

SYNTHETIC EXPERIMENTS IN THE BENZOPHYRONE SERIES

Part XXXVI. Nuclear Methylation of Nor-Eugenin and Chrysin, and Synthesis and Study of Related C-Methyl Compounds*

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Received April 24, 1953

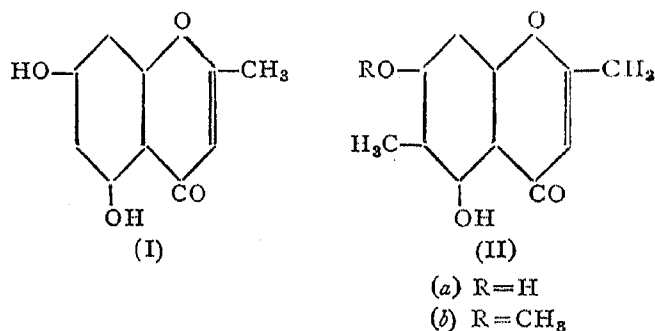
THE phenomenon of nuclear methylation seems to be assuming increasing importance and to be also closely related to the more well-known phenomenon of nuclear oxidation in flavones and related compounds.² A detailed study of the course of nuclear methylation has therefore been considered to be useful. In laboratory experiments the first observation of nuclear methylation was made by Perkin and Horsfall³ during their investigation of the constitution of genistein. When they used methyl iodide and methanolic potassium hydroxide, besides the normal dimethyl ether, they obtained as a minor product its C-methyl derivative. Similar results were reported by Perkin and Horsfall⁴ in the methylation of the flavone luteolin and by Perkin⁵ in the case of the flavonol quercetin. Since alkali fusion of these compounds gave C-methyl phloroglucinol monomethyl ether as a product, it was clear that the nuclear methyl group was present in the condensed benzene ring, but its location in the 6 or the 8 position was not established. However in the case of genistein, Baker and Robinson⁶ suggested that the C-methyl group may be present in the 6-position based on analogy with the behaviour of simpler polyhydroxy carbonyl compounds. This suggestion has been supported by work done in this laboratory.⁷

But the above analogy may not be altogether adequate as the following consideration will show. Earlier work on β -substituted resorcinol derivatives, *e.g.*, aldehyde, carboxylic acid and ketone show that the γ -position is predominantly active not only in nuclear methylation⁸ but also in other reactions such as allyl migration⁹ and aldehyde synthesis.¹⁰ It has been found that in flavones and chromones the predominantly reactive position is the 8-position and not the 6-position.¹¹ Hence there is need to make sure whether the methyl group enters the 6- or the 8-position adopting unambiguous methods. The present investigation has been undertaken

* See preliminary note on the above subject¹.

with a view to establish the constitution of these nuclear methylation products and is a continuation of our earlier work on the synthesis and study of C-methyl benzopyrone derivatives.^{7, 12} Further a number of C-methyl benzopyrone compounds have recently been reported to occur in nature^{13, 14, 15} and nuclear methylation may provide a convenient method of synthesis of some of these compounds.

