THE CHEMISTRY OF COUMARINS

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Received October 14, 1944

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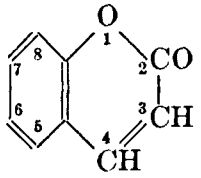
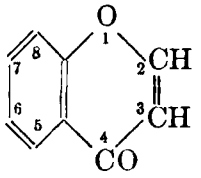
I. Introduction

The fusion of a pyrone ring with a benzene nucleus gives rise to a class of heterocyclic compounds known as benzopyrones, of which two distinct types are recognized: (*1*) benzo-α-pyrones, commonly called coumarins, and (*2*) benzo-γ-pyrones, called chromones, the latter differing from the former only in the position of the carbonyl group in the heterocyclic ring.



Benzo-α-pyrone

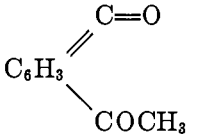


Benzo-γ-pyrone

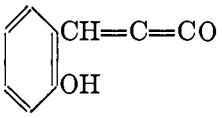
Representatives of these groups of compounds are found to occur in the vegetable kingdom, either in the free or in the combined state. Coumarin, the parent substance of the benzo-α-pyrone group, was first isolated from tonka beans in 1820. Several coumarin derivatives have been found to be widely distributed in the plant kingdom. Particularly the plants belonging to the natural orders of Orchidaceae, Leguminoceae, Rutaceae, Umbelliferae, and Labiatae are rich sources of naturally occurring coumarins (224).

Coumarin was initially considered to be a benzoic acid derivative, but its synthesis by W. H. Perkin, Sr., (160) from salicylaldehyde by means of his classical reaction established its relation to *o*-hydroxycinnamic acid, which loses a molecule of water in forming the lactone ring.

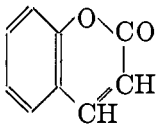
However, different constitutional formulae have been suggested from time to time. Of the various formulae proposed by Perkin (I), Basecke (II), Strecker, Fittig, and Tiemann (III), Salkowski (IV), and Morgan and Micklethwait (V), formula III has been found to be in complete accord with the known reactions of the coumarin derivatives and has been universally accepted as correct (*vide* Hugo Schiff (179)).



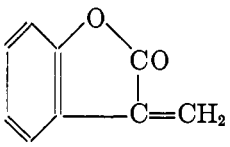
I
Perkin (1868)



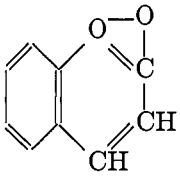
II
Basecke (1870)



III
Strecker (1867)
Fittig (1868)
Tiemann (1877)



IV
Salkowski (1877)



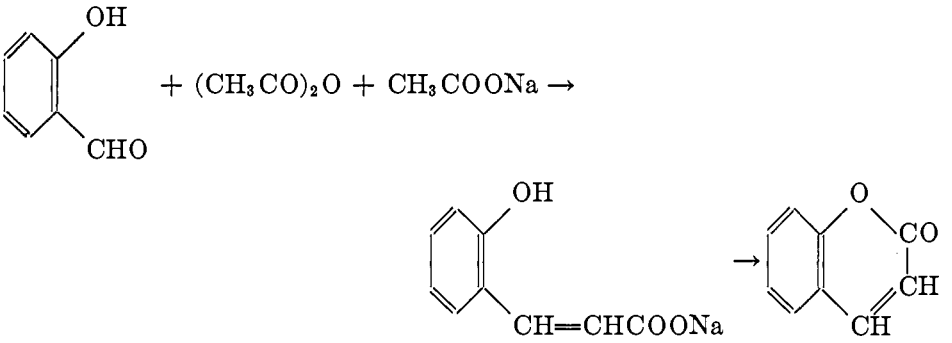
V
Morgan and Micklethwait (1906)
Clayton (1908)

Thus coumarins and their derivatives are, from the point of view of their chemical constitution, a group of lactones derived from *o*-hydroxycinnamic acids: alternately stated, a coumarin ring system is formed by the fusion of a benzene and a 1,2-pyrone ring, i.e., coumarins are a class of heterocyclic compounds containing oxygen as a member of the heterocyclic ring.

II. Methods for the Synthesis of Coumarin Derivatives

Of the number of synthetic methods, there are a few which have yielded important results; there are several others whose applications are less general. All these methods center round the possibility of building up the pyrone ring on a suitable benzene derivative.

