SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XXI. Isomerisation of C-(6 or 8)-methyl-5: 7-dihydroxy Chromones

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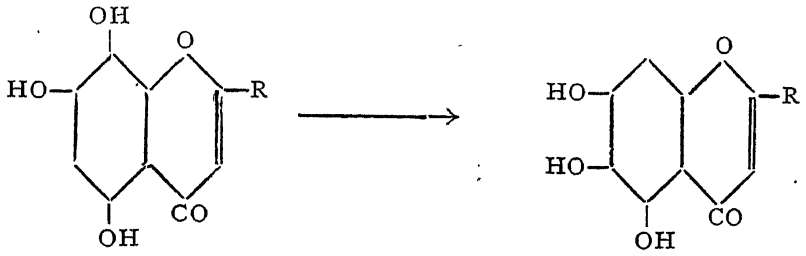
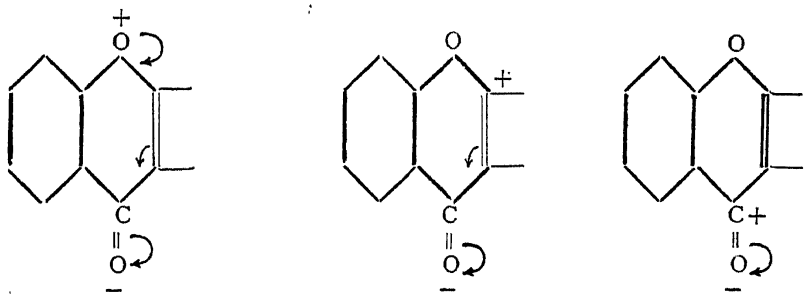
Mechanism of the isomeric change in hydroxy phloroglucinol derivatives

IN earlier publications[1–6] have been discussed in detail the conditions of isomeric change from 5: 7: 8-hydroxy chromones and flavones (I) into the 5: 6: 7-hydroxy isomers (II). The change takes place in the presence of boiling hydriodic acid or hydrobromic acid and it is prevented by the presence of a hydroxyl or phenyl group in the 3-position.[3, 5] The reverse change, *i.e.*, from (II) to (I) does not take place.[7] The explanation of this isomeric change may be briefly given as follows: (i) In the case of 3-hydroxy or phenyl substituted compounds, the pyrone ring is stable and does not open. (ii) In other cases, the ring opening takes place and the subsequent ring closure involves a different but more active hydroxyl group. (iii) The influence of the 3-hydroxyl or 3-phenyl group is exerted by inhibiting the opening of the pyrone ring.



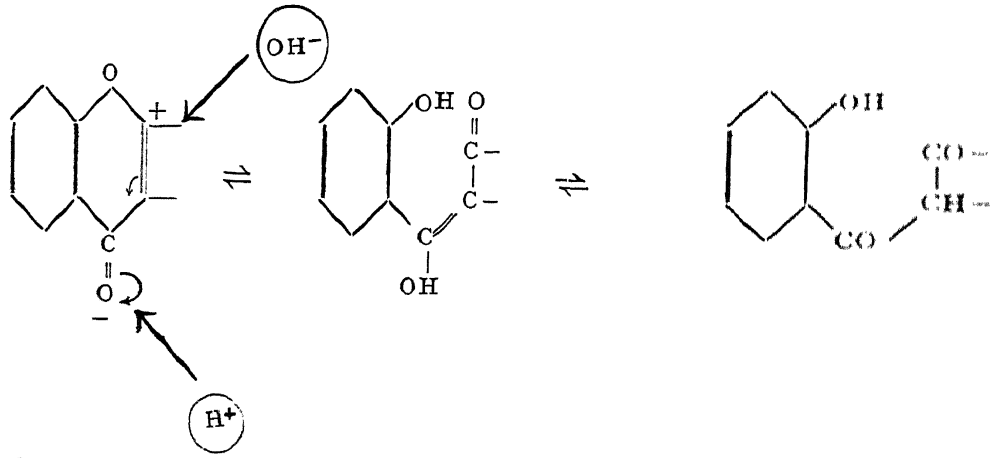
I $R = CH_3$ or C_6H_5 II

For detailed discussion, the main forms of the pyrone molecule can be represented by the following formulæ.

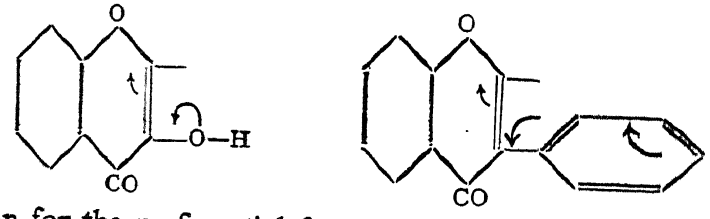


The electrophilic activity is mostly found in position 2. For example, the ring fission in alkaline solution can be formulated as being initiated by an

attack of this position by the nucleophilic reagent. Since boiling hydriodic acid brings about isomeric change, it should be accepted that in these cases the pyrone ring is capable of undergoing fission even in acid medium under these conditions. The change should be one of small degree and reversible so that when the system is cooled, only the pyrone is isolated. But this small degree reaction should be enough to bring about the isomeric change, since the alternative ring closure is favoured by the comparatively high reactivity of the alternative ortho hydroxyl group. It may be emphasised here that this isomeric change is a slow reaction and takes about two hours for completion.