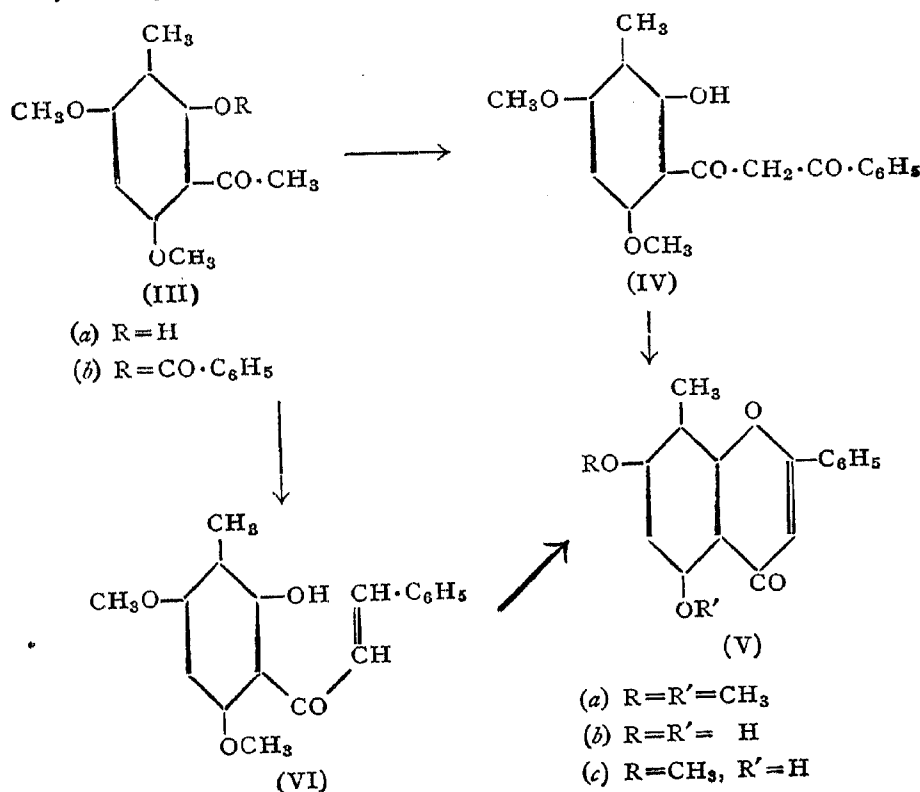
The simplest compound of this type, *viz.*, 2-methyl-5:7-dihydroxy chromone (nor-eugenin) (I)¹² has now been studied first. A number of C-methyl derivatives of this substance were reported earlier¹² and were readily available for direct comparison. Its nuclear methylation has now been carried out using excess of methyl iodide and methanolic sodium methoxide and the product is obtained in about 12% yield. It gives a blue colour with alcoholic ferric chloride showing thereby that it is a C-methyl derivative. It melts at 161–62° and is found to be identical with an authentic sample of 2:6-dimethyl-5-hydroxy-7-methoxy chromone (eugenitin) (II *b*).¹² This result therefore establishes that in the nuclear methylation, the methyl group enters the 6-position of the chromone unit and this preparation also constitutes a new synthesis of eugenitin.



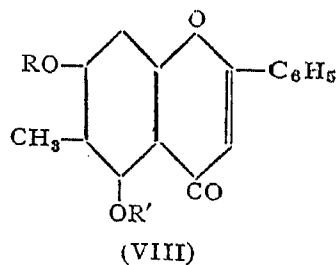
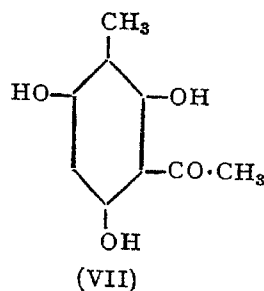
After submitting our preliminary communication on the nuclear methylation of benzo- γ -pyrones,¹ we have come across the note of Whalley¹⁶ in which he has recorded that eugenitin is obtained in an yield of 70% by long heating (12 hours) and by using a very large excess of methyl iodide. We have not been able to obtain this high yield under apparently the same conditions. Actually it is found that the best yield of the C-methyl derivative is obtained by heating the mixture for 4 hours and that longer heating decreases the yield of this product.

As already mentioned the flavone luteolin was subjected to nuclear methylation by Perkin and Horsfall.⁴ A more convenient representative of this group is chrysin and it has now been studied for its nuclear methylation. purposes of comparison authentic samples of 6-methyl chrysin and hyl chrysin were needed. For the preparation of 5:7-dimethoxy-