(*1*) *Perkin reaction:* This classical method has entered into every textbook of organic chemistry. As stated above, Perkin (160) first synthesized coumarin from salicylaldehyde by heating it with acetic anhydride and anhydrous sodium acetate:

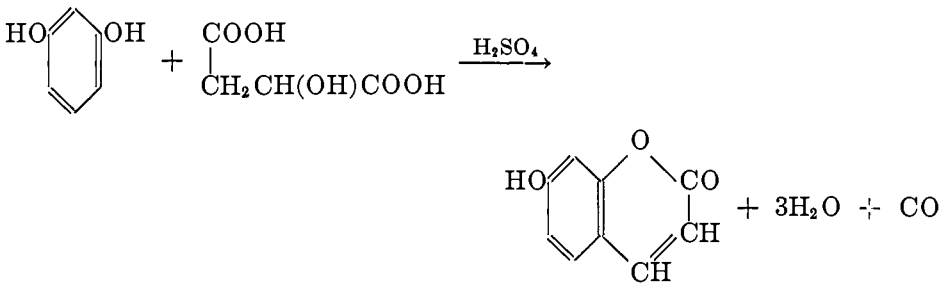


This reaction occurs with the formation of an intermediate *o*-hydroxycinnamic acid derivative which passes spontaneously into the lactone when liberated from its sodium salt. This method was successfully used by Tiemann and Herzfield (256), Taage (251), and, later on, by numerous workers in the field. In recent years, E. Späth (224) has utilized this reaction to synthesize several naturally occurring coumarins. It has, however, its limitations: the appropriate initial *o*-hydroxyaldehydes are rather difficult to obtain from many substituted phenols; the method gives coumarins unsubstituted in the pyrone ring; the yields obtained are also low. Yanagisawa and Kondo (270) claim to have improved the yields by using iodine as a catalyst in the reaction.

Dyson (81) obtained 3,3′-dicoumarin as the sole product of the reaction between salicylaldehyde, acetic anhydride, and sodium succinate instead of the expected coumarin-3-acetic acid. Dey and Sankaranarayanan (76) replaced acetic anhydride by succinic anhydride and obtained the coumarin-3-acetic acid in good yield.

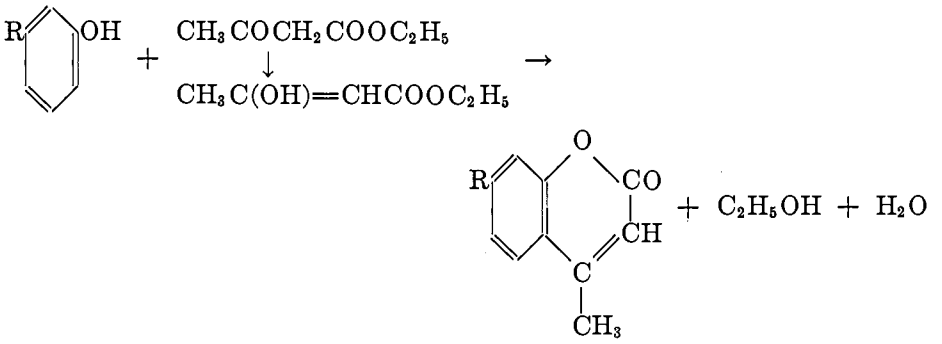
The Perkin reaction on *o*-vanillin for the synthesis of 8-methoxycoumarin leads to the production of the *trans* form of 2-hydroxy-3-methoxycinnamic acid in large quantity (67); this cinnamic acid derivative does not undergo ring closure to the coumarin.

(2) Pechmann reaction: Pechmann (152) found that a coumarin derivative is formed when a mixture of a phenol and malic acid is heated in the presence of concentrated sulfuric acid:



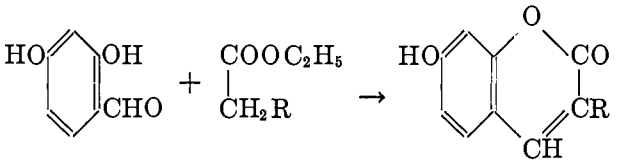
This method has limited applicability. Many substituted phenols do not undergo this reaction; only coumarins unsubstituted in the pyrone ring are obtained.

(*3*) *Pechmann–Duisberg reaction:* Pechmann and Duisberg (154) found that phenols condense with β-ketonic esters in the presence of sulfuric acid, giving coumarin derivatives:



This reaction has found extensive applications in the synthesis of various coumarin derivatives. It gives coumarins substituted in the pyrone ring. The various factors affecting the course of this reaction have been separately discussed (*vide infra*).

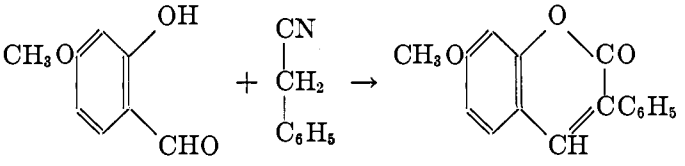
(*4*) *Knoevenagel reaction:* Knoevenagel (120) developed a method for the synthesis of coumarin derivatives from *o*-hydroxyaldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, etc., in the presence of piperidine, pyridine, and other organic bases:



(R = $COOC_2H_5$, $COCH_3$)

