcohol the compound develops a very pale brown colour. It does not answer Bargellini's test.

3 : 7-*Dimethoxy*-5-*hydroxy*-2-*methyl chromone* (*VII b*)

5 : 7-Dihydroxy-3-methoxy-2-methyl chromone (1 g.) was dissolved in dry acetone (35 c.c.), dimethyl sulphate (0·5 c.c.) and freshly ignited potassium carbonate (3 g.) were added and the mixture gently refluxed on a water-bath for 6 hours. The acetone solution was then filtered and the inorganic salts repeatedly washed with hot acetone. The solvent was distilled off and the residue on cooling solidified to a colourless crystalline mass. The dimethyl ether was crystallised from benzene when it was obtained as stout rhombohedral prisms melting at 121–22°. Yield, 0·8 g. (Found: C, 61·5; H, 5·0; $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1).

The compound is sparingly soluble in alcohol and the solution shows a faint green fluorescence. It gives a purple colour with alcoholic ferric chloride.

3 : 7-*Dimethoxy*-5 : 8-*dihydroxy*-2-*methyl chromone* (*VIII b*)

The above partial methyl ether (1 g.) was dissolved in redistilled pyridine (5 c.c.) and to the brown solution was added aqueous sodium hydroxide (0·75 g. in 10 c.c. of water) when the pale yellow sodium salt separated out. A little more pyridine (3 c.c.) was added when the sodium salt partly dissolved. The resulting mixture had a pale yellow colour with faint greenish fluorescence. To this suspension which was mechanically stirred and maintained at 10–15° C. by immersing the flask in an ice-water-bath, was added dropwise a saturated aqueous solution of potassium persulphate (2 g. in 35 c.c.). During the addition, which took about 5 hours, the solid gradually went into solution and the colour of the solution changed to pale brown. The stirring was continued for two hours more by which time the whole of the sodium salt dissolved, and the contents were left overnight at room temperature. Next day the solution was found to have acquired a deep brown colour; it was made just acidic to congo red with strong hydrochloric acid and the unreacted original compound (0·1 g.) recovered by ether extraction. The aqueous solution was made strongly acidic with concentrated hydrochloric acid (15 c.c.), sodium sulphite (3–4 g.) was added and the solution heated on a boiling water-bath for 20 minutes. After cooling, it was thoroughly extracted with ether, the extract concentrated and the lemon-yellow solid crystallised from benzene-acetone mixture when the quinol was obtained as stout golden yellow prisms turning brown at 190° and melting at 216–18° (decomp.). Yield, 0·4 g. (Found: C, 57·4; H, 5·2; $C_{12}H_{12}O_6$ requires C, 57·2; H, 4·8).

The compound gives a deep green colour with alcoholic ferric chloride which deepens with excess and changes overnight to deep brown. It dissolves immediately in aqueous sodium hydroxide to a deep yellow solution which on shaking with air turns rose-red, then purple and soon assumes a violet tinge; the colour slowly fades off. *p*-Benzoquinone produces a pale brown colour with an alcoholic solution of the substance.

3 : 5 : 7 : 8-*Tetramethoxy*-2-*methyl chromone* (*IX a*)

5 : 7 : 8-Trihydroxy-3-methoxy-2-methyl chromone (0·23 g.) was dissolved in dry acetone (25 c.c.), redistilled dimethyl sulphate (0·3 c.c.) and freshly ignited potassium carbonate (3 g.) were added and the mixture gently refluxed for 30 hours. The product was worked up as usual and the com-

pound crystallised from water containing a few drops of alcohol when it was obtained as colourless fine needles melting at 158–9° (Found: C, 53·7; H, 6·1; $C_{14}H_{16}O_6, 2H_2O$ requires C, 53·2; H, 6·3).

Demethylation of 5 : 7 : 8-*trihydroxy-3-methoxy-2-methyl chromone to* (*IX b*)

The trihydroxy chromone (1·3 g.) was dissolved in acetic anhydride (2. c.c.) by warming and to the solution was added hydriodic acid (15 c.c., d. 1·7) carefully in small quantities with cooling. The clear dark red solution was refluxed for 2 hours in an oil-bath at 140–50°. The mixture was diluted with a large quantity of a saturated solution of sodium bisulphite and left overnight. As only a small quantity of an yellow solid separated, the mixture was diluted with more water and thoroughly extracted with ether. On distilling off the solvent and removing acetic acid under reduced pressure a brownish-yellow solid was left behind. It crystallised from acetone-benzene mixture as yellow small prisms turning brown at 250° and decomposing at 270–73°. Yield, 0·63 g. (Found: C, 53·0; H, 4·0; $C_{10}H_8O_6$ requires C, 53·6; H, 3·6).