8-methyl flavone (V a) the method of Baker and Venkataraman^{17, 18} is adopted. The starting point is 2-hydroxy-3-methyl-4:6-dimethoxy acetophenone (III a)¹⁹ the benzoyl derivative (III b) of which gave the intermediate diketone (IV). This could be cyclised to the required flavone (V a). The same compound (V a) was originally obtained by Lindstedt and Misiorny¹⁵ by the oxidation of 2-hydroxy-3-methyl-4:6-dimethoxy chalcone (VI)²⁰ with selenium dioxide in amyl alcoholic solution. We have also used this method and found that the two products are identical. The demethylation of this substance has been carried out using anhydrous aluminium chloride in benzene solution. The absence of any isomerisation during this demethylation has been established by remethylation with excess of dimethyl sulphate and potassium carbonate in acetone solution whereby the dimethyl ether (V a) is again obtained. The demethylated product is therefore 8-methyl chrysin (V b). It melts at 255–56° and forms a diacetate (m.p. 182–83°). Partial methylation of (V b) with one mole of dimethyl sulphate and potassium carbonate in acetone solution gives rise to 5-hydroxy-7-methoxy-8-methyl flavone (V c) (m.p. 234–5°). It gives a greenish blue colour with ferric chloride and a bright yellow sodium salt with aqueous sodium hydroxide solution. The same compound is obtained when excess of methyl iodide is employed in the place of dimethyl sulphate thus proving that under these conditions, methyl iodide does not cause further nuclear methylation.



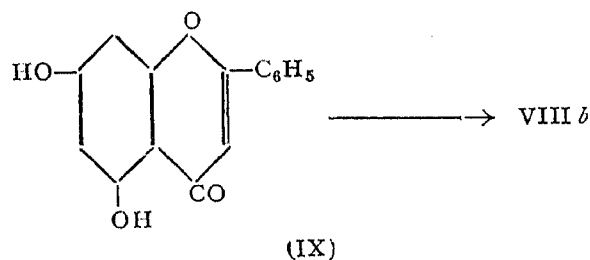
For the preparation of 6-methyl chrysin, Allan-Robinson benzoylation of C-methyl phloracetophenone (VII) seemed to be suitable. Similar method has been successfully employed for making eugenitol (II *a*) by vigorous acetylation¹²; the hydroxyl group para to the methyl group being more reactive and 6-C-methyl derivative alone seems to be produced. The benzoylation had been studied earlier by Furukawa.²¹ He however reported the formation of two products (m.p. 251–52° and 308–10°) and considered them to be 6 and 8-methyl derivatives of chrysin but did not assign any specific constitution individually to each of the products. It is well known that 3-benzoyl flavones are formed in this reaction²² and no special care seems to have been taken by Furukawa to remove the 3-acyl group. The crude mixture obtained from the reaction has now been subjected to further hydrolysis with 5% aqueous sodium carbonate as originally suggested by Rao, Rao and Seshadri.²³ The resulting mixture has been separated into two sharp melting fractions by crystallisation from alcohol. The more soluble fraction melts at 255–56° and is identical with 8-methyl chrysin (Vb) described above. The sparingly soluble fraction melts at 308–10° and it should therefore be the isomer, *viz.*, 6-methyl chrysin (VIII *a*). This is in agreement with the general observation that 6-C-methyl derivatives melt higher than the corresponding 8-C-methyl derivatives.⁷ Thus in the Allan-Robinson reaction, the behaviour of C-methyl phloracetophenone (VII) is markedly different from what has been met with in the chromone synthesis¹² and in methylation.¹⁹ In these two reactions, the hydroxyl para to the C-methyl group is found to be more reactive than the one present in the ortho position to it. In the flavone condensation both these hydroxyl groups are equally reactive and two products are obtained. An important intermediate in this vigorous acylation may be considered to be the diketone or ω -acyl ketone. The nature of the ω -acyl group would appear to play an important part in the subsequent ring closure.