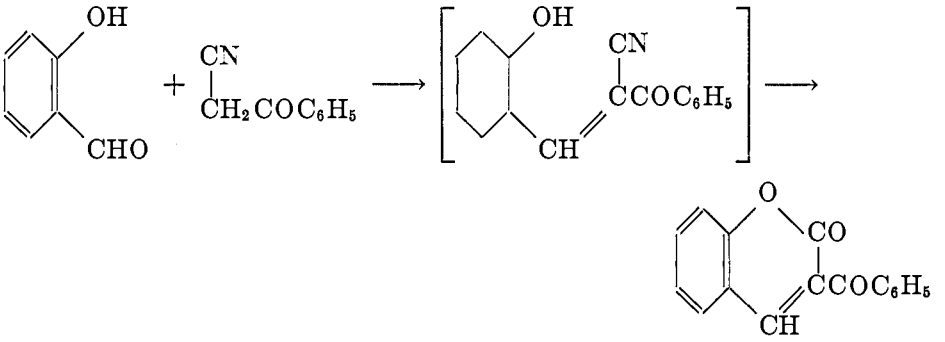
This reaction has been successfully used by various workers, notably by Shah and Shah (200), to prove the ortho position of the formyl group to the hydroxyl group in their studies on γ-substitution in the resorcinol nucleus. They have synthesized a large number of coumarin derivatives by this method by the condensation of formylated 4-acylresorcinols and other di- and tri-hydroxyacetophenones with malonic ester, acetoacetic ester, and cyanoacetic ester. This method has been found to be better than the Perkin–Robinson method (163) of pyrylium salt formation on account of the smoothness with which it works.

o-Hydroxyaldehydes and phenyl acetonitrile condense in the presence of sodium ethoxide or alcoholic potash, giving 3-phenylcoumarins (29, 118):

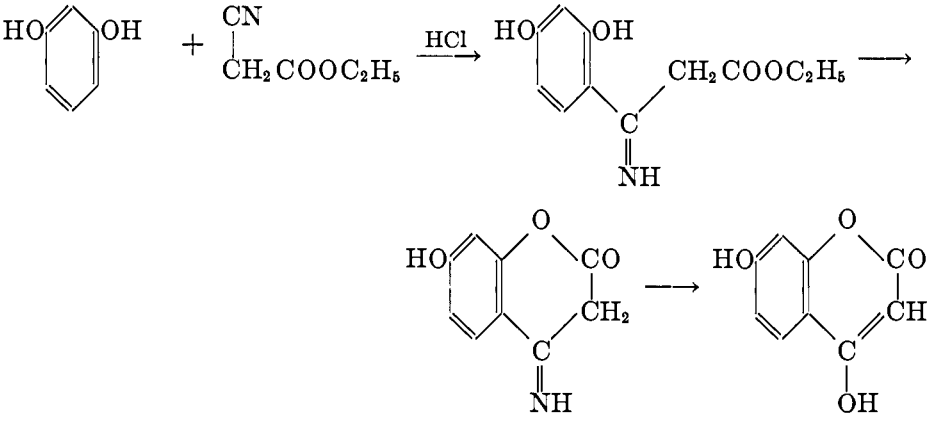


Pandya and his coworkers (126) have investigated the Knoevenagel reaction with various aldehydes in the presence of pyridine alone and have found that a trace of pyridine is efficacious in bringing about the condensation with nearly theoretical yields. Thus pyridine in traces is quite comparable to Knoevenagel's famous reagent piperidine in traces. In a series of papers, Pandya and his coworkers (117) have investigated many other bases, which have been found to possess a similar efficiency in promoting these reactions. They have also made a study of constitutional factors by using differently substituted aldehydes. Pandya and Sodhi (148) have obtained 3-aminocoumarin in excellent yield by condensing salicylaldehyde with glycine in the presence of a trace of pyridine.

Ghosal (91) found that the reaction between an *o*-hydroxybenzaldehyde and *ω*-cyanoacetophenone in the presence of hydrogen chloride gives a benzoylcoumarin instead of the expected pyrylium derivative.

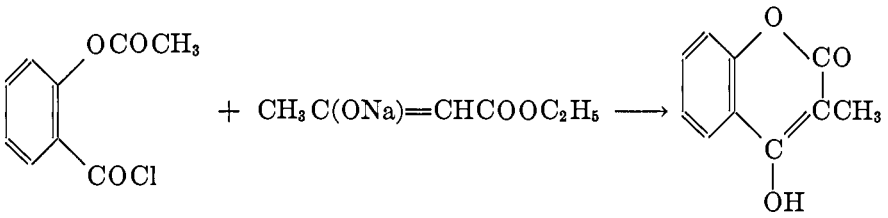


(*5*) Sonn (222) found that resorcinol condenses with cyanoacetic ester under the conditions of the Hoesch reaction (106); the ketimine hydrochloride obtained on hydrolysis gives ultimately 4,7-dihydroxycoumarin:



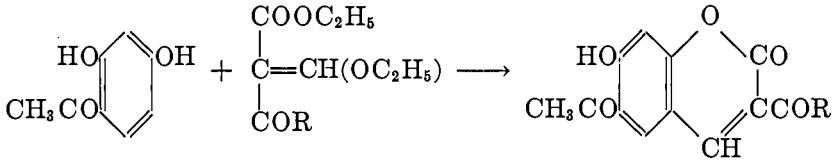
Still another method by which 4-hydroxycoumarins are obtained is due to Anschütz (7, 8), who condensed the sodium derivative of acetoacetic ester with *o*-acetoxybenzoyl chloride in ethereal solution and obtained 4-hydroxycoumarin

derivatives. He extended his work by using the sodium derivatives of malonic ester and cyanoacetic ester with various substituted acid chlorides. Heilbron and Hill (103) have obtained 3-methyl-, 3-benzoyl-, and 3-benzyl-coumarins by this method.



