EXPERIMENTS ON THE SYNTHESIS OF COUMARYL STYRENES

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Several hydroxy and methoxy stilbenes are found to occur in nature, particularly in the heartwoods of plants. Further, some stilbene derivatives have recently come into prominence for their marked physiological properties; *e.g.*, stilbamidine is a well-known drug for the treatment of trypanosome infections and stilbœstrol is a successful synthetic œstrogen. Coumaryl styrenes resemble stilbene derivatives in view of the aromatic characteristics exhibited by the pyrone ring. Certain coumaryl styrene derivatives were needed in connection with an investigation on insecticides and fish poisons. Besides these, there was another interest in the preparation of coumaryl styrenes. In the course of her work on the constitution of carthamidin, Kuroda[1] was able to isolate besides the normal flavanone tetra-acetate (α) (I), and the chalkone penta-acetate (β) (II), a third acetate by high temperature acetylation, which she designated γ-acetate and formulated as a coumaryl styrene (III).

This was based on the assumption that the chalkone structure of the β-acetate underwent further transformation analogous to Perkin's reaction producing a coumarin structure. But, no other evidence was provided in support, except analysis for carbon and hydrogen.

(I)   (II)

(III)
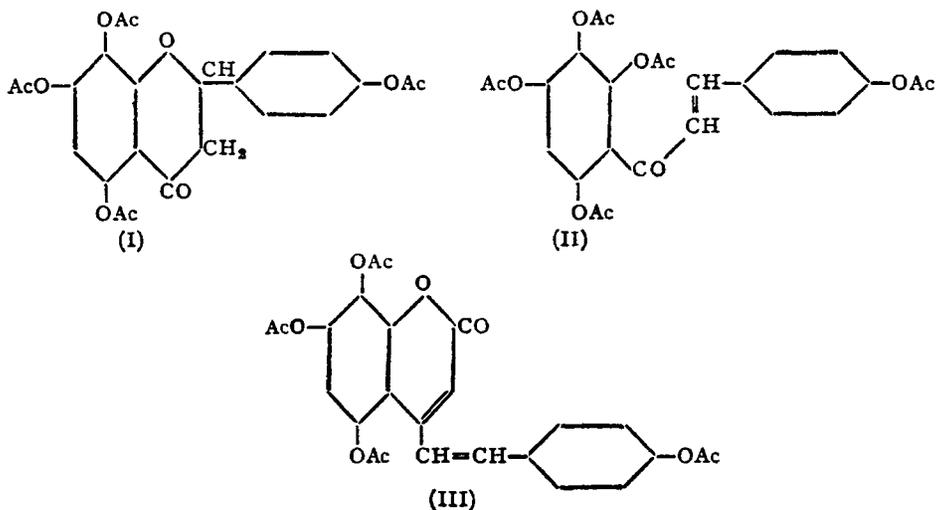
For the preparation of coumaryl styrenes, Dey and Row[2] utilised the reactivity of the methylene group in coumarin-4-acetic acids such as (IV) and condensed them with aromatic aldehydes in the presence of piperidine, whereby coumaryl styrenes were obtained.

IV, R=CH$_3$
VII, R=OH

V, R=CO$_2$H
VI, R=H
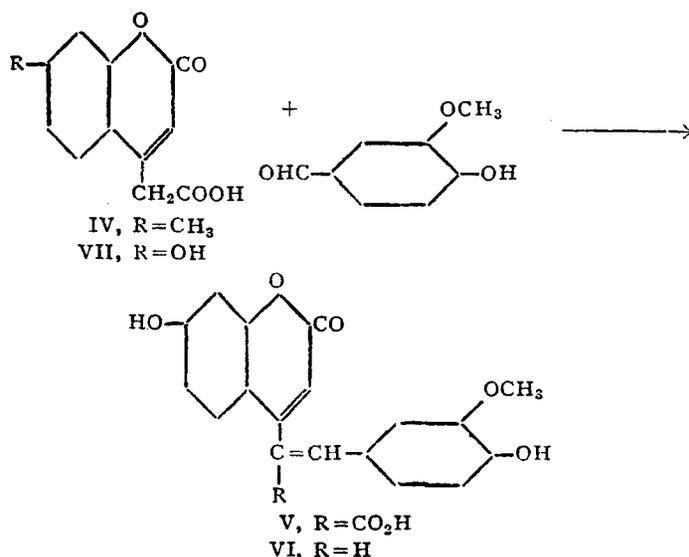
To serve our purpose, the following coumarin-acetic acids were prepared adopting the general method of Dey and Row[2] which consists in condensing the respective phenols with acetone dicarboxylic acid: 7-Hydroxy coumarin-4-acetic acid (VII), 5:7-dihydroxy coumarin-4-acetic acid (VIII), 5:7-dimethoxy coumarin-4-acetic acid (IX), 5:7-dimethoxy-6-hydroxy coumarin-4-acetic acid (X), 5:6:7-trimethoxy coumarin-4-acetic acid (XI) and 5:8-dimethoxy-7-hydroxy coumarin-4-acetic acid (XII).

