

SYNTHESIS OF COUMARINS AND CHROMONES.

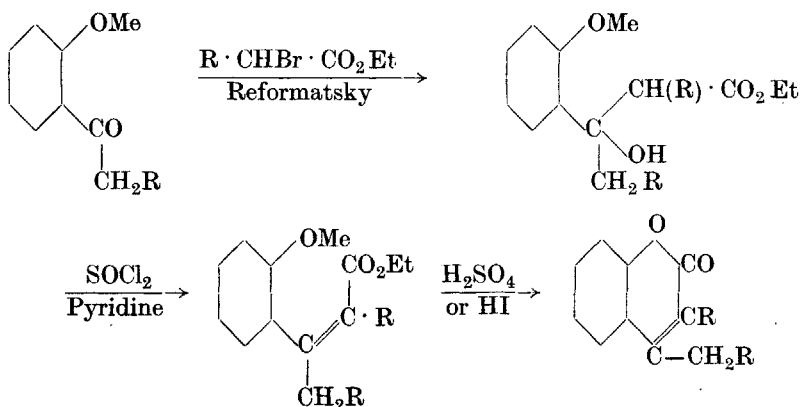
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The occurrence of a large number of coumarin and chromone derivatives in nature has led many investigators to find out general methods for the synthesis of compounds containing either the benzo- α -pyrone or the benzo- γ -pyrone ring leading to the synthesis of naturally occurring substances. It is proposed to discuss briefly in this paper some of the synthetical methods and their limitations.

The two most important methods for the synthesis of coumarin derivatives are due to Perkin¹ and Pechmann². The naturally occurring coumarins³ have been obtained either (i) by the closure of the lactonic ring with the necessary substituents in the benzene nucleus, or (ii) by the introduction of the substituents in the requisite coumarin. The action of the sodium salt of an aliphatic acid and its anhydride on an *o*-hydroxy-aldehyde with the intermediate formation of the *o*-hydroxy-cinnamic acid (Perkin's method) and the action of malic acid on phenols in the presence of sulphuric acid (Pechmann's method) have been very convenient methods for the synthesis of naturally occurring coumarins. The *o*-hydroxy-cinnamic acids have also been prepared by other methods and they easily lactonize to coumarins.

Chakravarti and Majumdar⁴ have described a method, which bids fair to be a general method for the synthesis of 3 : 4-dialkyl-coumarins not available by the usual methods. *o*-Hydroxy-aryl-alkyl ketones, which are readily available either by Hoesch's reaction or by Fries' rearrangement of acylated phenols, may readily be converted to coumarin derivatives in the following way:



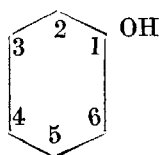
In attempting to synthesize naturally occurring coumarins by this method it has been found by Chakravarti and Majumdar⁵ that

(i) When there are two alkyl substituents namely in the α - and β -positions of the expected cinnamic acid, *cis*-cinnamic acid is formed and the coumarin is obtained in quantitative yield.

(ii) When there is no substituent in the α - and β -positions or when there is only one substituent in the α -position of the expected cinnamic acid, *trans*-cinnamic acid (*i.e.*, *o*-coumaric acid) is formed and ring-closure does not take place forming coumarin.

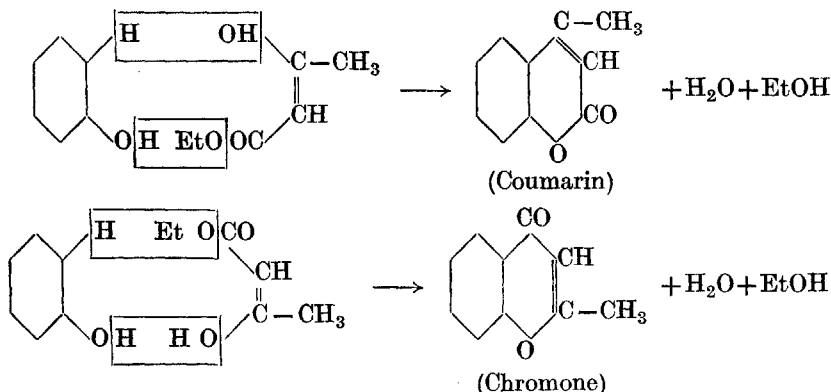
Thus this synthetical method may also be utilized for obtaining *o*-coumaric acids readily in quantity.