- (a) R=R'=H
 (b) R=CH₃, R'=H
 (c) R=R'=CH₃

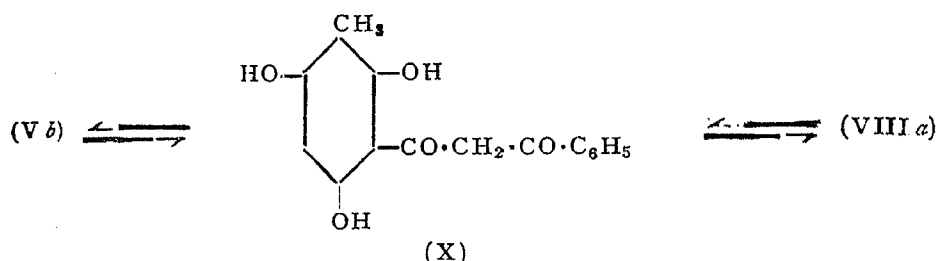
On methylation with one mole of dimethyl sulphate and potassium carbonate, 6-methyl chrysin (VIII *a*) yields its 7-methyl ether (VIII *b*). Further methylation has proved to be extremely difficult. By employing a very large excess of dimethyl sulphate in dry acetone solution and by refluxing the mixture for a number of days, this could be accomplished. The resulting dimethyl ether (VIII *c*) melts at 171–72°. The C-methyl derivatives of chrysin and their partial methyl ethers give a bright greenish blue colour with ferric chloride whereas chrysin and tectochrysin give only reddish pink colour. This is parallel to the behaviour of related chromone derivatives, *viz.*, eugenitol, eugenitin, isoeugenitol and isoeugenitin which give a blue ferric reaction whereas noreugenin and eugenin give only a pink ferric reaction (*cf.* Seshadri and Varadarajan⁷).

The nuclear methylation of chrysin (IX) has now been carried out under the same conditions as employed in the case of nor-eugenin. The product is obtained in an yield of 10% and is in every way identical with 5-hydroxy-6-methyl-7-methoxy flavone (VIII *b*), thus establishing that in this case also, the methyl group enters the 6-position. The identity has been confirmed by the preparation of the acetates.



The results of earlier work on ring isomerism in flavones and chromones brought about by the action of hydriodic acid have already been discussed in an earlier communication.¹² It has been established that 5:7:8-trihydroxy flavones and chromones undergo isomeric change into 5:6:7-trihydroxy compounds on treatment with this reagent. It has also been shown that when 2:6-dimethyl-5-hydroxy-7-methoxy chromone is treated with hydriodic acid, it gives rise to 2:8-dimethyl-5:7-dihydroxy chromone whereas 2:8-dimethyl-5:7-dihydroxy chromone does not suffer isomeric change on heating with this reagent.¹² In view of the mixture of products obtained in the Allan-Robinson condensation, the behaviour of C-methyl flavones towards this reagent has now been studied. When 5:7-dimethoxy-8-methyl flavone (V *a*) is treated with hydriodic acid, it yields a mixture of products which could be separated into 8-methyl chrysin (V *b*) and 6-methyl chrysin (VIII *a*) by fractional crystallisation. Part of the 8-methyl compound therefore undergoes change into the 6-methyl isomer. 5-Hydroxy-

6-methyl-7-methoxy flavone (VIII *b*) on similar treatment with hydriodic acid yields also a mixture from which both 6 and 8-methyl chrysin could be isolated. Roughly equal quantities are obtained in either of these demethylations. The behaviour of these methyl flavones is therefore markedly different from that of the hydroxy flavones and chromones or even the C-methyl chromones. As already described, even in the flavone ring closure using the Allan-Robinson condensation, both the isomeric methyl chrysin are obtained and hence in both these reactions the hydroxyl groups ortho and para to the methyl group seem to have equal reactivity. An equilibrium seems to exist between the two isomers, the intermediate being the open form, *i.e.*, the diketone (X). This result is rather novel and should be given full consideration in any theory dealing with this subject.



It should be mentioned here that other reagents also seem to bring about such isomeric change. Lindstedt and Misiorny¹⁵ reported that demethylation of 8-methyl chrysin dimethyl ether with pyridine hydrochloride (6 hours at 200°) yields a mixture from which a small amount of 6-methyl chrysin, produced by partial rearrangement, could be isolated.

In their study of the heart wood components of *Pinus strobus*, after the removal of the two flavanones strobo-pinin and crypto-strobin, Lindstedt and Misiorny¹⁵ isolated from the crude residues a yellow substance which was insoluble in ether (m.p. 285–88°) and had the properties of a flavone with the molecular formula C₁₆H₁₂O₄. Only 12 milligrams of the substance were available and using this quantity a careful study was made. The acetate was prepared and was found to melt at 190–91° and alkali fission was carried out and C-methyl phloroglucinol identified as one of the products. It was thus clear that the substance was a C-methyl chrysin with the methyl group in the 6 or in the 8 position.

