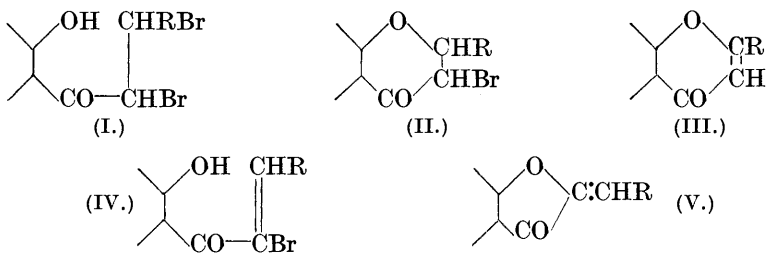


CCXXXII.—*Synthesis of Some Phenyl Styryl Ketones and Related Compounds.*

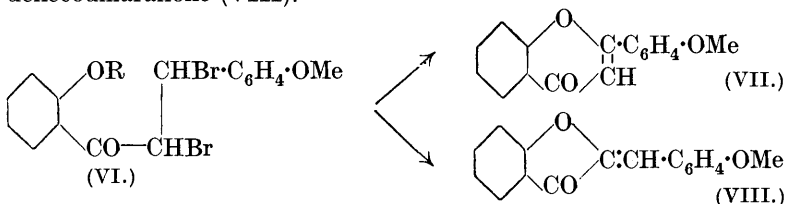
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ONE of the recognised methods for the synthesis of flavones is the action of sodium or potassium hydroxide on the dibromides of *o*-acetoxy- or *o*-hydroxy-phenyl styryl ketones. The possibility of the formation in this way of 5 : 7 : 2' : 4'-tetrahydroxyflavone was therefore investigated. The structure of this flavone was attributed by Dunstan and Henry (*Phil. Trans.*, 1901, **194**, 515) to lotoflavin, the yellow colouring matter of *Lotus arabicus*, but the recent synthesis of the flavone by Robinson and Venkataraman (this vol., p. 61; compare Cullinane, Algar, and Ryan, *Proc. Roy. Dublin Soc.*, 1928, **19**, 77) throws considerable doubt on this view. It frequently happens, however, that, instead of flavones, the isomeric benzylidenecoumaranones are produced in reactions of this kind. Kostanecki and Tambor (*Ber.*, 1899, **32**, 2263) consider that the

ease of formation of a 5- or a 6-membered ring in such cases depends upon the stability of the acetyl group of the *o*-acetoxychalkone dibromide. If the acetate is easily hydrolysed, the first product is a free hydroxychalkone dibromide (I), which by the further action of alkali loses hydrogen bromide, giving a flavone (III). If the acetate is hydrolysed with difficulty, hydrogen bromide is first eliminated in the chain, and the resulting α -bromohydroxychalkone (IV) yields a benzylidenecoumaranone (V).



However, this explanation was found to be unsatisfactory, for many *o*-hydroxychalkones are readily converted into benzylidenecoumaranones. Furthermore it was shown by Auwers and Anschütz (*Ber.*, 1921, 54, 1543) that it is possible in certain cases to obtain either a flavone or a coumaranone from the same *o*-hydroxy- or *o*-acetoxy-chalkone by altering the experimental conditions. For instance, 2-hydroxy- or 2-acetoxy-phenyl 4-methoxystyryl ketone dibromide (VI), on treatment with sodium hydroxide in the cold, gives 4'-methoxyflavone (VII), and in the heat 4'-methoxybenzylidenecoumaranone (VIII).

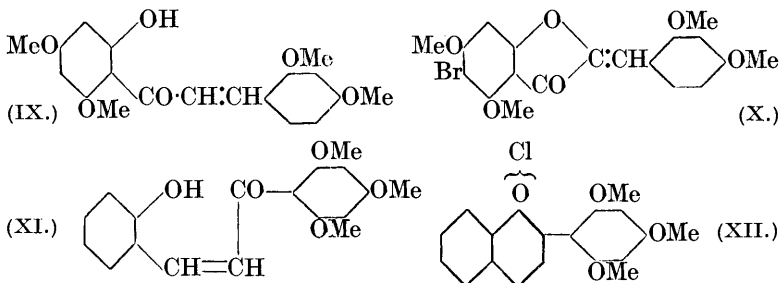


According to these authors, in the formation of flavone an intermediate substance (II) is produced, and actually such a compound has been isolated by them. In the formation of coumaranone the intermediate production of (IV) was indicated. It was concluded that both reactions go on simultaneously, the velocity of each being affected by the external conditions, and by the nature and position of the substituents in both benzene nuclei.