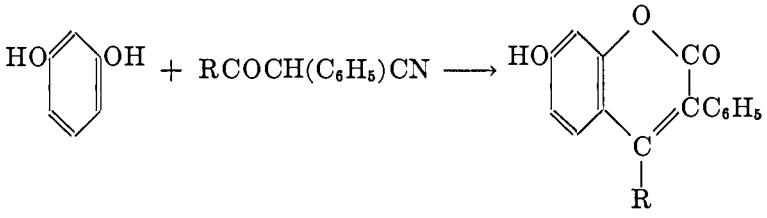
Pauly and Lockemann (151) synthesized 4-hydroxycoumarin from methyl acetylsalicylate by adding metallic sodium to the molten ester. Several 3-substituted 4-hydroxycoumarins have also been prepared by Stahmann *et al.* (249) from acylated derivatives of methyl salicylate.

(*6*) Weiss and Merksammer (261) found that resacetophenone on condensation with ethyl ethoxymethyleneacetoacetate by heating with alcoholic sodium ethoxide gave 7-hydroxy-3,6-diacetylcoumarin. Weiss and Kratz (260) extended the method and found that ethyl ethoxymethylenemalonate similarly condensed to give coumarin-3-carboxylates from resorcinol derivatives, the carbethoxyl group having hydrolyzed to the carboxyl group.



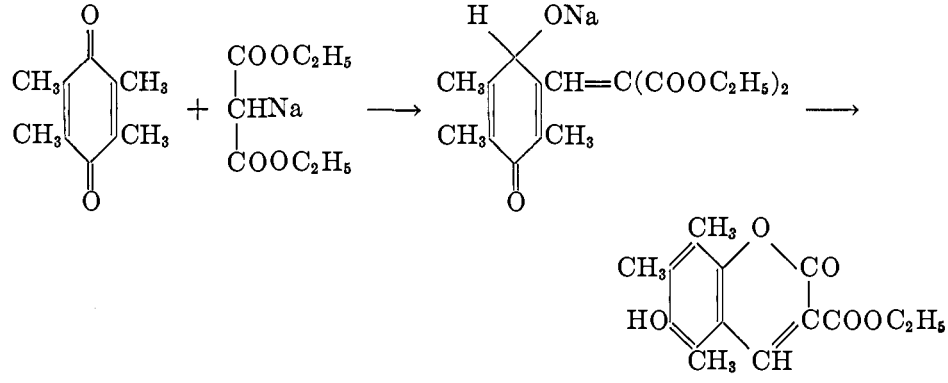
(R = CH_3, OC_2H_5, OH)

(*7*) Baker *et al.* (12) found that α-formylphenylacetonitrile and its derivatives condense with resorcinol and other phenols, in the presence of phosphorus oxychloride or dry hydrogen chloride as condensing agent, leading to the production of 3-phenylcoumarins in poor yields and not the isomeric 3-phenylchromones (isoflavones):



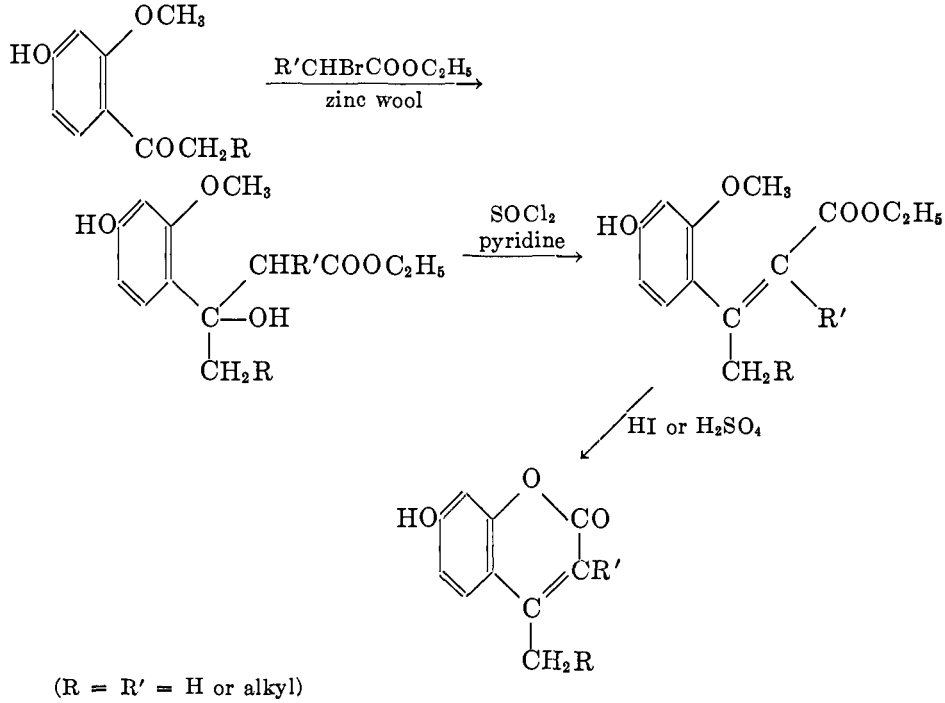
(R = CH_3, H, C_2H_5)