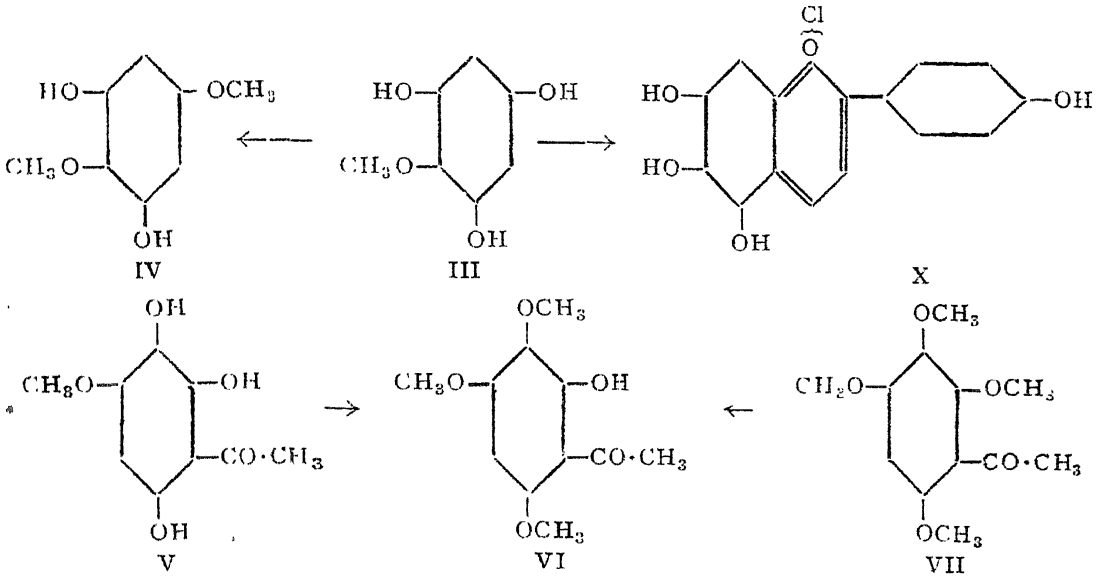


Hydroxyl and phenyl groups when located in the 3-position seem to act by increasing the availability of electrons in the 2-position. This will naturally reduce the already low electrophilic activity of this position in acid medium and thus prevent ring opening.

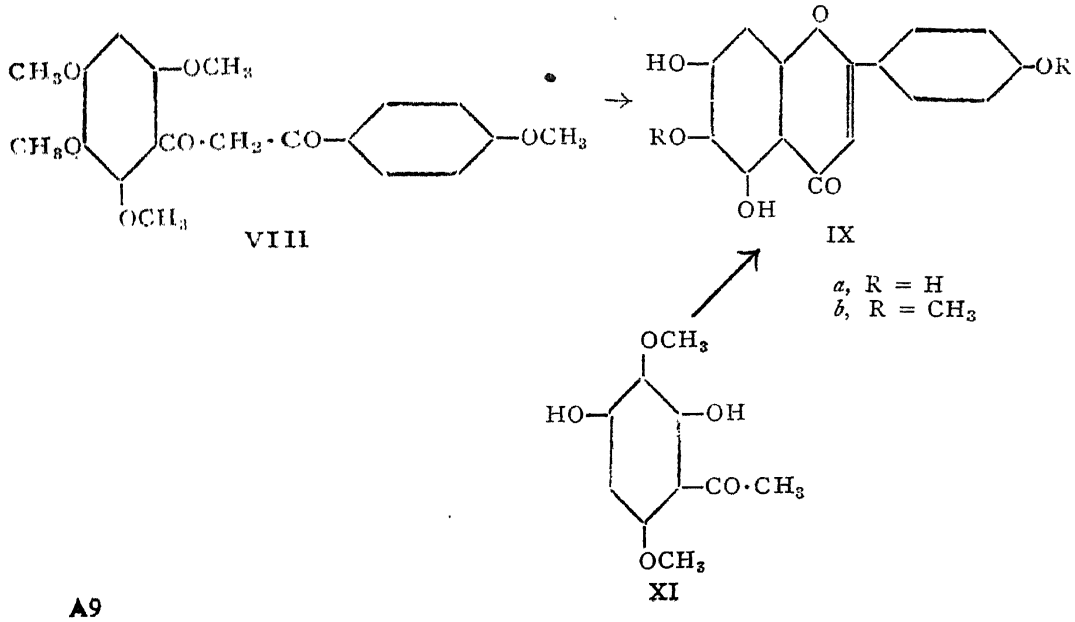


The reason for the preferential formation of 5 : 6 : 7-trihydroxy isomers is to be found in the greater reactivity of one of the two hydroxyl groups present ortho to the carbonyl group; it is located para to another hydroxyl (methoxyl) group. The greater reactivity of this hydroxyl group is independently established in several other reactions: (*a*) The methylation of iretol (III) has been shown to yield 1 : 3-dihydroxy-2 : 5-dimethoxy benzene (IV) and not the alternative 2 : 3-dimethoxy compound.[8] (*b*) Partial methylation of 2 : 3 : 6-trihydroxy-4-methoxy acetophenone (V) produces 2-hydroxy-3 : 4 : 6-trimethoxy acetophenone (VI).[9] (*c*) A similar behaviour is noticed in the demethylation of 2 : 3 : 4 : 6-tetramethoxy acetophenone (VII) which

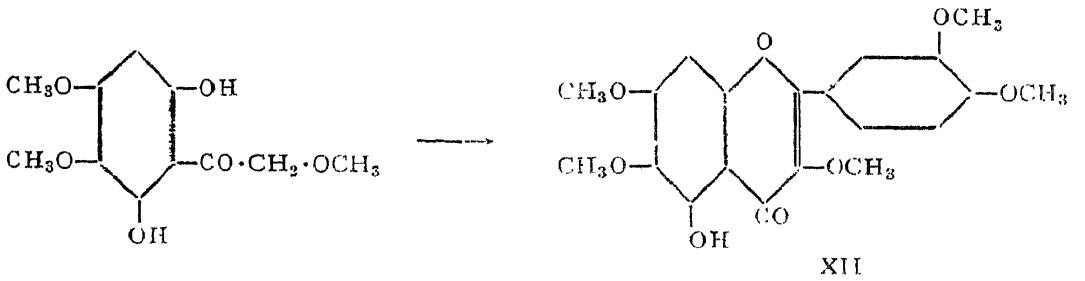
gives 2-hydroxy-3 : 4 : 6-trimethoxy acetophenone (VI) and not the isomeric 2-hydroxy-4 : 5 : 6-trimethoxy acetophenone[10] showing that the 6-methoxyl group is more stable.



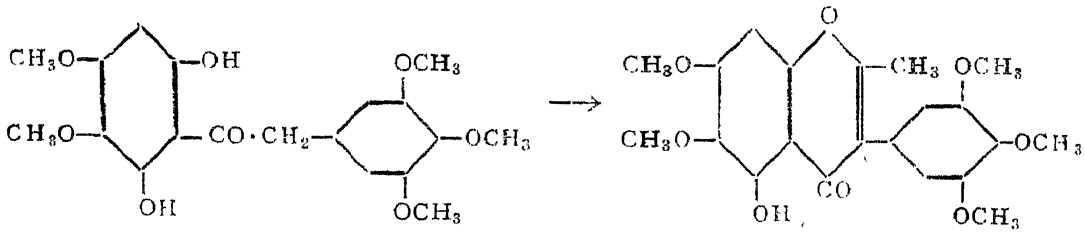
(*d*) A number of examples could be quoted from ring closure of various types. By heating 2 : 3 : 4 : 6 : 4′-pentamethoxy dibenzoyl methane (VIII) with hydriodic acid, scutellarein (IX *a*) is obtained as the product.[11] Similarly the condensation of iretol (III) with anisoyl acetaldehyde and subsequent demethylation of the product yields carajuretin hydrochloride (X).[8] The anisoylation of 2 : 4-dihydroxy-3 : 6-dimethoxy acetophenone (XI) using the Allan-Robinson procedure is accompanied by abnormal demethylation and the product is found to be scutellarein dimethyl ether (IX *b*).[12]