They also carried out the condensation of C-methyl phloracetophenone with sodium benzoate and benzoic anhydride. From the crude yellowish brown product, they separated out an ether-soluble fraction which after recrystallisation from ethanol yielded yellow crystals melting at 284–88°. Its acetate melted at 190–91° alone or when mixed with strobochrysin acetate.

This fraction was considered to be the same as strobochrysin and hence used as synthetic strobochrysin. When it was fully methylated using excess of dimethyl sulphate and potassium carbonate, a small amount of colourless crystals, m.p. 170–71°, was obtained. It gave no colour with ferric chloride and yellow colour with magnesium and hydrochloric acid. This was different in its melting point and colour reactions from 5:7-dimethoxy-8-methyl flavone, m.p. 230–31° which as already mentioned was obtained by selenium dioxide oxidation of 2-hydroxy-3-methyl-4:6-dimethoxy chalcone. Hence it was concluded that strobochrysin was 6-C-methyl chrysin (VIII *a*). Though the data reported in the present paper provide support to their constitution of strobochrysin the melting points recorded by them for the natural flavone (284–86°) and its acetate (190–91°) appear to be too low as compared with synthetic 6-methyl chrysin (308–10°) and its acetate (198–200°) indicating that their samples were not probably quite pure.

EXPERIMENTAL

2-Benzoyloxy-3-methyl-4:6-dimethoxy acetophenone (III b)

A solution of 2-hydroxy-3-methyl-4:6-dimethoxy acetophenone (III *a*) (2 g.) in dry pyridine (15 c.c.) was treated with excess of benzoyl chloride (3 c.c.) and the mixture gently refluxed on a wire-gauze for an hour. The mixture assumed a dark red colour after about 30 minutes. It was then cooled and poured into ice-cold dilute hydrochloric acid and stirred vigorously when the reddish brown oily mass that initially separated gradually solidified. The solid product was collected and washed with a small quantity of a mixture of ether and petroleum ether when most of the coloured impurities and the excess of benzoyl chloride were removed. The resulting light pink coloured solid was washed with aqueous sodium bicarbonate solution (5%). It crystallised from alcohol as colourless, stout rhombohedral prisms melting at 132–33°. Yield 2.5 g. (Found: C, 68.4; H, 5.6; C₁₈H₁₁O₅ requires C, 68.8; H, 5.7%).

2-Hydroxy-3-methyl-4:6-dimethoxy dibenzoyl methane (IV)

A mixture of the benzoate (III *b*) (1 g.), powdered sodamide (5 g.) and toluene (15 c.c.) was heated in a boiling water-bath for 6 hours after which the yellow sodium salts were filtered and washed thoroughly with hot dry benzene. When dry, the sodium salts were decomposed by throwing in small lots to ice-water. The yellow solution thus obtained was filtered to remove a small amount of suspended impurities and the clear yellow filtrate was saturated with carbon dioxide. The diketone separated out as a yellow sticky solid and was filtered off. It was crystallised first from a mixture

of benzene and petroleum ether and then from alcohol. It separated as pale lemon yellow thin rectangular plates melting at 127–28°. The compound gives a green colour with ferric chloride in alcoholic solution. Yield 0.5 g. (Found: C, 69.0; H, 5.4; $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%.) The same compound was obtained in poor yield by employing potassium carbonate in place of sodamide in the above reaction.

5:7-Dimethoxy-8-methyl flavone (Va)

The above diketone (0.4 g.) was dissolved in glacial acetic acid (10 c.c.) and heated with fused sodium acetate (1 g.) in a boiling water-bath for 2 hours. It was then cooled and diluted with ice-water when 5:7-dimethoxy-8-methyl flavone separated out as a yellow precipitate. This was collected and crystallised from alcohol when it came out as pale yellow long narrow rectangular prisms melting at 231–32° alone or when mixed with a sample obtained by the method of Lindstedt and Misiorny.¹⁵ (Found: C, 73.3; H, 5.1; $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%.)