VIII, R=H
IX, R=CH$_3$

X, R=H
XI, R=CH$_3$

XII
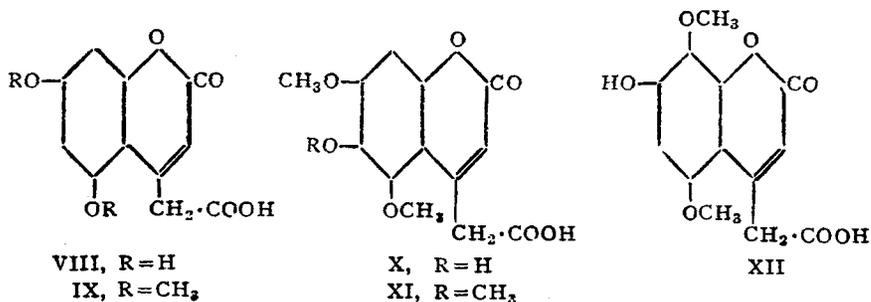
Compounds (VII) and (VIII) are already known.[3] For the preparation of 5:7-dimethoxy-coumarin-4-acetic acid (IX), the methylation of the corresponding dihydroxy compound does not lead to good results. The difficulty seems to be related in some way with the presence of the 5-hydroxyl group.

The direct condensation of O-dimethyl phloroglucinol with acetone dicarboxylic acid works smoothly and gives much better yields. On the other hand, 6-hydroxy-5 : 7-dimethoxy-coumarin-4-acetic acid (X) obtained from 2 : 6-dimethoxy quinol undergoes methylation quite satisfactorily, and the trimethoxy coumarin acetic acid (XI) could be obtained in good yield. For the preparation of 5 : 8-dimethoxy-7-hydroxy coumarin-4-acetic acid (XII), it has not been found to be necessary to use 2 : 5-dimethoxy resorcinol. Its dibenzyl ether, an earlier intermediate in its preparation, could be directly employed. If the temperature of the reaction mixture, during the condensation, is kept between 10° and 12° and not allowed to go too low, the coumarin condensation is accompanied by debenzylation giving the required hydroxycoumarin acetic acid.

Of these, 7-hydroxycoumarin-4-acetic acid undergoes condensation with benzaldehyde and vanillin, giving rise to the corresponding coumaryl styrenes. There is considerable decomposition of the acid during this reaction giving rise to the simultaneous formation of 4-methyl umbelliferone which has to be removed by repeated fractional crystallisation. The products have all the properties of coumaryl styrenes. Particularly characteristic is the colour reaction in alkaline solutions exhibited by the 4'-hydroxy compound. The other coumarin acetic acids do not undergo condensation with aromatic aldehydes, but they suffer decomposition yielding the corresponding 4-methyl coumarins. To avoid this, the Knœvenagel condensation has been tried at temperatures lower than 120°; but the components do not react. Protection of the carboxylic group by esterification also leads to inactivity. Hence, this method of preparing coumaryl styrenes is of limited applicability and other alternative methods are being explored.

Meanwhile, some experimental work has been carried out to test the validity of the suggestion of Kuroda[1] regarding the constitution of γ-acetates, using simpler and more easily available flavanones and chalkones. 7-Hydroxy flavanone and 2 : 4-dihydroxy chalkone have been subjected to acetylation under various conditions. With acetic anhydride and sodium acetate at 100° both yield as the main product 7-acetoxy flavanone (m.p. 104°). The diacetate of the chalkone could be obtained as a liquid by treatment of the dihydroxy chalkone with acetyl chloride and pyridine. Both these acetates do not give any colour with ferric chloride.