Further examples are provided by the syntheses of quercetagetin pentamethyl ether (XII)[13] and 2-methyl irigenin-7: 3'-dimethyl ether (XIII).[14]

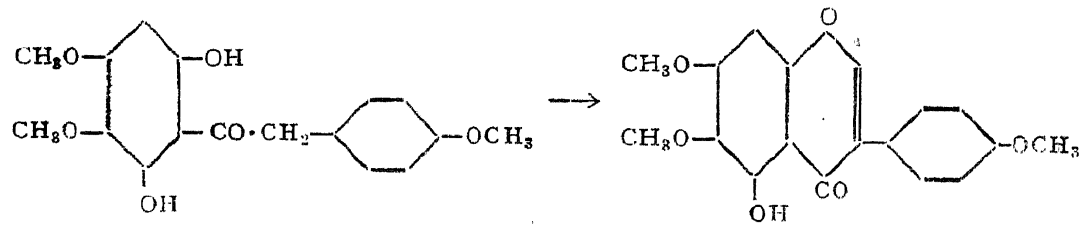


XII



XIII

Based on such results Baker and Robinson[14] have stated that " it appears a general rule that when a derivative of 1:2:3:5-tetrahydroxy benzene undergoes ring closure, it is the hydroxyl in the position 5 which is concerned ". This conclusion has been further supported by the synthesis of tectorigenin dimethyl ether (XIV) from 2:6-dihydroxy-4:5:4'-trimethoxy phenyl benzyl ketone (XV).[15]



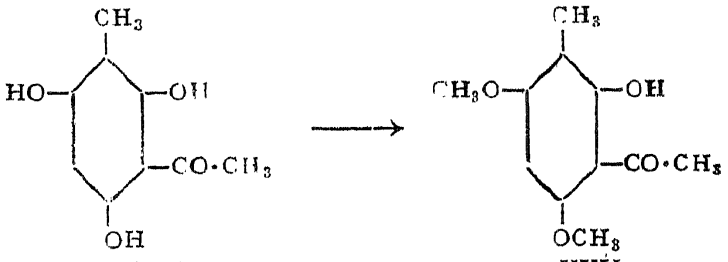
XIV

In all these cases the ring closure takes place in such a manner as to yield a compound of 5:6:7-trihydroxy type.

Isomeric change in C-methyl phloroglucinol derivatives

In the isomeric change from 5:7:8 to 5:6:7-hydroxy compounds it seemed probable that the 8-hydroxyl group may be playing some part in facilitating the opening of the pyrone ring. In order to test this point, the effect of substitution of a methyl group in this position would appear to be interesting. Actually compounds of this type having C-methyl groups in the condensed benzene ring have been recently isolated from *Eugenia caryophyllata*. From this source, Schmid and co-workers have obtained a

number of compounds which are closely related. These are eugenin (XXVIII),[16] eugenone (XXVI *b*),[17] eugenitin (XXV),[18] isoeugenitin (XXII *b*)[19] and isoeugenitol (XXII *a*).[20] Their constitutions were established by appropriate degradation reactions. They noticed that isoeugenitin methyl ether (XXI) could be demethylated with hydriodic acid to yield isoeugenitol (XXII *a*) without any isomeric change[21] whereas eugenitin (XXV) under the same conditions underwent isomeric change to form isoeugenitol.[18] This observation is of an extraordinary nature and the change is just the opposite of what happens with analogous trihydroxy compounds. Further it is not even in accordance with the behaviour of methyl phloroglucinol derivatives either in methylations or in reactions involving ring closure. In all these reactions a methyl group has the same effect as the hydroxyl group and it is the particular hydroxyl group which is para to the methyl group that is found to be more reactive. For example, the methylation of 2:4:6-trihydroxy-3-methyl acetophenone (XVI) yields 2-hydroxy-3-methyl-4:6-dimethoxy acetophenone (XVII).[22] Similarly methyl phloroglucinol (XVIII) gives the α-methyl ether (XIX).[22, 23] In the synthesis of eugenitin (XXV) starting from 2:4:6-trihydroxy-3-methyl acetophenone (XVI) it is this hydroxyl group which is para to the methyl group that is again reactive.[21] Hence the observation of Schmid and co-workers about the isomeric change appeared to be exceptional and seemed to require careful re-examination. Further several of the steps in the synthesis of eugenitin were not fully characterised by the earlier workers.



Present work

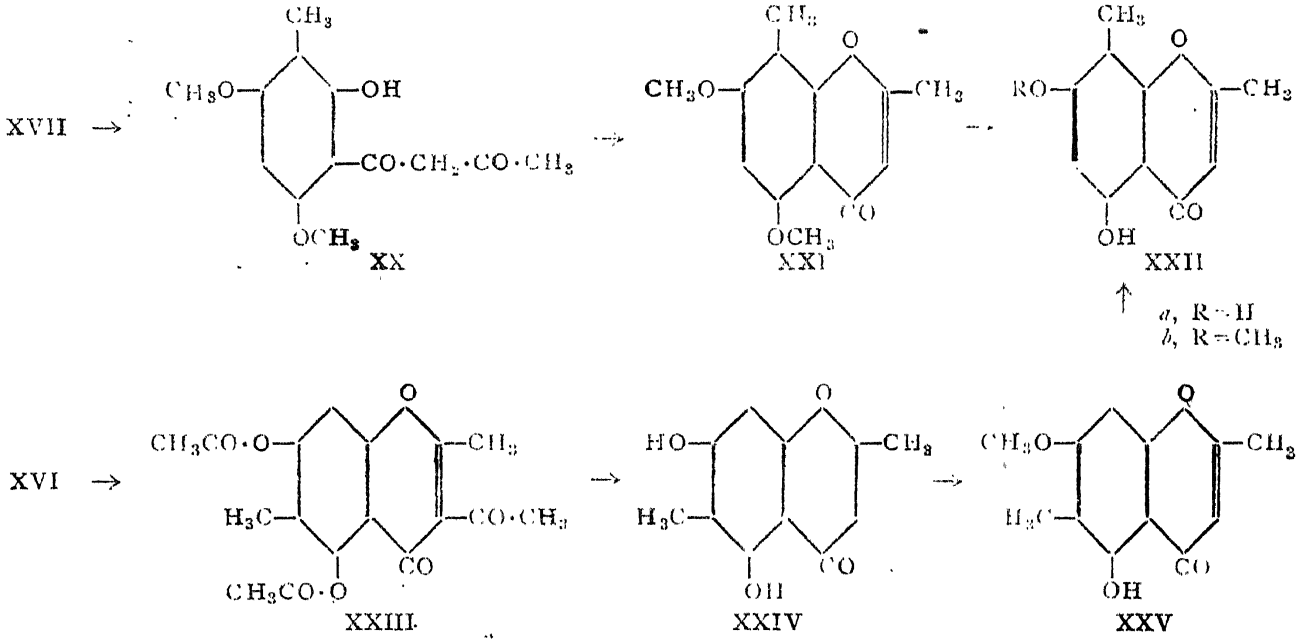
2-Hydroxy-3-methyl-4:6-dimethoxy acetophenone (XVII)[22] is converted into isoeugenitin methyl ether by way of the diketone (XX) according to