(*8*) One more method of general applicability but of limited interest has been put forward by Smith and his collaborators. Smith and Dobrovolny (219) showed that 3-carbethoxy-5,7,8-trimethyl-6-hydroxycoumarin was produced when duroquinone reacted with ethyl sodiomalonate in benzene solution.



This reaction between completely methylated quinones and sodium enolates appears to be a promising method for the synthesis of 6-hydroxy-5,7,8-trimethylcoumarins substituted in the 3-position by such groups as carbethoxyl, acyl, cyano, etc. Smith and coworkers (216, 217, 218, 220) have exhaustively investigated this reaction with various brominated methylquinones and found that they may react with a metallic enolate to produce either a coumarin by reaction with a methyl group or a quinone malonic ester by direct replacement of a bromine atom.

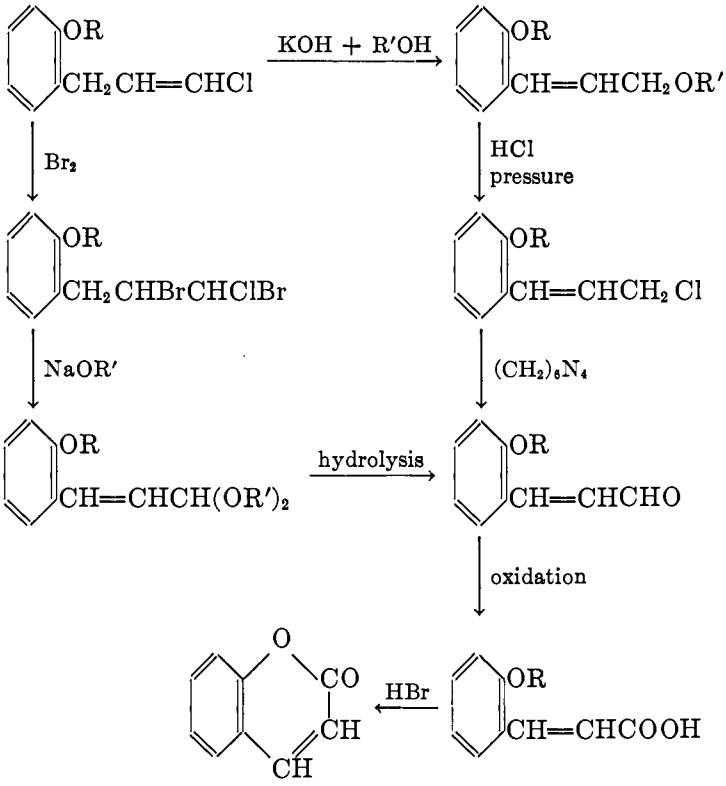
(*9*) Chakravarti and Majumdar (44) have developed a method by which 3,4-dialkyl-substituted coumarins not available by the usual methods may be synthesized: *o*-hydroxyaryl alkyl ketones, under the conditions of the Reformatsky reaction, are ultimately converted into coumarin derivatives.



(R = R′ = H or alkyl)

In their attempts to synthesize some coumarins by this method, the same authors found that (*1*) when there are two alkyl substituents, namely, in the α- and β-positions of the expected cinnamic acid, a *cis* acid is formed, which can be easily cyclized to the coumarin derivative in quantitative yield; (*2*) when there is no substituent in the α- or β-position or only one in the α-position of the expected cinnamic acid, a *trans* acid, i.e., *o*-coumaric acid, is formed and the coumarin ring closure does not take place. Further, they found that methyl ethers of *o*-hydroxyaldehydes when subjected to the above reaction also gave *trans*-cinnamic acids, which could not be converted into coumarins.