Pechmann *et al*⁶ prepared various coumarin derivatives with alkyl substituents in the pyrone ring by the condensation of a phenol with a β -ketonic ester in the presence of sulphuric acid as the condensing agent. In Pechmann's reaction for the synthesis of coumarins Clayton⁷ found that different phenols condense with varying degree of readiness and the reaction is always facilitated by the presence of a hydroxyl or an alkyl group in position 3, position 6 being occupied by the carbon atom taking part in the condensation.



Though the presence of a halogen atom in the phenolic nucleus greatly hinders Pechmann's reaction a substituent like nitro or carboxyl group totally inhibits the reaction; but a phenol like resorcinol, which has the faculty of forming a coumarin with great readiness, reacts readily with acetoacetic ester even if there be a halogen atom or a nitro or a carboxyl group in the phenolic nucleus⁸.

The condensation of a phenol with a β -ketonic ester may lead to two different products either a coumarin or a chromone:



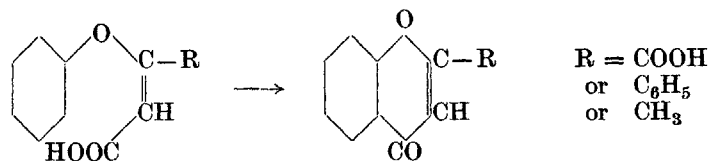
Pechmann⁶ showed that coumarins are obtained by using sulphuric acid as the condensing agent and Simonis⁹ showed that chromones are obtained by using phosphorus pentoxide. These two reactions have been extensively studied by Chakravarti and co-workers^{10, 8} and Robertson and others¹¹ with special reference to the part played by the condensing agent and the influence of any substituent in the molecule of the β -ketonic ester or the phenol. The generalization made by Chakravarti¹² that "those phenols which readily give coumarins with β -ketonic esters in the presence of sulphuric acid also give coumarins and not chromones in the presence of phosphorus pentoxide and those phenols which give coumarins with sulphuric acid in poor yield or do not react at all, produce good yields of chromones", has been supported by numerous experimental facts and it has also been shown by Chakravarti *et al*^{10, 8} that the chromone condensation could be facilitated by the introduction of halogen and nitro groups into the molecules of those phenols which do not satisfactorily respond to Pechmann's reaction, specially in the case of the monohydric phenols.

The halogen and nitro groups exert an inhibiting effect in Pechmann's reaction in the formation of coumarins and a favourable influence in chromone formation in Simonis' reaction. It is noteworthy that neutral, basic or acidic condensing agents like sodium acetate, sodium ethoxide, hydrochloric acid, boric anhydride, zinc chloride, phosphoric acid, aluminium chloride, etc., bring about coumarin condensation¹³ and the behaviour of phosphorus pentoxide is remarkable. Goodall and Robertson¹⁴ have found that phosphoryl chloride in some cases brings about chromone condensation.

If there is condensation under Pechmann's condition coumarins are invariably formed. β -Naphthol is the only phenol which has been found by Dey and Lakshminarayanan¹⁵ to give a mixture of coumarin and chromone by Pechmann's reaction (only with unsubstituted acetoacetic ester). With alkyl-acetoacetic ester, however, β -naphthol condenses in the presence of sulphuric acid to form a coumarin and not a chromone.¹⁶