5:7-Dihydroxy-8-methyl flavone (Vb)

A solution of 5:7-dimethoxy-8-methyl flavone (0.6 g.) in dry benzene (35 c.c.) was treated with powdered anhydrous aluminium chloride (2 g.) when the aluminium chloride complex separated out at once. The mixture was heated under reflux in a water-bath for 2 hours and then benzene was distilled off. The residual brownish complex was decomposed with ice and hydrochloric acid and the resulting deep yellow precipitate was collected. It was crystallised twice from ethyl acetate when it came out as deep yellow long rectangular prisms with tapered edges melting at 255–56°. It forms a deep yellow sodium salt with aqueous sodium hydroxide solution and gives a greenish brown ferric reaction in alcoholic solution. Yield 0.45 g. (Found: C, 71.9; H, 4.9; $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%.)

The acetate prepared by the acetic anhydride—pyridine method crystallised from alcohol as colourless clusters of rectangular rods melting at 182–83°. (Found: C, 68.1; H, 4.7; $C_{20}H_{16}O_6$ requires C, 68.2; H, 4.6%.)

Remethylation to (Va)

A solution of 5:7-dihydroxy-8-methyl flavone (0.5 g.), as obtained above, was dissolved in dry acetone (100 c.c.) and treated with dimethyl sulphate (1 c.c.) and ignited potassium carbonate (5 g.) and the mixture refluxed in a water-bath for 30 hours. The solvent was then evaporated and water was added to the residue to dissolve the potassium salts. The mixture was left at room temperature for 2 days to decompose the excess

of demethyl sulphate. The product was then filtered and crystallised from alcohol when it was obtained as pale yellow rectangular prisms melting at 230–31° alone or when mixed with a sample of (V a) described earlier.

5-Hydroxy-7-methoxy-8-methyl flavone (V c)

To a solution of 5:7-dihydroxy-8-methyl flavone (0.7 g.) in dry acetone (50 c.c.) containing dimethyl sulphate (0.3 c.c., 1.1 mole) was added ignited potassium carbonate (3 g.) and the mixture was refluxed in a water-bath for 4 hours. The solvent was then evaporated and water was added to the residue to dissolve the inorganic salts when a pale yellowish product separated. This was collected and crystallised from a mixture of chloroform and alcohol when it came out as yellow long thin rectangular plates and rods melting at 234–35°. Lindstedt and Misiorny¹⁵ gave the melting point of this compound as 230–31°. It was sparingly soluble in alcohol, acetone and ethyl acetate but easily soluble in chloroform and benzene. It gave a greenish blue colour with ferric chloride in alcoholic solution and was sparingly soluble in aqueous sodium hydroxide solution. (Found: C, 72.4; H, 5.2; C₁₇H₁₄O₄ requires C, 72.4; H, 5.0%.)

The same compound was obtained by using an excess of methyl iodide in place of dimethyl sulphate in the above methylation.

The acetate of the above compound was prepared by the acetic anhydride-pyridine method and was crystallised from ethyl acetate when it came out as colourless short rectangular prisms melting at 208–9°. (Found: C 70.8; H, 5.0; C₁₉H₁₆O₅ requires C, 70.4; H, 4.9%.)

Allan-Robinson condensation with 3-methyl phloracetophenone

An intimate mixture of C-methyl phloracetophenone (5.0 g.), benzoic anhydride (32 g.) and dry sodium benzoate (6 g.) was heated under reduced pressure at 180–85° for 5 hours. The product was refluxed with alcohol (160 c.c.) for 20 minutes and to the clear solution thus obtained was added a solution of potassium hydroxide (24 g.) in water (25 c.c.) followed by some more alcohol (50 c.c.). The mixture was refluxed for 20 minutes and then the alcohol was distilled off under reduced pressure. Water (500 c.c.) was added to the residue and the solution was filtered and saturated with carbon dioxide. The yellow precipitate was collected, washed and pressed as dry as possible. It was then suspended in aqueous sodium carbonate solution (200 c.c., 5%) and heated under reflux for 2 hours. The mixture was then cooled and filtered to remove a small amount of undissolved matter. The clear filtrate was cooled in an ice-bath and acidified with ice-cold hydrochloric acid. The resulting yellow precipitate was filtered and subjected to

fractional crystallisation from alcohol. The more soluble fraction separated as deep yellow long narrow rectangular prisms with tapered edges melting at 255–56° and a mixed melting point with an authentic sample of 5:7-dihydroxy-8-methyl flavone (V *b*) was not depressed. Yield 1.6 g. Furukawa²¹ gave the melting point of this compound as 251–52°. The acetate melted at 182–83° and a mixed melting point with a sample of 5:7-diacetoxy-8-methyl flavone, described earlier, was not depressed. Furukawa²¹ gave the melting point of this acetate as 180.5–181°.