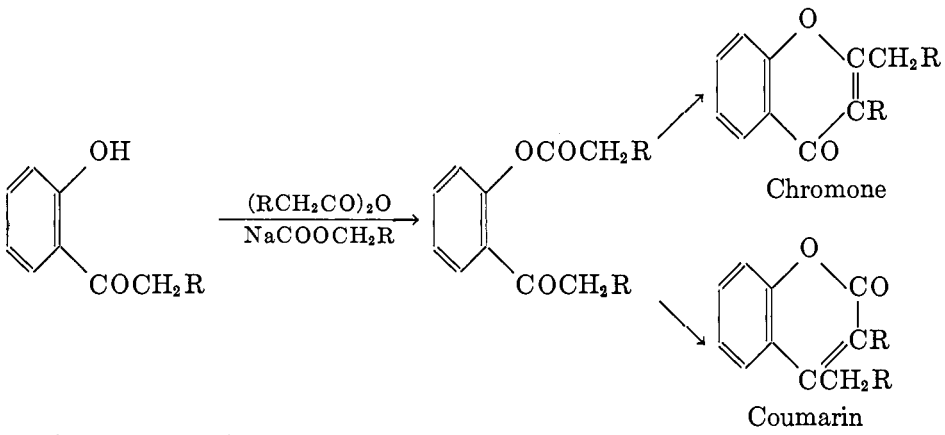
(*10*) Recently Bert (27) has developed a general method for synthesizing coumarins, which consists in condensing phenolic ethers with $CH_2ClCH{=}CHCl$ either by the Friedel–Crafts reaction or in the presence of zinc dust to obtain $ROC_6H_4CH_2CH{=}CHCl$, which can also be synthesized by condensing $CH_2ClCH{=}CHCl$ with *o*-bromophenolic ether through the Grignard reaction. This is then converted into the corresponding coumarin in two ways, as shown below:



(*11*) *Kostanecki acylation of o-hydroxyketones:* This is a method of coumarin formation with an element of uncertainty in it. Kostanecki and Rozycki (121) showed that the products obtained by Nagai (144) and Tahara (252) by heating

resacetophenone and its monomethyl ether with acetic anhydride and sodium acetate were chromone derivatives. This method was further developed by Allan and Robinson (6) for the synthesis of a large number of chromones and chromonols occurring in nature.

It has been found, however, that this method is not exclusively applicable for chromone formation, inasmuch as chromones or coumarins or a mixture of both may result from the above reaction, since there are two ways in which the intermediate acyl derivative may lose water, giving a chromone or a coumarin:



(R = H or alkyl)

Wittig (268) found that the Kostanecki acetylation of 4-chloro-6-acetylphenol leads to the production of a mixture of 6-chloro-4-methylcoumarin and 6-chloro-2-methylchromone. Later, he and his coworkers (269) isolated 2-methylchromone and 4-methylcoumarin in the Kostanecki acetylation of *o*-hydroxyacetophenone. Bargenilli (23) and Baker and Eastwood (17) showed that the use of phenylacetic anhydride and sodium phenylacetate in the Kostanecki reaction leads to coumarin and not chromone formation.

Heilbron and his collaborators (100, 101, 102) have also investigated this reaction and shown that the coumarins are formed as by-products. Chakravarti and coworkers (40, 45) have shown by a detailed study of the Kostanecki reaction on halogenated aceto-, propio-, and butyro-phenones that the halogen atom has no marked influence upon chromone formation.

Recently, Sethna and Shah (197) have studied the Kostanecki acylation of orcacetophenone and its monomethyl ether and have shown the exclusive formation of a coumarin. However, γ-orcacetophenone has been found to give on Kostanecki acetylation a mixture consisting mainly of chromone and a small quantity of coumarin (63). Trivedi, Sethna, and Shah (258) similarly investigated orcpropiophenone, which on acylation has been found to give exclusively chromones.

The formation of coumarin or chromone in this reaction is dependent not only on the acid anhydride and the salt used but also on the nature of the

o-hydroxyphenyl ketone. When sodium acetate and acetic anhydride are used, the introduction of higher alkyl substituents in the side chain of the hydroxyketone favors chromone formation: e.g., resacetophenone gives chromone; respropiophenone also gives chromone (32). Chadha, Mahal, and Venkatraman (36) find that an ω-substituent in an *o*-hydroxyaryl methyl ketone favors chromone formation. They also find that chromone formation takes place as a rule more readily in the naphthalene than in the benzene series.

The ketone being the same, if the anhydride and the sodium salts of higher acids like propionic and butyric acids are taken, there is a tendency towards coumarin formation.

When benzoic anhydride and sodium benzoate or their derivatives are used, the products obtained are always flavone derivatives (2-phenylchromones); with phenylacetic anhydride or acetic anhydride and sodium phenylacetate the products formed are mostly 3-phenylcoumarin derivatives. In the case of *o*-hydroxybenzophenones, only 4-phenylcoumarin derivatives are formed.