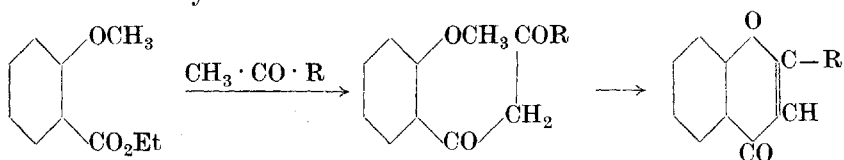
A large volume of work has been done on chromones and quite a number of methods is available for synthesizing derivatives of chromones and chromonols. Chromones, on hydrolysis with different hydrolytic agents, break up into phenols, *o*-hydroxy-acetophenones and *o*-hydroxy-acids, and methods have been developed to build up the chromones from any one of these fission products but some of these methods form along with the γ -pyrones the α -pyrones.

The phenols have been used by Ruhemann¹⁷ and Simonis⁹ for the synthesis of chromone derivatives. Ruhemann condensed sodium phenolates with ethyl chloro-fumarate, ethyl phenyl-propiolate and ethyl β -chloro-crotonate and treated the intermediate products, thus obtained, with concentrated sulphuric acid or better with phosphorus pentachloride and aluminium chloride whereby the desired chromones were obtained:



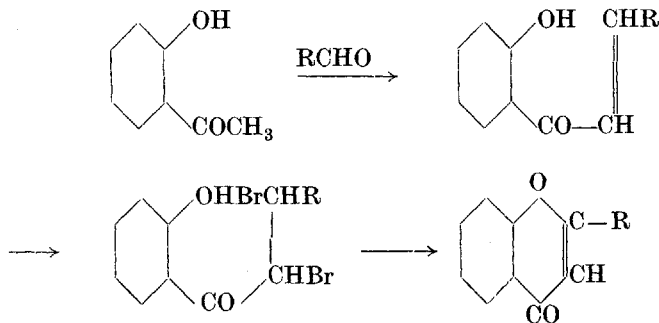
With ethyl phenyl-propiolate the yield was satisfactory but with the other two the yields were far from being so. Simonis' method is a modification of Pechmann's method from phenols and β -ketonic esters, but in this reaction α -pyrones are also formed and it has a very limited applicability (*vide supra*).

The only attempt at synthesizing chromones from *o*-hydroxy-acid was made by Kostanecki¹⁸ who condensed ethyl *o*-methoxy-benzoate with acetone and acetophenone and obtained the chromones on heating the intermediate β -diketones with hydriodic acid:

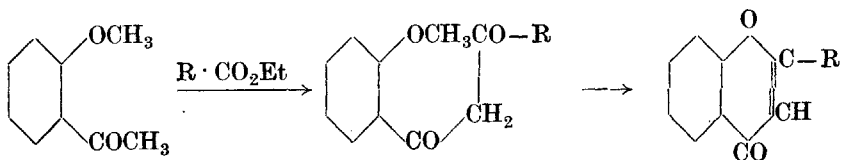


The *o*-hydroxy-acetophenones have been largely used for the synthesis of chromone derivatives:

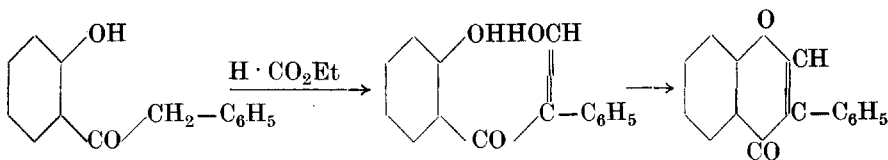
(i) Kostanecki¹⁹ condensed *o*-hydroxy-acetophenones with aldehydes giving rise to chalcones, the dibromides of which on treatment with alkali form chromones.