the method of Schmid and Bolleter.[21] These authors have reported that this chromone is dimorphic and the two forms melt at 132° and 174° respectively and that both are anhydrous. Both of them were obtained by these authors by sublimation under reduced pressure. It has now been found that when crystallised from dilute alcohol the compound is hydrated and is found to have a melting point of 96–97°. The anhydrous form could however be obtained by repeated dissolution of the hydrated compound in dry benzene and evaporation. This form melts at 174° agreeing with one of the forms reported by Schmid and Bolleter. Under these conditions, the crystal modification melting at 132° could not be obtained. On demethylation with aluminium chloride in benzene solution, the compound yields the normal product, 2:8-dimethyl-5:7-dihydroxy chromone (XXII *a*). This reagent is known to produce demethylation without any isomeric change.[1, 4, 6, 24] The product and its acetate agreed in all respects with isoeugenitiol and its acetate. The product obtained by treating 2:8-dimethyl-5:7-dimethoxy chromone with boiling hydriodic acid could not however be obtained easily pure by crystallisation. However, on acetylation, it yields an acetate which is found to be identical with 2:8-dimethyl-5:7-diacetoxy chromone and the product obtained on methylation with excess of dimethyl sulphate and potassium carbonate in acetone medium is found to be identical with 2:8-dimethyl-5:7-dimethoxy chromone thus clearly showing the absence of any rearrangement during this demethylation with hydriodic acid. On boiling isoeugenitiol (XXII *a*) with methyl iodide and potassium carbonate in acetone solution, a good yield of isoeugenitin (XXII *b*) agreeing with the natural product is obtained. Its acetate which has not been reported earlier has now been prepared.

The synthesis of eugenitin (XXV) itself has now been carried out on the same lines as those adopted by Schmid and Bolleter.[21] The starting material for this synthesis, 3-methyl phloracetophenone (XVI) was first made by the Hoesch condensation of C-methyl phloroglucinol with acetonitrile.[22] This is found to give only very poor yields of the ketone. Although the ketimine hydrochloride is formed in a good yield, during hydrolysis, considerable resinification takes place. It has now been found that 3-methyl phloracetophenone (XVI) could be obtained in nearly quantitative yield by the demethylation of 2-hydroxy-3-methyl-4:6-dimethoxy acetophenone (XVII) with aluminium chloride in benzene solution. The product is easily isolated in the pure state and is identical with the ketone obtained by the method of Curd and Robertson.[22]

On heating 3-methyl phloracetophenone (XVI) with acetic anhydride and sodium acetate for 18 hours at 170–75°, 2:6-dimethyl-3-acetyl-5:7-

diacetoxy chromone (XXIII) is obtained which on boiling with aqueous sodium carbonate gives 2:6-dimethyl-5:7-dihydroxy chromone (XXIV). The properties of this substance as well as its diacetate are different from those of isoeugenitol (XXII *a*) and its diacetate respectively. By subsequent methylation with dimethyl sulphate and potassium carbonate in acetone solution, eugenitin (XXV) is obtained. Its acetate has the same melting point as reported by Schmid.[18] Heating eugenitin with hydriodic acid gives rise to a dihydroxy chromone identical with isoeugenitol as reported by Schmid.[18] This has now been confirmed by the preparation of the acetate also.

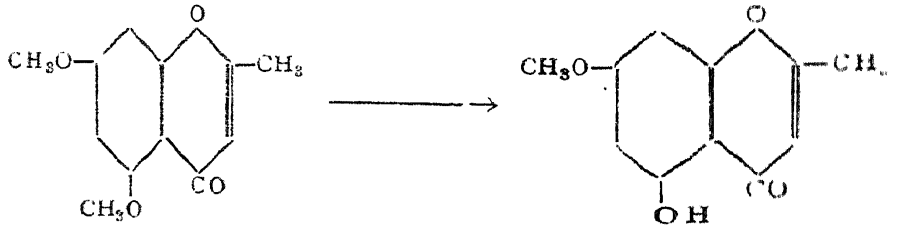


The observations of Schmid and Bolleter[18, 21] regarding the isomeric change have thus been confirmed. The very exceptional nature of this change has already been discussed. At present there is not sufficient data to explain this phenomenon. However it could be suggested as a possibility that the reactivity of the hydroxyl groups may differ under different conditions. Even though in methylations and chromone ring formation using acetic anhydride and sodium acetate, the hydroxyl para to the methyl may be more active, it may be just the reverse in the presence of boiling hydriodic acid. However this is peculiar to the C-methyl phloroglucinol derivatives and is not found in C-hydroxy phloroglucinol derivatives. Further investigation is in progress.