With alcoholic ferric chloride the compound gives a transient green colour which changes to brown. The colour deepens on addition of excess of the reagent. The substance slowly dissolves in sodium bicarbonate solution with a pink colour which on shaking turns rose-red, purple, violet and deep rose-red in quick succession. The colour gradually fades in two hours and completely disappears in 24 hours. In aqueous sodium carbonate and hydroxide purple solutions are obtained which quickly turn violet on shaking with air; the colour fades off overnight. *p*-Benzoquinone produces a brownish colour with an alcoholic solution of the compound; the solution slowly turns yellow which fades away. With sodium amalgam in absolute alcohol an immediate purple colour is produced which gradually changes to violet. In 2 hours the solution becomes colourless and a small quantity of a purple precipitate settles down.

Remethylation to (*IX a*)

The tetrahydroxy chromone (0·45 g.) was methylated in dry acetone solution with redistilled dimethyl sulphate (0·82 c.c.) in the presence of anhydrous potassium carbonate (5 g.) by refluxing for 32 hours. The tetramethyl ether was isolated as usual and crystallised from ethyl acetate-petroleum ether mixture. It was obtained as colourless fine needles melting at 157–8°. The mixed melting point with 3 : 5 : 7 : 8-tetramethoxy-2-methyl chromone (IX *a*) prepared by direct methylation of (VIII *a*) was undepressed proving their identity.

7 : 8-*Dihydroxy-3-methoxy-2-methyl chromone* (*XVII*)

7-Hydroxy-3-methoxy-2-methyl chromone-8-aldehyde[7] (0·6 g.) was dissolved in aqueous sodium hydroxide (0·12 g. in 15 c.c. of water). To the bright yellow solution which was cooled in ice-water was added a solution of hydrogen peroxide (4·5 c.c. of 6% hydrogen peroxide diluted with 10 c.c. of water) in small quantities with frequent shaking. The mixture was left for 6 hours at room temperature, acidified with dilute hydrochloric acid and extracted with a large quantity of ether. On distilling off the solvent colourless glistening crystals separated. The dihydroxy compound crystallised from water as colourless prismatic needles melting at 208–9°. Yield, 0·39 g. (Found: C, 59·3; H, 4·0; $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5.)

The substance gives an emerald green colour with alcoholic ferric chloride.

3 : 7 : 8-*Trimethoxy-2-methyl chromone* (*XVIII*)

The dihydroxy chromone (0·57 g.) was dissolved in dry acetone (30 c.c.), dimethyl sulphate (0·54 c.c.) and ignited potassium carbonate (3 g.) were added and the mixture gently refluxed over a water-bath for 8 hours. The trimethyl ether after isolation was crystallised from water when it was obtained as colourless flat needles melting at 112–3° after drying in the vacuum. (Found: C, 63·0; H, 5·7; $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6.)

2-*Hydroxy*-3 : 4 : 6-*trimethoxy acetophenone* (*XI*)

This ketone was prepared by the method of Baker.[8] The only modification introduced was in the preparation of pyrogallol trimethyl ether where the methylation was done under a layer of petroleum ether thus obviating the necessity of having an inert gas atmosphere in a gas-tight vessel. The product was quite colourless and was readily obtained.

2-*Hydroxy*-3 : 4 : 6-*trimethoxy-ω-acetyl acetophenone* (*XII*)

The above ketone (2 g.) was dissolved in ethyl acetate (20 c.c.) and the solution was added in two lots to powdered sodium (1 g.) just covered with a layer of dry ether. When the initial reaction was over the mixture was heated under reflux in a water-bath when the pale yellow sodium salt began to separate in about twenty minutes. After heating for about an hour more ethyl acetate (20 c.c.) was added and refluxing continued for another 3 hours. The mixture was then cooled, the yellow sodium salt was dissolved in ice-cold water (150 c.c.) and the brownish-red solution separated from the layer of ethyl acetate. The aqueous solution was acidified with glacial acetic acid till a turbidity appeared when the diketone separated as a pale

yellow oil which solidified on adding a little petroleum ether. The mixture was left in the refrigerator overnight, the pale yellow solid filtered and crystallised from a mixture of chloroform and ether; the diketone was obtained as light fawn-coloured plates melting at 123-24°. The substance gave a violet-brown colour with alcoholic ferric chloride. Yield, 1·6 g. (Found: C, 58·7; H, 5·7; $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0.)

5:7:8-*Trimethoxy-2-methyl chromone* (*X*)

The above diketone was crystallised by refluxing a solution of the substance (1·4 g.) in absolute alcohol (10 c.c.) containing 2 drops of concentrated sulphuric acid for 15 minutes. The mixture was cooled, diluted with water (60 c.c.) and made just alkaline with sodium hydroxide solution. It was extracted with chloroform (3 × 10 c.c.) and the trimethoxy chromone was obtained as a colourless solid by removing the solvent. It crystallised from a mixture of chloroform and ether as colourless needles melting at 170–71°. Yield, 1·2 g. (Found: C, 62·0; H, 5·1; $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6.)