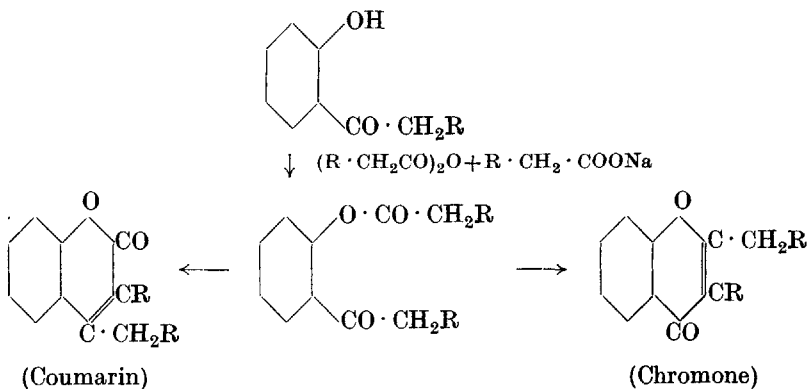
(ii) Kostanecki²⁰ condensed esters with *o*-methoxy-acetophenones and from the intermediate β -diketones formed chromones were obtained on boiling with hydriodic acid.



(iii) Späth²¹ condensed *o*-hydroxy-phenyl-benzyl-ketones with ethyl formate and the intermediate oxy-methylene ketones gave isoflavones on ring closure with hydrochloric acid. This method has been modified by Mahal, Rai and Venkataraman²².



(iv) Nagai²³ and Tahara²⁴ heated resacetophenone and pæniol with sodium acetate and acetic anhydride and obtained compounds which were shown by Kostanecki and Rozycki²⁵ to be derivatives of chromones. This very convenient method has been further developed by Robinson²⁶ and used by him in synthesizing a large number of chromones and chromonols occurring in nature by heating various *o*-hydroxy-aryl-ketones with the anhydrides and the corresponding sodium salts of aliphatic and aromatic acids. Recent researches²⁷, however, have shown that the method is not of general applicability, inasmuch as chromones or coumarins or a mixture of them may result from the above reaction, since there are two ways in which the intermediate acyl derivative may lose the elements of water giving a chromone or a coumarin:



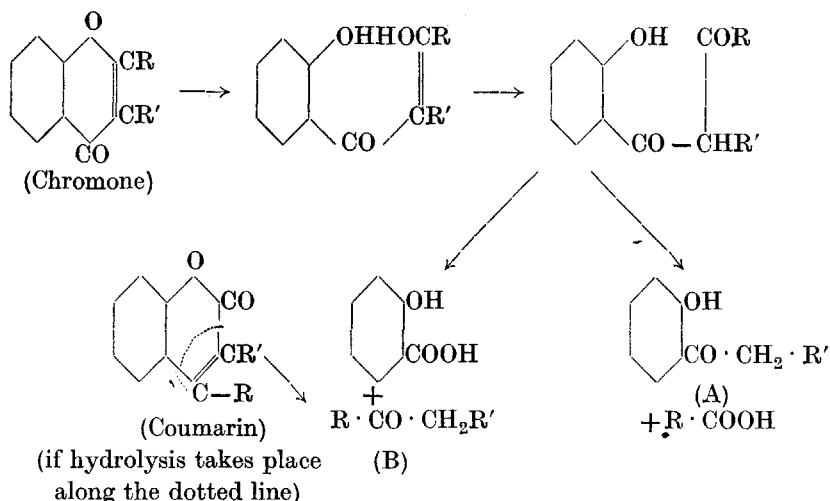
Heilbron and co-workers²⁸ have found that the nature of the product in this reaction depends on (i) the nature of the *o*-hydroxy-ketone and (ii) the acid anhydride and the salt used. The following Table summarizes the experimental facts regarding the formation of coumarins and chromones by the application of Kostanecki's reaction.

Ketone used.	Acid anhydride used.	Product obtained.
<i>o</i> -Hydroxy-acetophenone	Acetic anhydride + Sodium acetate.	Chromone (sometimes with traces of coumarin.)
<i>o</i> -Hydroxy-acetophenone	Propionic anhydride + Sodium propionate.	Coumarin.
<i>o</i> -Hydroxy-propiofenone	Acetic anhydride + Sodium acetate.	Chromone.
<i>o</i> -Hydroxy-propiofenone	Propionic anhydride + Sodium propionate.	Chromone.
<i>o</i> -Hydroxy-propiofenone	Butyric anhydride + Sodium butyrate.	Chromone.
<i>o</i> -Hydroxy-acetophenone	Phenylacetic anhydride + Sodium phenylacetate.	Coumarin.
<i>o</i> -Hydroxy-propiofenone	„ „ „	Coumarin.