The above 7-hydroxy flavanone and dihydroxy chalkone were heated with sodium acetate and acetic anhydride at 180° using conditions approximating as closely as possible to Perkin's reaction, in order to get exclusively the γ-acetate. Both yield as the main product a substance melting at 118°.

Its composition agrees with the expectations for a coumaryl styrene structure, but its properties do not agree with 7-acetoxy-coumaryl styrene. Not only are the melting points widely different, but on deacetylation with alcoholic hydrochloric acid, the γ-acetate yields a colourless product which melts with decomposition at about 128°, does not give colour with ferric chloride and dissolves in sodium hydroxide giving a colourless solution. 7-Hydroxy coumaryl styrene melts much higher; it is yellow and gives an orange coloured solution with alkali.

2-Hydroxy-4-methoxy chalkone, when acetylated at 180° with sodium acetate and acetic anhydride yields a product, which should be considered to be the chalkone acetate (β-acetate). This behaviour is markedly different from that of the hydroxy compound. The nature of the product is clear, not only from its composition, but also from its hydrolysis giving rise to the original chalkone. This would indicate that a γ-acetate is not invariably formed when high temperatures are employed for the acetylation.

As a more suitable example for verifying Kuroda's suggestion, the acetylation of naringenin has been examined next. In this case, the α- and β-acetates have been prepared earlier by Asahina.[1] The first was obtained by him by boiling naringenin with acetic anhydride and a drop of concentrated sulphuric acid and its melting point was recorded as 55–56°. A more convenient method[5] adopted in this laboratory is to use acetyl chloride and pyridine in the cold and the melting point has been found to be higher (80°). The β-acetate was obtained by Asahina *et al.* by heating naringenin with acetic anhydride and sodium acetate. Its melting point has been recorded as 133–36°. A third acetate has now been obtained by acetylation of naringenin with acetic anhydride and sodium acetate at 180°. It is very sparingly soluble in solvents and melts at 193°. These and its composition agree with the expectations for a γ-acetate. For reasons already explained, the required styrene derivative (5 : 7 : 4′-triacetoxy coumaryl styrene) could not be prepared for comparison. But the reactions of the γ-acetate show definitely that it is not a coumaryl styrene derivative. Deacetylation with alcoholic hydrochloric acid yields a product which is colourless, does not give ferric chloride reaction and forms a pale yellow solution in alkali. On the other hand, coumaryl styrenes having hydroxyl groups, particularly one in the 4′-position, are yellow in colour and give bright colours with dilute alkali.

From the results described in the above paragraphs, it should be concluded that the γ-acetates are not coumaryl styrene derivatives and their mode of formation cannot be as suggested by Kuroda. Among other possibilities, they could not have the simple chalkone or flavanone skeletons because the product of deacetylation from naringenin γ-acetate does not

give any ferric chloride colour. This should be observed if it were a 2-hydroxy chalkone or a 5-hydroxy flavanone.

EXPERIMENTAL

7-Hydroxy coumaryl styrene

7-Hydroxy coumarin-4-acetic acid[3] (6 g.) was mixed with benzaldehyde (3·5 g.), piperidine (10 drops) was added and the mixture heated under air reflux at 130–35° in an oil-bath for 4 hours. The resulting dark red sticky mass was extracted with hot alcohol; the alcoholic solution on standing for a week deposited an yellow crystalline mass of the styrene which was filtered off and recrystallised from methyl alcohol, when fine needles were obtained. The yield was 1·5 g. The styrene melted at 213–14°, dissolved readily in aqueous sodium carbonate, and gave no colour with ferric chloride in alcohol. It dissolved in 10% sodium hydroxide to form an orange solution which on standing or when warmed in a water-bath at 70° for a minute became colourless and on acidification gave the original substance (Found: C, 77·7; H, 5·1. $C_{17}H_{12}O_3$ requires C, 77·3; H, 5·4%).

7-Acetoxy-coumaryl styrene

7-Hydroxy coumaryl styrene (0·5 g.) was heated with acetic anhydride (5 c.c.) and fused sodium acetate (1 g.) in an oil-bath at 100° for an hour. The product crystallised from dilute alcohol as colourless needles (0·4 g.) melting at 198° (Found: C, 74·6; H, 4·7. $C_{19}H_{14}O_4$ requires C, 74·5; H, 4·5%).