The sparingly soluble fraction was obtained in the form of pale yellow tiny rectangular rods melting at 308–10° and this was 5:7-dihydroxy-6-methyl flavone (VIII *a*). Furukawa²¹ gave the same m.p. Yield 1.4 g. (Found: C, 71.6; H, 4.5; C₁₆H₁₂O₄ requires C, 71.6; H, 4.5%.)

The acetate of 5:7-dihydroxy-6-methyl flavone was prepared by the acetic anhydride-pyridine method and when crystallised from alcohol it was obtained as colourless long silky needles melting at 198–200°. Lindstedt and Misiorny¹⁵ gave the m.p. as 190–91° and Furukawa gives m.p. 196.5–197.5°.

5-Hydroxy-6-methyl-7-methoxy flavone (VIII b)

A solution of 5:7-dihydroxy-6-methyl flavone (0.7 g.) in dry acetone (200 c.c.) was refluxed with dimethyl sulphate (0.3 c.c.) and anhydrous potassium carbonate (2 g.) for 6 hours. Acetone was then distilled off and water was added to the residue. The undissolved methyl ether was collected, washed with water and crystallised from a mixture of chloroform and alcohol when it separated as very pale yellow long thin needles melting at 171–72°. It gave a green colour with ferric chloride in alcoholic solution. (Found: C, 72.4; H, 5.3; C₁₇H₁₄O₄ requires C, 72.4; H, 5.0%.) The same product was obtained when excess of methyl iodide was used in the above methylation in place of dimethyl sulphate.

The acetate of the above partial methyl ether was prepared by heating with acetic anhydride and a few drops of pyridine. When crystallised from alcohol twice and then from ethyl acetate, it separated as colourless short rectangular prisms melting at 187–89°. (Found: C, 70.6; H, 4.8; C₁₉H₁₆O₅ requires C, 70.4; H, 4.9%.)

5:7-Dimethoxy-6-methyl flavone (VIII c)

A suspension of 5:7-dihydroxy-6-methyl flavone (0.5 g.) in acetone (75 c.c.) was treated with dimethyl sulphate (4 c.c., excess) and ignited potassium carbonate (10 g.). The mixture was heated under reflux for about 50 hours, more dimethyl sulphate (2 c.c.) and potassium carbonate (4 g.)

being added after 30 hours. The solvent was then evaporated and water was added to the residue to dissolve the potassium salts, when a greenish brown pasty product separated. This was filtered after 24 hours and washed with a little dilute alcohol when coloured impurities were removed and a pale greenish yellow residue was left behind. Crystallisation from dilute alcohol (charcoal) yielded 5:7-dimethoxy-6-methyl flavone as pale yellow thin rectangular plates melting at 171–72°. Lindstedt and Misiorny¹⁵ gave the same m.p. The product did not give any colour with alcoholic ferric chloride. (Found: C, 72.6; H, 5.4; C₁₈H₁₆O₄ requires C, 73.0; H, 5.4%.)

Demethylation of 5:7-dimethoxy-8-methyl flavone (Va) with hydriodic acid

5:7-Dimethoxy-8-methyl flavone (1 g.) was dissolved in acetic anhydride (25 c.c.) and the cooled solution was treated cautiously with hydriodic acid (15 c.c., d. 1.7). The mixture was heated under reflux in an oil-bath at 140–45° for 2 hours, cooled and poured into ice-water containing some sodium sulphite when a dark coloured precipitate was obtained. This was collected after 2 hours. The product was macerated with a little warm alcohol and filtered again when all the dark impurities dissolved and a yellow residue (0.72 g.) was left behind. This was fractionally crystallised from alcohol when two products were obtained. The more soluble fraction on repeated crystallisation gave 5:7-dihydroxy-8-methyl flavone (Vb) melting at 255–56°. It was identical with an authentic specimen described earlier. Yield 0.3 g.