Many examples are known of the influence of substituents upon the formation of 5- or 6-membered rings in the above-mentioned

type of reaction. It is noteworthy that when the chalcone is a phloroacetophenone derivative the production of a coumaranone is favoured. Furthermore, on bromination of such a chalcone bromine is liable to enter the phloroglucinol nucleus (compare Kostanecki and Tambor, *loc. cit.*; also Tambor, *Ber.*, 1911, **44**, 3219). In the present investigation analogous results were obtained. 2-Hydroxy-4 : 6-dimethoxyphenyl 2 : 4-dimethoxystyryl ketone (IX) was prepared by the condensation of phloroacetophenone 4 : 6-dimethyl ether and 2 : 4-dimethoxybenzaldehyde. On bromination of the chalcone it was found that bromine had entered the nucleus, for the bromide on treatment with alkali (even under conditions which, according to the experiments of Auwers and Anschütz, *loc. cit.*, favoured the production of flavone) was converted into a bromo-derivative of a tetramethoxybenzylidenecoumaranone, from analogy with the results of previous investigators probably 3 : 5 : 2' : 4'-tetramethoxy-4-bromobenzylidenecoumaran-2-one (X).

Phloroacetophenone trimethyl ether was combined with salicylaldehyde, yielding 2 : 4 : 6-trimethoxyphenyl 2-hydroxystyryl ketone (XI). This compound was readily converted by Robinson's method into 2' : 4' : 6'-trimethoxyflavylium chloride (XII).



EXPERIMENTAL.

2-Hydroxy-4 : 6-dimethoxyphenyl 2 : 4-Dimethoxystyryl Ketone (IX).—This compound was prepared by the condensation of phloroacetophenone 4 : 6-dimethyl ether and 2 : 4-dimethoxybenzaldehyde. The aldehyde can be obtained by Gattermann's method from resorcinol dimethyl ether (Gattermann, *Annalen*, 1907, **357**, 369; compare Liebermann and Lindenbaum, *Ber.*, 1908, **41**, 1612). It can also be readily obtained in very good yield by the following method, which avoids the use of anhydrous hydrogen cyanide.

Resorcylaldehyde-aniline, $C_6H_3(OH)_2 \cdot CH(OH) \cdot NH \cdot C_6H_5$ (formed by the combination of formanilide and resorcinol), on hydrolysis with 5% sodium hydroxide solution, yields β -resorcylaldehyde (Dimroth and Zöppritz, *Ber.*, 1902, **35**, 995). This substance (8 g.)

was mixed with methyl sulphate (70 c.c.), and a 50% solution of potassium hydroxide in water added in small portions with vigorous shaking until the mixture was permanently alkaline, the temperature being kept below 60°. A further 30 c.c. of methyl sulphate were then added and the above process was repeated, addition of alkali being continued until the mixture was strongly alkaline. Water was then added to the product and the precipitate was collected, washed with water, and recrystallised from alcohol, giving 2 : 4-dimethoxybenzaldehyde, m. p. 71°. The original filtrate was acidified and extracted with ether, but no residue was left after evaporation of the solvent, indicating that complete methylation had taken place.