7-Methoxy-coumaryl styrene

7-Hydroxy coumaryl styrene (0·5 g.) was dissolved in dry acetone (20 c.c.), anhydrous potassium carbonate (3 g.) and dimethyl sulphate (0·3 c.c.) were added and the mixture refluxed for 6 hours. The acetone solution was filtered and evaporated whereby a colourless semi-solid was obtained. It solidified in contact with alcohol and on crystallisation from alcohol gave colourless needles having a pale yellow tinge and melting at 149–51° (Found: C, 78·2; H, 5·4. $C_{18}H_{14}O_3$ requires C, 77·7; H. 5·0%).

7 : 4'-Dihydroxy-3'-methoxy-coumaryl styrene (VI)

7-Hydroxy coumarin-4-acetic acid (4·8 g.) and vanillin (3·3 g.) were mixed with piperidine (10 drops) and the mixture refluxed in an oil-bath, the temperature of which was gradually raised to 130–35°. Raising the temperature rapidly causes profuse decomposition of the coumarin-4-acetic acid into 4-methyl umbelliferone. After 3·5 hours the deep red reaction mixture was allowed to cool, when an yellow viscous product was obtained. It was

macerated with a small quantity of alcohol and left in the refrigerator when it solidified to an yellow amorphous solid. It was subjected to repeated fractional crystallisation from alcohol. The more sparingly soluble portion was collected and crystallised from absolute methyl alcohol, when yellow rectangular plates melting at 218° were obtained. It dissolved in aqueous sodium bicarbonate with difficulty but was readily soluble in aqueous sodium carbonate. It formed a bright red solution in aqueous sodium hydroxide, but the solution became colourless on standing or when warmed in a water-bath for a short time (Found: C, 67·4; H, 5·0. $C_{18}H_{14}O_5$, $\frac{1}{2}H_2O$ requires C, 67·7; H, 4·7%).

5: 7-*Dimethoxy-coumarin*-4-*acetic acid* (IX)

(i) 5: 7-Dihydroxycoumarin-4-acetic acid[3] (3·5 g.) obtained from phloroglucinol and acetone dicarboxylic acid was methylated by boiling with dimethyl sulphate (5·5 c.c. excess) and potassium carbonate (30 g.) in dry acetone (120 c.c.) for 6 hours. When the mixture was filtered and the filtrate evaporated 5: 7-dimethoxy-coumarin-4-acetic acid methyl ester separated out as a pale pink amorphous solid. On re-crystallisation, a colourless product melting between 120° and 130° was obtained. It was found to be mixed with 5: 7-dimethoxy-4-methyl coumarin from which it could not be separated. However, after boiling with 10% sodium carbonate for an hour (hydrolysis), filtration and acidification of the carbonate solution, 5: 7-dimethoxy coumarin-4-acetic acid was obtained. It was purified by dissolution in aqueous sodium carbonate and reprecipitation with hydrochloric acid. It then melted with decomposition at 177°.

(ii) O-Dimethyl phloroglucinol[6] (12·5 g.) was condensed in the usual way with acetone dicarboxylic acid from 24 g. of citric acid, keeping the temperature of the reaction strictly below 5°. The product (8 g.) was quite pure and first melted at 205° with decomposition, but on boiling with alcohol in which it was very sparingly soluble, it got converted into the stable form which melted at 177° (decomp.) (Found: C, 59·2; H, 5·0. $C_{13}H_{12}O_6$ requires C, 59·1; H, 5·0%).

5: 7-*Dimethoxy*-6-*hydroxy coumarin*-4-*acetic acid* (X)

2: 6-Dimethoxy quinol[7] (8 g.) was condensed in the usual way[3] with acetone dicarboxylic acid (from 11·5 g. of citric acid) when 5: 7-dimethoxy-6-hydroxy coumarin 4-acetic acid (6·2 g.) melting at 234° was obtained. The acid dissolved in aqueous sodium carbonate to give an yellow solution with green fluorescence. On recrystallisation from alcohol, extremely long silky needles of the stable form of the acid melting at 200° (decomp.) were obtained (Found: C, 56·0; H, 4·6. $C_{13}H_{12}O_7$ requires C, 55·7; H, 5·0%).