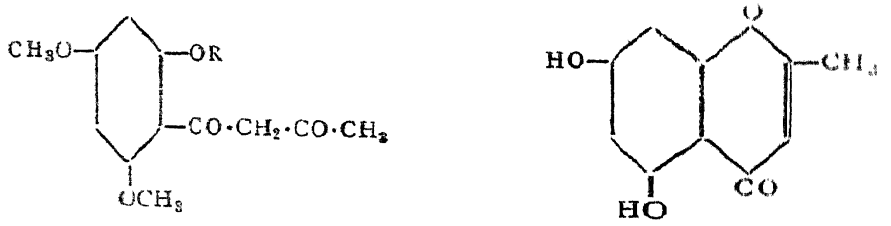
Synthesis of eugenin

In the reactivity of the hydroxyl groups of the condensed benzene ring, the isoflavone derivatives differ markedly from the corresponding flavones. This was explained by Aghoramurthy *et al.*[25] as due to the presence of the

phenyl group in the 3-position instead of the 2-position. As a consequence it is easy to effect partial demethylation of methyl ethers of isoflavones using even hydriodic acid and obtain the 7-methyl ethers, *e.g.*, santal (XXX *a*),[26] prunetin (XXX *b*)[27] and isoformononetin (XXXI).[25] Similar conditions should prevail in the case of the simpler chromones in which the side phenyl group is absent. This has now been confirmed by carrying out the demethylation of 2-methyl-5 : 7-dimethoxy chromone (XXVII) using hydriodic acid at 115° for 30 minutes and a good yield of eugenin (XXVIII) is obtained. The required dimethyl ether (XXVII) was originally made by Mckenzie, Robertson and Whalley[22] by cyclising 2-hydroxy-4 : 6-dimethoxy-ω-acetyl acetophenone (XXVI *a*). This methyl ether has now been made by methylation of 2-methyl-5 : 7-dihydroxy chromone (XXIX) with dimethyl sulphate by the dry method.

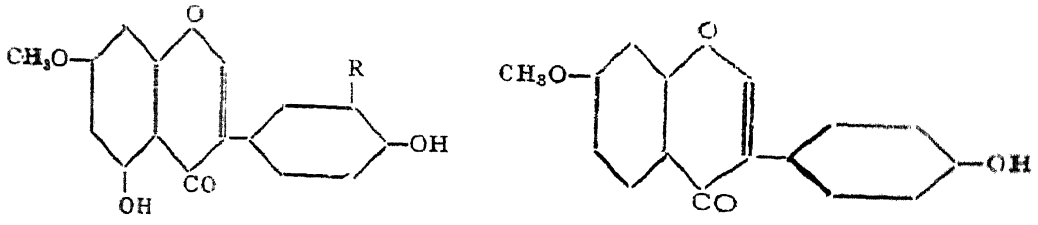


XXVII XXVIII



XXVI XXIX

a, R = H
b, R = CH_3



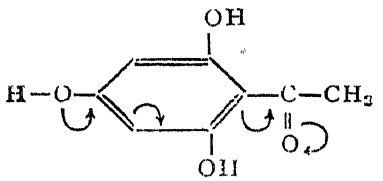
XXX XXXI

a, R = OH
b, R = H

In view of the reported nuclear methylation of genistein by means of methyl iodide and potassium carbonate in anhydrous acetone solution,[29] the reaction has now been carried out using 2-methyl-5: 7-dihydroxy chromone (XXIX). However no nuclear methylation takes place and a good yield of eugenin is again obtained. There seems to be therefore no need for using the more costly and difficultly available reagent diazomethane for the synthesis of this substance as was originally done by Meijer and Schmid.[16]

The theory of reactivity of C-hydroxy (methoxy) and C-methyl phloroglucinol derivatives

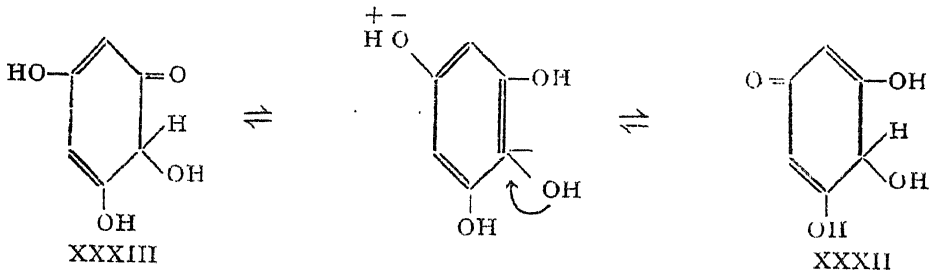
No explanation seems to have been offered so far for the marked difference in reactivity of the hydroxyl groups in C-hydroxy (methoxy) phloroglucinol derivatives discussed in the earlier paragraphs. However a detailed study has been made of phloracetophenone and similar compounds. In these, the para hydroxyl is definitely far more reactive in alkylations[30] as well as in benzoylation[31] as compared with ortho hydroxyl groups. This is obviously due to the effect of the C = O group which produces maximum positive charge on the nuclear position para to it and thus makes the para hydroxyl group most acidic and most reactive.



It is significant that even a hydroxyl or methoxyl group produces the same effect as a carbonyl group. A number of examples of C-hydroxy and C-methoxy phloroglucinol derivatives have already been given in which a hydroxyl para to these substituents is found to be more reactive as compared with the ortho hydroxyl group. These substituents, unlike the carbonyl, act as electron sources and hence a different type of mechanism should be involved.

It seems to be reasonable to consider that all phenolic compounds exhibit tautomerism and exist to some extent in the isomeric carbonyl forms; the facility with which this tautomerism is possible determines their reactivity. This is supported by the behaviour of 1: 4-dihydroxy-2-methyl naphthalene when it undergoes substitution with phytyl group leading to the synthesis of vitamin K.[32] Hydroxyl and similar electron donating groups can create nucleophilic activity on the carbon atom to which they are linked and they may be expected to help this tautomerism. Of the possible

structures, the para quinonoid form (XXXII) is obviously more easily produced than the isomeric ortho quinonoid type (XXXIII) and hence the para hydroxyl would be more reactive than the one at the ortho position.



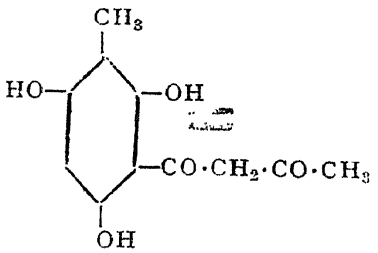
XXXIII XXXII

Extending this consideration to the ketones derived from C-hydroxy and C-methoxy phloroglucinol, the most reactive hydroxyl naturally should be the one para to the C = O group. When this is protected by methylation, subsequent reaction takes place involving the hydroxyl ortho to the carbonyl and para to the C-hydroxyl or C-methoxyl group.

As already mentioned, the influence of the methyl group in C-methyl phloroglucinol and C-methyl phloracetophenone derivatives in methylations and chromone ring closure is very similar to that of a hydroxyl or methoxyl group and the explanation given above should therefore be extended to these cases also; a methyl group is also an electron source though not so efficient as a hydroxyl or methoxyl group. But the behaviour of C-methyl chromones under the influence of boiling hydriodic acid is exceptional and other factors, hitherto un-understood, may be involved. This requires further investigation using related compounds before it could be fully understood.