For the preparation of the chalkone, phloracetophenone 4 : 6-dimethyl ether (4 g.) and 2 : 4-dimethoxybenzaldehyde (3.6 g.) were dissolved in 30 c.c. of alcohol and potassium hydroxide (6 g. in 8 c.c. of water) was added. The solution was kept at 60° for 12 hours and then in a warm place over-night. The product was diluted with water, and acidified with 5% acetic acid while the mixture was cooled. The yellow oily solid obtained, after being washed with water, soon solidified completely, and then crystallised from alcohol in yellow needles (4 g.), m. p. 128° (Found : C, 65.7; H, 5.8. Calc. for $C_{19}H_{20}O_6$: C, 66.3; H, 5.8%). The chalkone was slightly soluble in ligroin or ether, but readily soluble in hot alcohol, acetic acid, chloroform, or acetone. On addition of concentrated sulphuric acid the crystals became red and dissolved to a deep red solution. This substance is mentioned by Kostanecki and Tambor (*Ber.*, 1904, **37**, 792), who give the m. p. as 152°.

3 : 5 : 2' : 4'-Tetramethoxy-4-bromobenzylidenecoumaran-2-one (X ?). —To a solution of the chalkone (4 g.) in chloroform (15 c.c.) cooled in a freezing mixture, bromine (2.5 g.) in the same solvent (1 vol. of bromine to 9 vols. of chloroform) was added drop by drop with continuous shaking, hydrogen bromide being evolved. The mixture was kept over-night in the freezing mixture; the bromide had then partly separated. The product remaining after evaporation of the chloroform was washed with hot alcohol; the residue, a reddish powder readily soluble in acetone or chloroform, decomposed at about 230°. It was not further purified but was treated directly with alkali. Alcohol (150 c.c.) was added to the bromide (1 g.) and 6 c.c. of 50% aqueous sodium hydroxide were poured into the hot mixture. The liquid was boiled for 10 minutes, and the yellow precipitate produced was collected after a while and washed with boiling alcohol and acetone. From a solution of the residue in chloroform, the *benzylidenecoumaranone* was obtained by evaporation of the solvent. It crystallised from acetone-chloroform in small,

bright yellow leaflets, not melting below 300° (Found : Br, 18.9. $C_{19}H_{17}O_6Br$ requires Br, 19.0%). The substance was only slightly soluble in benzene, alcohol, or acetone, but dissolved readily in chloroform. The solution in concentrated sulphuric acid was purplish-red.

2 : 4 : 6-*Trimethoxyphenyl 2-Hydroxystyryl Ketone* (XI).—This was prepared from phloracetophenone trimethyl ether (2 g.) and salicylaldehyde (1.3 g.) in alcohol (20 c.c.), and potassium hydroxide (5 g. in 5 c.c. of water) in the same way as the preceding chalkone. It crystallised from hot alcohol in yellow prisms (1.5 g.), m. p. 205.5° (decomp.) (Found : C, 68.4; H, 5.6. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%). The *chalkone* was slightly soluble in benzene, and readily soluble in ether, alcohol, or acetone. On treatment with concentrated sulphuric acid the crystals first became red and then dissolved, giving an orange solution. The solution in sodium hydroxide was bright yellow.

2' : 4' : 6'-*Trimethoxyflavylium Chloride* (XII).—Into a solution of the ketone (XI) in 40 c.c. of glacial acetic acid (a dark red colour developed on warming), dry hydrogen chloride was passed for 4 hours. After 24 hours, the *flavylium chloride* partly separated, and the remainder was precipitated by the addition of much ether. The product, which was obtained in excellent yield, consisted when pure of red, woolly, hygroscopic needles, m. p. 162° . It may be recrystallised from methyl alcohol—concentrated hydrochloric acid (Found : Cl, 10.8. $C_{18}H_{17}O_4Cl$ requires Cl, 10.7%). The salt is only slightly soluble in water or dilute hydrochloric acid, giving a deep yellow solution, decolorised by sodium hydroxide. The solution in concentrated sulphuric acid is orange. The chloride is not very soluble in acetone (orange solution), but is readily soluble in methyl or ethyl alcohol, or acetic acid (orange-red solution in each case).

The *ferrichloride* was precipitated by addition of a hot solution of ferric chloride in concentrated hydrochloric acid to a boiling solution of the flavylium chloride in acetic acid. Recrystallisation from acetic acid yielded reddish-brown prisms, m. p. 198° (Found : Fe, 11.5. $C_{18}H_{17}O_4Cl_4Fe$ requires Fe, 11.3%). The product was moderately readily soluble in hot acetic acid.

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