Hence Heilbron and co-workers conclude²⁹ 'In each case it is the hydrogen of the reactive methylene group between phenyl and carbonyl which takes part in the ring closure. This influence is sufficiently powerful to outweigh the weaker effects introduced either by replacing the methyl ketone by the ethyl ketone or by using derivatives of propionic acid in place of those of acetic acid. The influence of the phenyl group on the course of the Kostanecki's reaction, though more powerful, is in the same direction as that of the methyl group. When substituted in the sodium salt and the acid anhydride both groups favour coumarin formation, but when substituted in the hydroxy-acetophenone side chain both groups favour chromone formation.'

The above generalization of Heilbron has also been supported by the work of Flynn and Robertson³⁰ and of Chakravarti and Bagchi³¹. Chakravarti and Majumdar³² have further shown by a detailed study of Kostanecki's reaction on the halogenated aceto-, propio-, and butyro-phenones that the halogen atom has no marked influence towards the formation of γ -pyrones as in Simonis' reaction (*vide supra*).

It has often been a puzzle for the investigators in this line to distinguish whether a compound is an α -pyrone or a γ -pyrone derivative and absolute reliance on the hydrolytic method has often misled workers to assign a γ -pyrone structure to a compound having an α -pyrone structure.³³ According to Baker³⁴ the only safe criterion of a chromone structure is the formation on hydrolysis of a hydroxy-ketone of the type (A). The formation of a neutral ketone of the type (B) is also possible for an isomeric coumarin:



On treatment with alkali the lactonic ring of the coumarin breaks up and it is difficult to isolate the coumarinic acid thus formed as it easily lactonizes forming the original coumarin unless the coumarinic acid changes to *o*-coumaric acid (*vide* Sen and Chakravarti³⁵). Canter and Robertson³⁶ have found out a convenient method for distinguishing the coumarins by methylating the *o*-hydroxy-cinnamic acid, thus formed, and isolating *o*-methoxy-cinnamic acid. This method has been very helpful to distinguish a coumarin from an isomeric chromone.

The reactivity of the 2-methyl group in 2-methyl-chromones (*cf.* Heilbron, Barnes and Morton³⁷) has been taken advantage of by Chakravarti¹⁰ to distinguish the 2-methyl-chromones, which easily form styryl derivatives by condensation with aromatic aldehydes in the presence of alcoholic sodium ethoxide. The reactivity of the 2-methyl group is not in any way influenced by the presence of a group in the benzene nucleus particularly in position 7. Similarly the 2-ethyl-chromones have also been found to form styryl derivatives though rather slowly by Heilbron, Hey and Lowe,³⁸ but in certain cases it has not been possible to prepare 2-styryl derivatives from authentic 2-ethyl-chromones (Chakravarti and Majumdar³²).

Wittig³⁹ developed a method for the separation of the coumarins from the chromones. This method is based on the fact that by the action of alcoholic sodium ethoxide on a coumarin, the lactonic ring breaks up and the coumarin is regenerated on acidification, whereas in the case of a chromone, the pyrone ring opens with the formation of a diketone, which forms the chromone only on heating with sulphuric acid or acetic acid. Though this method has often been used (Heilbron, Hey and Lythgoe⁴⁰), Chakravarti and Majumdar³² have come across irregularities in the course of this reaction. Some authentic coumarins, *e.g.* coumarin itself, on keeping overnight with alcoholic sodium ethoxide, give on acidification along with the original coumarin a large

proportion (about 50%) of *o*-coumaric acid. Again chromones on treatment with alcoholic sodium ethoxide give in some instances the *o*-hydroxy-ketone by the further hydrolysis of the diketone formed³².

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