The sparingly soluble fraction was crystallised from a large volume of a mixture of ethyl acetate and alcohol when a pale yellow product melting at 308–10° was obtained. It was identical with an authentic specimen of 5:7-dihydroxy-6-methyl flavone (VIIIa) obtained as one of the products of Allan-Robinson condensation of C-methyl phloracetophenone as described earlier. Yield 0.25 g.

Demethylation of 5-hydroxy-6-methyl-7-methoxy flavone (VIIIb)

5-Hydroxy-6-methyl-7-methoxy flavone was demethylated with hydriodic acid under the same conditions as employed for 5:7-dimethoxy-8-methyl flavone above. Two products were isolated by fractional crystallisation from alcohol and were identified as 6-methyl chrysin (VIIIa) and 8-methyl chrysin (Vb) respectively.

Nuclear methylation of 2-methyl-5:7-dihydroxy chromone

2-Methyl-5:7-dihydroxy chromone (5 g.) was added to an ice-cold solution of sodium methoxide (from 8 g. of sodium) in absolute methanol (200 c.c.) and the resulting dark brown solution was treated with methyl iodide (24 c.c.) which was added all in one lot. The mixture was allowed to stand in the

cold for 15 minutes and then was gently refluxed in a water-bath for 3 hours. Most of the methanol was then distilled off under reduced pressure and the resulting brownish pasty mass was treated with cold water (100 c.c.). The suspension thus obtained was extracted repeatedly with ether. The ether extract was washed once with aqueous sodium hydroxide solution (10%) and then with water. On evaporation of ether, a crystalline solid was obtained which was recrystallised twice from alcohol and then once from ethyl acetate when 2:6-dimethyl-5-hydroxy-7-methoxy chromone separated as colourless thick prisms melting at 161–62° alone or when mixed with an authentic sample of eugenitin.¹² Yield 0.6 g. It gave a blue colour with alcoholic ferric chloride.

The acetate crystallised from a mixture of ethyl acetate and petroleum ether as thin rectangular plates melting at 176–77° undepressed by admixture with an authentic sample of eugenitin acetate.¹²

Nuclear methylation of chrysin (IX)

To a cold solution of sodium methoxide (from 7 g. of sodium) in absolute methanol (200 c.c.) was added 5:7-dihydroxy flavone (5 g.) in a finely powdered form and the resulting dark brown solution was treated with methyl iodide (20 c.c.) added all at once. The mixture was gently heated under reflux in a water-bath for 3 hours. Methanol was then removed under reduced pressure and the residual solid was suspended in water (100 c.c.). The mixture was repeatedly extracted with ether containing a small amount of chloroform. The extract was washed once with water, dried (sodium sulphate) and evaporated when a crystalline solid was obtained. This, when crystallised twice from a large volume of alcohol, yielded 5-hydroxy-6-methyl-7-methoxy flavone as pale yellow long thin needles melting at 171–72° alone or when mixed with an authentic sample of the substance described earlier. Yield 0.5 g.

The acetate crystallised from alcohol as colourless rectangular prisms melting at 187–89° alone or on admixture with an authentic sample of 5-acetoxy-6-methyl-7-methoxy flavone described earlier.

SUMMARY

Nuclear methylation of nor-eugenin (2-methyl-5:7-dihydroxy chromone) and chrysin has been carried out. It takes place in the 6-position. The former yields eugenitin (2:6-dimethyl-5-hydroxy-7-methoxy chromone) and the later yields 6-methyl tectochrysin. For the synthesis of reference compounds several methods have been examined and authentic samples of 6 and 8-methyl chrysin and their derivatives obtained. It is found that Allan-

Robinson condensation of 3-methyl phloracetophenone and benzoic anhydride yields a mixture of 6 and 8-C-methyl chrysin. Further, hydroiodic acid demethylation of the methyl ethers of each of these C-methyl chrysin again gives rise to a mixture of these C-methyl chrysin. In both these reactions the yields are almost equal. Aluminium chloride in boiling benzene solution does not produce isomeric change. The results of present work support the structure of strobochrysin proposed by Lindstedt and Misiorny.¹⁵

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