Biogenesis

Schmid and Bolleter[20] have suggested that eugenitin and isoeugenitol can arise in the plant from the hypothetical intermediate, 2: 4: 6-trihydroxy-3-methyl-ω-acetyl acetophenone (XXXIV). They consider that the ring closure can take place in two ways giving rise to a 6 or 8-methyl chromone.



XXXIV

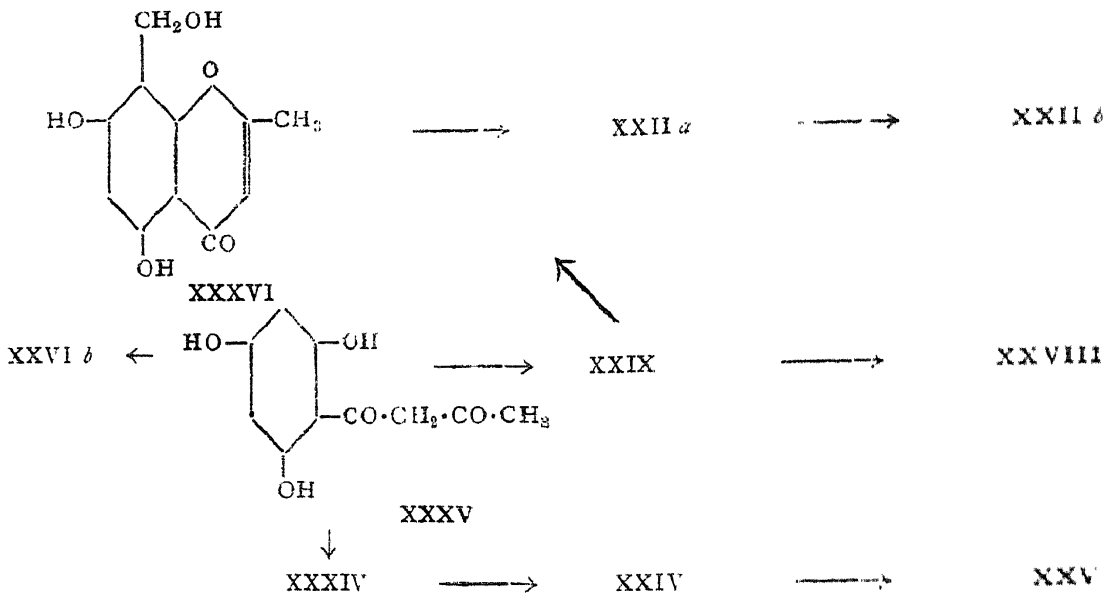
There is difficulty in accepting this as a biogenetic possibility. Taking laboratory analogy, under one set of conditions, only one isomer seems to

be formed. When 2 : 4 : 6-trihydroxy-3-methyl-ω-acetyl acetophenone (XXXIV) is subjected to ring closure under mild acid conditions, the 6-hydroxyl will be more reactive and only the 6-C-methyl chromone will be obtained and this may be expected to be the normal reaction in the plant. It is not reasonable to expect the drastic conditions of boiling hydriodic acid under the conditions of plant life. Hence a different process should be prescribed for the formation of the 8-methyl compounds, isoeugenitol (XXII *a*) and isoeugenitin (XXII *b*). Further, the occurrence of eugenone (XXVI *b*) and eugenin (XXVIII) in the same plant cannot be explained assuming the above hypothetical intermediate (XXXIV) of Schmid and Bolleter.

A more comprehensive scheme has therefore to be considered. For this purpose, a near derivative of eugenone, nor-eugenone (XXXV) offers a better starting point. By complete O-methylation, it would yield eugenone (XXVI *b*). In this case even the resistant 2-hydroxyl group of the diketone (XXXV) gets methylated and hence a fairly powerful mechanism should be available for this purpose. Ring closure of this diketone (XXXV) would give nor-eugenin (XXIX) which on subsequent partial methylation would give eugenin (XXVIII).

The other three compounds contain C-methyl groups; of these, isoeugenitol is the simplest, without any O-methylation in it. For its biogenesis, nor-eugenone (XXXV) is again the simpler starting point; chromone ring closure may be considered to take place first followed by nuclear methylation in the 8-position. Laboratory experiments indicate that the 8-position in chromones is the reactive one and they combine with hexamine to produce the corresponding 8-aldehydes[33] which can undergo reduction to the 8-methyl compounds.[34] A similar process could be postulated for the biogenesis of the 8-methyl chromones in the plant, the necessary important intermediate being a chromone containing a carbinol group in the 8-position (XXXVI). In the above nuclear methylation, as in many others of the same type, formaldehyde should be considered to be the normal methylating agent, the initial stage being a carbinol undergoing subsequent reduction to a C-methyl.[35] Subsequent ether formation could yield isoeugenitin (XXII *b*) from isoeugenitol (XXII *a*), the more resistant 5-hydroxyl being left free.

For the evolution of eugenitin (XXV), nor-eugenone (XXXV) may be considered to undergo nuclear methylation to (XXXIV) followed by ring closure and subsequent partial etherification. This is in accordance with laboratory analogy as already shown earlier. Partial methylation that follows could methylate the more reactive 7-hydroxyl group.



EXPERIMENTAL

2: 8-*Dimethyl*-5: 7-*dimethoxy chromone* (XXI)

2-Hydroxy-3-methyl-4: 6-dimethoxy-ω-acetyl acetophenone[21] (1·6 g.) was dissolved in absolute alcohol (25 c.c.) and the solution refluxed with 2 drops of concentrated hydrochloric acid for 30 minutes on a water-bath. The mixture was concentrated to 10 c.c. and diluted with hot water (100 c.c.) and allowed to cool when crystals of 2: 8-dimethyl-5: 7-dimethoxy chromone separated. On recrystallisation from dilute alcohol, it was obtained in the form of fine colourless needles and rectangular rods melting at 96–97°. Yield 1·4 g. (Found: C, 60·2; H, 6·6. $C_{13}H_{14}O_4$, $1\frac{1}{2}$ H_2O requires C, 59·8; H, 6·5%).

This sample (0·1 g.) was dissolved in dry benzene (5 c.c.) and the benzene evaporated off. The process was repeated thrice. The residue was crystallised from a mixture of benzene and petroleum ether, when it came out as colourless prisms melting at 174° (Found: C, 67·1; H, 6·3; $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). When this sample was crystallised again from dilute alcohol, it had a m.p. 96–97°.