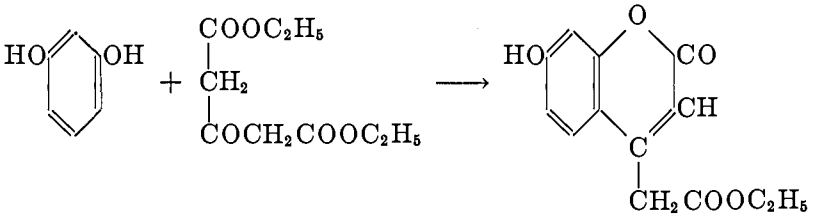
III. Pechmann Condensation of β-Ketonic Esters with Phenols

A rapid development in the chemistry of coumarins is due mainly to the synthetic method universally known as the Pechmann reaction, which consists in reacting phenols with β-ketonic esters in the presence of sulfuric acid. As stated before, this elegant method has found extensive application. However, the course of the reaction is influenced by all the factors: *viz.*, (*1*) the nature of the phenol, (*2*) the nature of the β-ketonic ester, and (*3*) the condensing agent.

A. Effect of substituents in the phenol and the β-ketonic esters

Pechmann and Duisberg condensed resorcinol, phenol, and *p*-cresol with acetoacetic ester and its α-methyl derivative; then they extended the reaction to *o*-cresol, pyrogallol, orcinol, phloroglucinol, and α- and β-naphthols. They found that *m*-dihydroxyphenols and α-naphthol condensed readily, giving good yields of coumarins, while monohydric phenols and β-naphthol failed to give anything but poor yields. Fries and Klostermann (84) also found that while the formation of coumarins from phenol, *o*-cresol, and *p*-cresol under the conditions of the Pechmann reaction proceeds with difficulty, it takes place readily with *m*-cresol. Pechmann and Maxshaal (159) condensed various aminophenols, using anhydrous zinc chloride instead of sulfuric acid as condensing agent. It was observed that *m*-diethylaminophenol condensed more readily than the isomeric *o*- and *p*-derivatives. Pechmann and Hancke (156) obtained 3-chlorocoumarins by the Pechmann condensation of ethyl α-chloroacetoacetate with phenols.

Various workers have studied the Pechmann reaction, using various substituted phenols and different β-ketonic esters. Biginelli (28) condensed quinol with ethyl oxalacetate in the presence of sulfuric acid and obtained 6-hydroxycoumarin-4-carboxylic acid. Pechmann with Kraft (157) and Graeger (155) extended this reaction to other phenols. Dey (64) condensed various phenols with acetonedicarboxylic acid ester and made a systematic study of the reactivity of the coumarin-4-acetic acids thus synthesized:



Clayton (48) found that the phenols with alkyl, hydroxy, and dialkylamino groups in the positions marked X in the formulas given below undergo condensa-

tion with β-ketonic esters, giving good yields of coumarins. Chlorine as a substituent in these positions has a similar effect but to a less appreciable extent. The introduction of such substituents as nitro, carboxyl, carbethoxyl, and acetyl prevents the condensation. This generalization is based on Clayton's own work and on that of previous investigators on substituted monohydric phenols, which are known to be less reactive than the polyhydric phenols.

An exception to the above rule is met with in the case of oxalacetic ester and quinol, as mentioned above. This is rather interesting, as quinol condenses with other β-ketonic esters with difficulty. *m*-Cresol reacts very feebly with this ester; pyrogallol and orcinol give no coumarins with it.

Recently some work has been done on the influence of substituents on the reactivity of the resorcinol nucleus in the Pechmann condensation. Chakravarti and his coworkers (41, 43) found that 2-nitro- and 4-nitro-resorcinols readily condense with acetoacetic ester to give 7-hydroxycoumarin derivatives. On condensing the same phenols with α-alkylacetoacetates, they found that 2-nitroresorcinol condensed with α-methylacetoacetate but failed to condense with α-ethyl- and other higher α-alkyl-acetoacetates. 4-Nitroresorcinol did not condense even with α-methylacetoacetate. Thus the presence of a nitro group in the resorcinol nucleus greatly depresses its reactivity, and a nitro group in the 4-position inhibits the Pechmann reaction more than a nitro group in the 2-position.

Chakravarti and Ghosh (43) also condensed 4-chlororesorcinol with various β-ketonic esters and obtained 6-chloro-7-hydroxycoumarin derivatives in all cases, the condensation taking place readily.

Shah *et al.* (208) found that methyl β-resorcylate condenses with ethyl acetoacetate, giving a 7-hydroxycoumarin derivative. Sethna and Shah (195) extensively studied the reaction of this phenolic ester with several substituted β-ketonic esters and obtained coumarins in all cases, a result which shows that a 4-carbomethoxyl group in the resorcinol nucleus has but little retarding influence on the course of the Pechmann reaction. The same authors (198) have also condensed *p*-orsellinic acid with ethyl acetoacetate and obtained 7-hydroxy-4,5-dimethylcoumarin-8-carboxylic acid; this result is very interesting as, on decarboxylation,

7-hydroxy-4,5-dimethylcoumarin, which cannot be obtained ordinarily by the condensation of orcinol with acetoacetic ester (51), was easily synthesized.

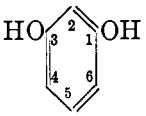
Sethna (192) condensed methyl phloroglucinolcarboxylate with acetoacetic ester and obtained methyl 5,7-dihydroxy-4-methylcoumarin-6(or 8)-carboxylate, but the free acid could not be condensed as it decomposes into phloroglucinol and carbon dioxide. γ-Resorcylic acid easily condenses with ethyl acetoacetate under the usual conditions of the Pechmann reaction.