Demethylation of 5:7:8-*trimethoxy-2-methyl chromone* (*X*): *Preparation of* 5:6:7-*trihydroxy-2-methyl chromone* (*XIII*)

The trimethoxy chromone (1 g.) was dissolved in acetic anhydride (15 c.c.) and the cooled solution was treated cautiously with hydriodic acid (20 c.c., d. 1·7). The solution was refluxed in an oil-bath at 140° for two hours, then treated with ice-water and the free iodine removed by adding sodium sulphite solution. On standing for about two hours a white powder separated. This was collected, washed several times with water and crystallised from alcohol (in which it was moderately soluble) when the trihydroxy chromone was obtained as fine leaflets having a very pale yellow colour. It melted at 284–86° with slight sintering at 280°. Yield, 0·8 g. (Found: C, 57·8; H, 4·0; $C_{10}H_8O_5$ requires C, 57·7; H, 3·9.) The compound gave an intense bluish-green colour with ferric chloride in alcoholic solution.

Methylation of the demethylated product: *Preparation of* 5:6:7-*trimethoxy-2-methyl chromone* (*XIV*)

The demethylated product (0·47 g.) was dissolved in dry acetone (75 c.c.), treated with excess of dimethyl sulphate (1 c.c., 4 mols.) and anhydrous potassium carbonate (6 g.) and the mixture was gently refluxed on a water-bath for 12 hours. The acetone solution was then filtered from the inorganic salts and the solvent removed when a brownish oil was left behind. By adding water it dissolved to a clear brown solution; this was allowed to stand for about two days to decompose all dimethyl sulphate.

The solution was made alkaline with a few drops of aqueous sodium hydroxide and extracted with ether. On removal of the solvent the trimethoxy chromone was left behind as a brown oil which solidified on the addition of a little ethyl acetate-petrol mixture and cooling. It was filtered and recrystallised several times from ethyl acetate-petroleum ether mixture when the trimethyl ether was obtained as starry bunches of colourless needles melting at 99–100°. The melting point was not depressed on admixture with an authentic sample of 5:6:7-trimethoxy-2-methyl chromone (described below). (Found: C, 62·3; H, 5·3; $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6.)

2-*Hydroxy*-4:5:6-*trimethoxy*-ω-*acetyl acetophenone*

2-Hydroxy-4:5:6-trimethoxy acetophenone (XV)[5] (3 g.) was dissolved in ethyl acetate (25 c.c.), the solution was added to powdered sodium (1·5 g.) and the mixture refluxed on a water-bath. The solution turned deep brown and sodium went into solution slowly. After an hour more sodium (0·5 g.) and ethyl acetate (10 c.c.) were added and the heating continued for another 3 hours. The excess of ethyl acetate was then distilled off under reduced pressure, the brownish gummy mass dissolved in ice-water and the solution filtered from a small quantity of undissolved fluffy matter. The clear aqueous solution was acidified with glacial acetic acid till a turbidity appeared; the mixture was left in the refrigerator overnight when a mass of pale cream-coloured crystals separated. These were filtered, washed with a little ether and crystallised from ethyl acetate when the diketone was obtained as pale cream-coloured glistening plates melting at 141–42°. Yield, 2·4 g. (Found: C, 58·5; H, 6·3; $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0). The compound gave a brown colour with alcoholic ferric chloride.

5:6:7-*Trimethoxy*-2-*methyl chromone* (*XIV*)

The above diketone (0·5 g.) was dissolved in absolute alcohol (10 c.c.) and 2 drops of concentrated sulphuric acid were added to it. The mixture was heated under reflux for 15 minutes, the pale violet-coloured solution was cooled and diluted with ice-water (60 c.c.) and then made alkaline with a few drops of sodium hydroxide solution. The alkaline solution was extracted with ether and the solvent evaporated when the trimethoxy chromone was obtained as a pale yellow oil which turned into colourless solid on the addition of a little petroleum ether and cooling. It crystallised from ethyl acetate-petroleum ether mixture as starry bunches of colourless needles melting at 99–100°. Yield, 0·4 g. (Found: C, 62·3; H, 5·3; $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6.)

SUMMARY

Methods of nuclear oxidation are applied for the preparation of chromone derivatives, many of which have been required for the study of isomeric change. Just as in the flavone group the presence of a methoxyl (hydroxyl) in the 3-position prevents isomeric change from the 5:7:8 to the 5:6:7 arrangement of hydroxyl groups; in its absence the isomeric change takes place.

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