Schmid and Bolleter[21] carried out this cyclisation using alcoholic sulphuric acid and give melting points 132° and 174°. Both these samples were obtained by them by vacuum sublimation and were anhydrous.

2: 8-*Dimethyl*-5: 7-*dihydroxy chromone* (*Isoeugenitol*) (*XXII a*)

(i) To a solution of 2: 8-dimethyl-5: 7-dimethoxy chromone (1 g.) in dry benzene (20 c.c.) cooled to 0°, anhydrous aluminium chloride (3 g.) was

added in small lots with shaking. The aluminium chloride complex began to separate immediately. After the addition, the mixture was heated under reflux on a water-bath for 2 hours. Benzene was then distilled off and the residual complex decomposed by the addition of ice (30 g.) and hydrochloric acid (4 c.c.). The precipitate was filtered off and after drying, was crystallised from a mixture of alcohol and ethyl acetate. 2: 8-Dimethyl-5: 7-dihydroxy chromone separated as pale yellow rectangular prisms melting at 236–37°. Yield 0·8 g.

The diacetate was prepared by heating the chromone (0·25 g.) with acetic anhydride (5 c.c.) and a few drops of pyridine at 140° for 2 hours. It crystallised from alcohol as colourless thick rectangular plates melting at 150–51° (Found: C, 62·2; H, 5·1; $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·9%). Schmid and Bolleter[21] give same m.p.

(ii) 2: 8-Dimethyl-5: 7-dimethoxy chromone (1 g.) was dissolved in acetic anhydride (25 c.c.) and the solution was cooled in an ice-bath. Hydriodic acid (25 c.c., d., 1·7) was then added cautiously with stirring and the mixture heated in an oil-bath at 140° for 2 hours. It was then cooled and diluted with a saturated aqueous solution of sodium bisulphite. After 12 hours, the yellow precipitate was collected, washed with water and dried. On crystallisation from a mixture of alcohol and ethyl acetate, it was obtained as pale yellow rectangular prisms melting at 220–30°. It did not crystallise readily from alcohol but yielded a crystalline acetate and methyl ether more easily. It gave a blue colour with ferric chloride in alcoholic solution. It was easily soluble in alcohol and sparingly soluble in ethyl acetate.

The acetate prepared by the acetic anhydride-pyridine method had a m.p. 150-51° and was in every way identical with 2: 8-dimethyl-5: 7-diacetoxy chromone described in (i) above.

Remethylation

The dihydroxy-dimethyl chromone (0·4 g.) obtained by the hydriodic acid demethylation above, was dissolved in dry acetone (100 c.c.) and the solution refluxed on a water-bath for 20 hours with dimethyl sulphate (0·8 c.c.) and anhydrous potassium carbonate (4 g.). The potassium salts were filtered off and then washed with warm acetone twice. Acetone was distilled off from the combined filtrate and the residue treated with water (100 c.c.). On setting aside for two days, some solid separated. It was filtered and crystallised thrice from dilute alcohol when it was obtained in the form of fine colourless needles and long rectangular rods melting at 96–97°. It did not give any colour with ferric chloride in alcoholic solution and a mixed

melting point with 2: 8-dimethyl-5: 7-dimethoxy chromone (XXI) described earlier was not depressed.

2: 8-*Dimethyl-5-hydroxy-7-methoxy chromone* (*Isoeugenitin*) (*XXII b*)

2: 8-Dimethyl-5: 7-dihydroxy chromone (0·42 g.) was dissolved in dry acetone (150 c.c.). Methyl iodide (0·5 c.c.) and anhydrous potassium carbonate (2·5 g.) were added and the mixture refluxed for 3 hours. The potassium salts were filtered off and washed with acetone. The crystalline residue left on distillation of the solvent, was recrystallised from alcohol twice. It came out as colourless needles melting at 148–49°. Schmid,[18] who carried out this methylation with excess of diazomethane in methyl alcohol at − 10° gives m.p. 147–48°. It gave a blue colour with alcoholic ferric chloride (Found: C, 65·2; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

The acetate, prepared by acetylation with acetic anhydride and pyridine, crystallised from dilute alcohol as colourless rectangular rods and prisms and melted at 136–37° (Found: C, 64·4; H, 5·5; $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·4%).

2: 4: 6-*Trihydroxy-3-methyl acetophenone* (*XVI*)

2-Hydroxy-3-methyl-4: 6-dimethoxy acetophenone (XVII)[22] (4 g.) was dissolved in dry benzene (35 c.c.) and well powdered, anhydrous aluminium chloride (12 g.) was added. The aluminium chloride complex separated out. The mixture was refluxed in a water-bath for 2 hours. Benzene was then distilled off completely and the residue cooled and treated with crushed ice and hydrochloric acid (20 c.c.). After two hours, the almost colourless precipitate was filtered, washed with water and treated with excess of aqueous sodium carbonate (10%). A small amount of undissolved matter was filtered off and the filtrate acidified. The colourless precipitate was collected. Yield 3·0 g., m.p. 208–10°. On crystallisation from boiling water, 3-methyl phloracetophenone was obtained as clusters of colourless needles melting at 211–12°. A mixed melting point with an authentic sample of the ketone prepared according to the method of Curd and Robertson[22] was not depressed.

2: 6-*Dimethyl-3-acetyl-5: 7-diacetoxy chromone* (*XXIII*)

An intimate mixture of 2: 4: 6-trihydroxy-3-methyl acetophenone (5 g.) and fused sodium acetate (12 g.) was heated with acetic anhydride (100 c.c.) at 150° for half an hour and then at 170–75° for 18 hours. The clear red solution was poured into crushed ice. The dark solid that separated on leaving overnight was filtered and washed with water. On maceration with

cold alcohol, the coloured impurities dissolved. The colourless solid was filtered, washed with cold alcohol and crystallised from the same solvent twice. 2: 6-Dimethyl-3-acetyl-5: 7-diacetoxy chromone was obtained in the form of colourless rectangular prisms melting at 159–61°. Yield 2·1 g. (Found: C, 63·0; H, 5·2. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%).

The mother liquors on concentration gave 2: 4: 6-triacetoxy-3-methyl acetophenone as a colourless crystalline solid (1·7 g.) which when recrystallised from alcohol had a m.p. 114–15°. Curd and Robertson[22] give m.p. 111° for this compound.