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5 : 6 : 7-*Trimethoxy-coumarin-4-acetic acid methyl ester*

5 : 7-Dimethoxy-6-hydroxycoumarin-4-acetic acid (2·1 g.) was suspended in dry acetone (250 c.c.), anhydrous potassium carbonate (20 g.) and dimethyl sulphate (4 c.c.) were added and the mixture refluxed for 30 hours. The potassium salts were filtered off and the acetone solution concentrated. The solid left behind (1·8 g.) was crystallised from acetone when colourless needles melting at 140–41° were obtained. It was insoluble in aqueous sodium carbonate as well as in sodium hydroxide, sparingly soluble in alcohol and readily soluble in acetone (Found: C, 58·5; H, 4·5. $C_{15}H_{16}O_7$ requires C, 58·4; H, 4·5%).

5 : 6 : 7-*Trimethoxy-coumarin-4-acetic acid* (XI)

The above ester (1·8 g.) was dissolved in the minimum quantity of alcohol, 10% sodium carbonate solution (40 c.c.) was added to it and then heated on a steam-bath. After half an hour the ester was found to remain unchanged and hence 10% sodium hydroxide solution (20 c.c.) was added and the heating continued for a further half hour. The solution was then filtered from a small quantity of insoluble material and then cooled in ice and acidified. The crude product on crystallisation from alcohol gave long stout needles melting at 177° (decomp.). It dissolved in aqueous sodium carbonate without any fluorescence. It was readily soluble in alcohol and moderately soluble in acetone and chloroform (Found: C, 53·4; H, 4·7. $C_{14}H_{14}O_7$, H_2O requires C, 53·8; H, 5·1%).

5 : 8-*Dimethoxy-7-hydroxycoumarin-4-acetic acid* (XII)

2 : 6-Dibenzyloxy-1 : 4-dimethoxy benzene[8] (8 g.) was condensed with acetone dicarboxylic acid (from 5·5 g. of citric acid) keeping the temperature of the reaction between 10° and 12°. If the temperature was kept low, debenzylation did not take place effectively, the product became pasty and the yield was considerably reduced. The maximum yield realised was 3·5 g. The product on crystallisation from alcohol gave rectangular plates melting with decomposition at 198° (Found: C, 52·6; H, 4·6. $C_{13}H_{12}O_7$, H_2O requires C, 52·3; H, 4·7%).

γ-*Acetate of 7-hydroxy flavanone*

7-Hydroxy flavanone (0·6 g.) was suspended in acetic anhydride (9 c.c.), fused sodium acetate (0·7 g.) added and the mixture heated under air reflux in an oil-bath at 180° for 8 hours. It was allowed to cool and the excess of acetic anhydride decomposed in the usual way by adding crushed ice to the reaction mixture. After allowing it to stand overnight, the precipitated acetate was filtered off and repeatedly crystallised from a mixture of one

part of ethyl acetate and four parts of petroleum ether. The yield was very poor, 50 m.g., m.p. 118°. The product on recrystallisation from alcohol gave clusters of colourless needles melting at 119-20° (Found: C, 70·5; H, 6·0; loss on drying *in vacuo* at 110°, 5·9%. 7-Acetoxy coumaryl styrene formula: $C_{19}H_{14}O_4$, H_2O requires C, 70·3; H, 4·9; H_2O loss, 5·6%).

Acetylation of 2: 4-*dihydroxy chalkone at elevated temperatures*

2: 4-Dihydroxy chalkone (1 g.) was suspended in acetic anhydride (10 c.c.), fused sodium acetate (2 g.) added and the mixture refluxed for 8 hours at 180° in an oil-bath. The product was worked up in the usual way, and crystallised from a mixture of ethyl acetate and petroleum ether. It melted at the same temperature as the γ-acetate of 7-hydroxy flavanone (118°–19°) and the mixed m.p. was undepressed. It gave no colour with ferric chloride in alcohol solution.

Acetylation of 2: 4-*dihydroxy chalkone at lower temperatures*

(i) 7-*Acetoxy flavanone.*—2: 4-Dihydroxy chalkone (0·5 g.), fused sodium acetate (1 g.) and acetic anhydride (5 c.c.) were mixed together and heated under air reflux at 100-10° in an oil-bath for 2 hours. The product when worked up in the usual way, yielded a colourless substance having a pale yellow tinge and melting at 96-98°. The yield was quantitative. When crystallised from alcohol glistening long needles melting at 104-05° were obtained. The substance was found to be identical with 7-acetoxy flavanone (see Ellison,[9] m.p. 98°).

(ii) *Chalkone diacetate.*—2: 4-Dihydroxy chalkone, acetic anhydride and fused sodium acetate were mixed in the same proportions as above and heated at 125-30° in an oil-bath for 5 hours. After cooling, acetic anhydride was removed under reduced pressure, the acetate taken up in ethyl acetate and petroleum ether was added until turbidity appeared. It was allowed to stand for a short time and then filtered and concentrated. The acetate was obtained as a viscous oil and it gave no colour with ferric chloride. In contact with water, it was found to undergo hydrolysis giving positive colour test with alcoholic ferric chloride.

(iii) 2: 4-Dihydroxy chalkone (1 g.) was acetylated in the cold, with acetyl chloride (0·72 c.c.) and pyridine (7 c.c.). The resulting product was taken up in ethyl acetate and the ethyl acetate solution washed repeatedly with ice-cold 1% hydrochloric acid to remove the pyridine and once with ice-cold sodium bicarbonate solution. It was again washed with cold water, the solution dried over sodium sulphate and the solvent finally distilled off.

The resulting oily product did not solidify even on keeping in the refrigerator for a long time.

Acetylation of 2-hydroxy-4-methoxy chalkone: 2-Acetoxy-4-methoxy chalkone

2-Hydroxy-4-methoxy chalkone (1 g.) was heated with acetic anhydride (10 c.c.) and fused sodium acetate (2 g.) at 180° in an oil-bath for 8 hours. It was allowed to cool, and crushed ice was added to the reaction mixture and the precipitated sticky mass of the acetate was purified by repeated crystallisation from ethyl acetate and petroleum ether mixture, when colourless rectangular prisms (150 mg.) melting at 66–68° were obtained (Found: C, 73·6; H, 5·9; $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). When deacetylated with aqueous alcoholic hydrochloric acid it yielded the original chalkone.

γ-Acetate of naringenin

Naringenin (1 g.) was suspended in acetic anhydride (10 c.c.), fused sodium acetate (2 g.) added and the mixture heated under air reflux in an oil-bath at 180° for 8 hours. After cooling, the mixture was treated with crushed ice and allowed to stand in order to decompose the excess of acetic anhydride. The precipitated solid was crystallised from a large volume of alcohol when colourless glistening needles were obtained; m.p. 192–93°. Yield, 0·2 g. (Found: C, 64·9; H, 4·6. Calculated for 5:7:4'-triacetoxy coumaryl styrene formula: $C_{23}H_{18}O_8$. C, 65·4; H, 4·2%). The acetate was dissolved in hot alcohol and an equal volume of hot concentrated hydrochloric acid was added, when a lemon yellow colour was produced, which disappeared after two minutes. The mixture was boiled for 15 minutes (even a longer period, 2 hours gave the same result) in a water-bath, allowed to cool, diluted with water and extracted with ether. On removal of ether, a colourless product melting at 270–74° separated out. Recrystallisation from alcohol yielded colourless plates melting with decomposition at 274–5°. The substance was very soluble in alcohol and gave no colour with ferric chloride and dissolved in aqueous sodium hydroxide to form a pale yellow solution. It did not give a positive reaction with magnesium and hydrochloric acid for a flavanone (Found: C, 64·2; H, 4·9; loss on drying *in vacuo* at 120° for 10 hours, 5·6%. Coumaryl styrene structure, $C_{17}H_{12}O_5$, H_2O requires C, 64·9; H, 4·5. Water loss, 5·7%).

SUMMARY

A number of hydroxy and methoxy coumarin acetic acids have been prepared by the method of Dey and Row with a view to convert them into the corresponding coumaryl styrenes. Except the simplest of them, *i.e.*, 7-hydroxy coumarin-4-acetic acid, the others do not undergo the condensation with aromatic aldehydes, but suffer only decarboxylation. A study of

the γ-acetates obtained by the high temperature acetylation of simpler chalkones and flavanones indicates that they are not coumaryl styrene derivatives, though their compositions agree with such.

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