2: 6-*Dimethyl*-5: 7-*dihydroxy chromone* (*XXII*)

The above 3-acetyl compound (1·75 g.) was heated with 10% aqueous sodium carbonate (100 c.c.) under reflux for 2 hours. The solid slowly went into solution. The solution was filtered from any insoluble matter, cooled to 0° and acidified with ice-cold hydrochloric acid (1 : 1) and then heated to 80° in a water-bath to coagulate the precipitated solid. The mixture was cooled to 0° again and the precipitate filtered off. Yield 1·0 g. When crystallised twice from alcohol, 2: 6-dimethyl-5: 7-dihydroxy chromone separated as colourless clusters of irregular prisms melting at 274–76° (decomp.). It gave a blue colour with alcohloic ferric chloride and was very sparingly soluble in alcohol (Found: C, 64·4; H, 5·2. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

The diacetate was prepared by heating the dihydroxy chromone with acetic anhydride and pyridine. When crystallised from alcohol twice, it was obtained in the form of clusters of colourless narrow rectangular plates melting at 200–02° (Found: C, 61·6; H, 4·6. $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·9%).

2: 6-*Dimethyl*-5-*hydroxy*-7-*methoxy chromone* (*Eugenitin*) (*XXV*)

2: 6-Dimethyl-5: 7-dihydroxy chromone (XXIV) (0·9 g.) was dissolved in acetone (150 c.c.) and treated with freshly distilled dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (1·5 g.). The mixture was refluxed for 6 hours on a water-bath. Acetone was then distilled off and the potassium salts were dissolved in water (150 c.c.). The bluish solid was filtered and washed with water and crystallised from alcohol twice and then once from ethyl acetate, when 2: 6-dimethyl-5-hydroxy-7-methoxy chromone separated as colourless thick prisms melting at 161–62°. It gave a blue colour with alcoholic ferric chloride. Yield 0·4 g. Schmid[18] gives the m.p. of natural eugenitin as 162° (Found: C, 65·6; H, 5·4; $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

The acetate prepared by the pyridine method, crystallised from alcohol as thin colourless rectangular plates melting at 176–77°. Schmid[18] gives the same m.p. for eugenitin acetate.

Demethylation

Eugenitin (0·27 g.) was heated with hydriodic acid (5 c.c., d., 1·7) for 2 hours in an oil-bath. The deep brown solution was poured into an ice-cold saturated aqueous solution of sodium bisulphite (75 c.c.). After 12 hours, the pale yellow solid was collected and washed with water. On crystallisation from alcohol twice, it was obtained as colourless thick rectangular plates melting at 236–37°. It was easily soluble in alcohol and the melting point did not rise on further crystallisation. A mixed melting point with an authentic sample of 2: 8-dimethyl-5: 7-dihydroxy chromone (XXII *a*) was not depressed.

The acetate, prepared by acetylation with acetic anhydride and pyridine, crystallised from alcohol and melted at 150–51° alone or when mixed with a sample of 2: 8-dimethyl-5: 7-diacetoxy chromone.

2-*Methyl*-5: 7-*dimethoxy chromone* (*XXVII*)

A solution of 2-methyl-5: 7-dihydroxy chromone (XXIX)[36] (1 g.) in dry acetone (100 c.c.) was heated with dimethyl sulphate (1·5 c.c.) and potassium carbonate (5 g.) for 15 hours. Acetone was then distilled off and water was added to the residue. After setting aside for two days, the solution was filtered through cotton and the filtrate extracted with ether. The brown oil which was left on distilling off the solvent from the ether solution, solidified on the addition of a small quantity of petroleum ether. It was filtered and crystallised from a mixture of ethyl acetate and petroleum ether when it separated as colourless plates melting at 124–25°. Yield 0·5 g. Mckenzie, Robertson and Whalley,[28] who obtained this compound by a different route give m.p. 124°.

2-*Methyl*-5-*hydroxy*-7-*methoxy chromone* (*Eugenin*) (*XXVIII*)

(i) 2-Methyl-5: 7-dihydroxy chromone[36] (0·7 g.) in acetone (100 c.c.) was mixed with methyl iodide (3 c.c.) and potassium carbonate (3 g.) and the mixture refluxed for 3 hours on a water-bath. The solvent was then distilled off and the residue treated with water. The undissolved methyl ether was filtered and crystallised from alcohol. It separated as colourless prisms melting at 118–19°. Yield 0·5 g. It gave a wine red colour with ferric chloride in alcoholic solution. Meijer and Schmid,[16] who carried out this methylation with diazomethane in methanol report the m.p. as 119–20°.

The acetate, prepared by acetylation with acetic anhydride and pyridine, crystallised from alcohol as colourless irregular prisms melting at 152–53°. Meijer and Schmid[16] give m.p. 152·5–153·5°.

(ii) 2-Methyl-5 : 7-dimethoxy chromone (XXVII) (0·35 g.) was dissolved in acetic anhydride (8 c.c.) and treated with hydriodic acid (12 c.c., d., 1·7). The mixture was heated in an oil-bath at 115° for 30 minutes and diluted with aqueous sodium bisulphite. The solution was neutralised with sodium bicarbonate. The precipitated solid was filtered and washed with water. It was insoluble in aqueous sodium carbonate. When crystallised from alcohol (Norit), it was obtained as colourless prisms melting at 118–19°. A mixed m.p. with the sample obtained in (i) above was not depressed.

Summary

A review of ring isomeric change of flavones and chromones is made as also of the reactivity of C-hydroxy phloroglucinol and C-hydroxy phloracetophenone derivatives in methylation, benzoylation and ring closure. The results are consistent showing the greater reactivity of a hydroxyl group of the quinol unit as compared with that of the catechol unit. A tentative explanation is given.

A synthetic study has been made of the chromones of *Eugenia caryophyllata*. All the intermediates in the synthesis of eugenitin have now been isolated and fully characterised. A convenient route for the preparation of the starting material for this synthesis, *viz.*, 3-methyl phloracetophenone has now been found. Two new syntheses of eugenin are also recorded. The observation of Schmid and Bolleter that eugenitin (6-methyl) undergoes change into isoeugenitol (8-methyl) when demethylated with boiling hydriodic acid and that isoeugenitin methyl ether (8-methyl) does not undergo isomeric change under the same conditions, is confirmed. This is the reverse of what has been observed in the case of C-hydroxy phloracetophenone derivatives. Further it is extraordinary because C-methyl phloroglucinol and C-methyl phloracetophenone behave like the C-hydroxy (methoxy) compounds in methylations and chromone ring closure.

An attempt has been made to develop a comprehensive scheme of biogenesis which includes all the five components occurring in *Eugenia caryophyllata*. The basic compound is taken to be nor-eugenone and all the stages are based on analogy with laboratory experiments.

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