A 4-acyl group in the resorcinol nucleus completely inhibits the Pechmann condensation, as resacetophenone does not condense with acetoacetic ester in the presence of sulfuric acid or sodium ethoxide, while 2-acylresorcinols present no such difficulty and easily condense with various β-ketonic esters, giving 7-hydroxy-8-acylcoumarin derivatives (129, 204). The qualitative order of the above groups with regard to the deactivating effect is therefore

$$-COCH_3 > -NO_2 > -COOCH_3$$

Desai and Mavani (62) have studied various substituted pyrogallol derivatives with a view to ascertaining their reactivity in the Pechmann condensation. They found that all the above groups exercise an inhibiting effect to a varying extent. The same authors have investigated the quinol derivatives with a similar object. The presence of acetyl and halogen substituents exerts an inhibiting effect, while alkyl groups exert no such retarding influence.

From the above results, a plausible explanation on the basis of the electronic conception can be advanced for the capacity of phenols and their substitution products to undergo coumarin condensation with β-ketonic esters (60). The feeble power possessed by ordinary phenol is enhanced by the presence of electron-donating groups in the meta position, e.g., CH_3, OH, OCH_3, NH_2 etc., but is depressed and almost annihilated by electron-attracting groups in the same position, e.g., NO_2, SO_3H, COOH, $COOCH_3$, CHO, etc. Thus, resorcinol derives its extraordinary power to undergo coumarin condensation at position 4 (the 4- and 6-positions are identical) from the accession of electrons from the additional hydroxyl group in position 1, which is para to the point of attack. This activation of position 4 is so great that even the presence of electron-attracting groups at the 2- or 6-position is not sufficient to destroy this power. When position 6 is occupied by groups which are electron sinks, the resorcinol forms



coumarins with difficulty, while groups which are electron sources do not seriously interfere with this property. Moreover, as 2-substituted resorcinols form coumarins easily but 4-substituted ones do not, it follows that electron sinks exercise a greater deactivating influence at position 4 than at position 2.

So far we have mainly considered the effect of different substituents in the phenolic nucleus. We shall now consider the different substituents in the acetoacetic ester molecule with regard to their effect on the course of the Pechmann reaction.

Several α-substituted acetoacetates with simple alkyl groups like methyl, ethyl, propyl, butyl, allyl, and benzyl have been investigated from time to time. In the case of reactive phenols like resorcinol, pyrogallol, phloroglucinol, orcinol, and α-naphthol, coumarins are obtained more or less readily irrespective of the substituent in the ester used. In the case of *m*-cresol, the unsubstituted ester gives coumarin but on the introduction of α-substituents in the ester molecule, the yield begins to decrease and as the propyl group is introduced, the reaction is inhibited altogether. It is interesting to note, however, that α-allylacetoacetate gives a coumarin with *m*-cresol easily (145). *m*-Cresol does not give a coumarin with α-phenylacetoacetate when sulfuric acid is used as condensing agent. In the case of less reactive phenols, such as phenol, *p*-cresol, quinol, β-naphthol, etc., the unsubstituted acetoacetate gives coumarins in poor yield. The introduction of an α-alkyl group has a retarding influence on coumarin formation, the effect increasing progressively with the bulk of the alkyl group. β-Naphthol does not condense with α-ethyl-, α-propyl-, or α-isopropyl-acetoacetates (38).

For groups other than alkyl, α-chloroacetoacetate has been studied to some extent. In addition to the usual phenols, it condenses with *p*-cresol, giving the corresponding 3-chlorocoumarin (172).

Ahmed and Desai (2) have systematically studied the formation of coumarins from phenols and cyclic β-ketonic esters. They find generally that the cyclic β-ketonic esters behave similarly to open-chain ones, the fused cyclo ring having an effect comparable to that of an α-methyl substituent.

Recently Shah and his coworkers (203, 209, 124) in a series of papers have systematically studied the Pechmann condensation of ethyl acetosuccinate, ethyl α-acetoglutarate, and ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate with a view to finding the effect of $-CH_2COOC_2H_5$, $-CH_2CH_2COOC_2H_5$, and $-CH(OH)CCl_3$ substituents in the α-position of the acetoacetic ester molecule on the course of the reaction. The results show that the behavior of the phenols with the above esters is similar to their reactivity with other β-ketonic esters. Ethyl acetosuccinate also gives coumarins in good yields with *m*-cresol and β-naphthol. In spite of the heavier bulk of its substituent, the acetosuccinate is as reactive as, or even more reactive than, the corresponding simple α-alkylacetoacetate. The introduction of a negative group like carbethoxyl in the alkyl group tends to increase the reactivity of the ester, a result which may be attributed to its greater enolization. Similar observations have also been made in the case of α-acetoglutarate, the next homolog of the acetosuccinate.

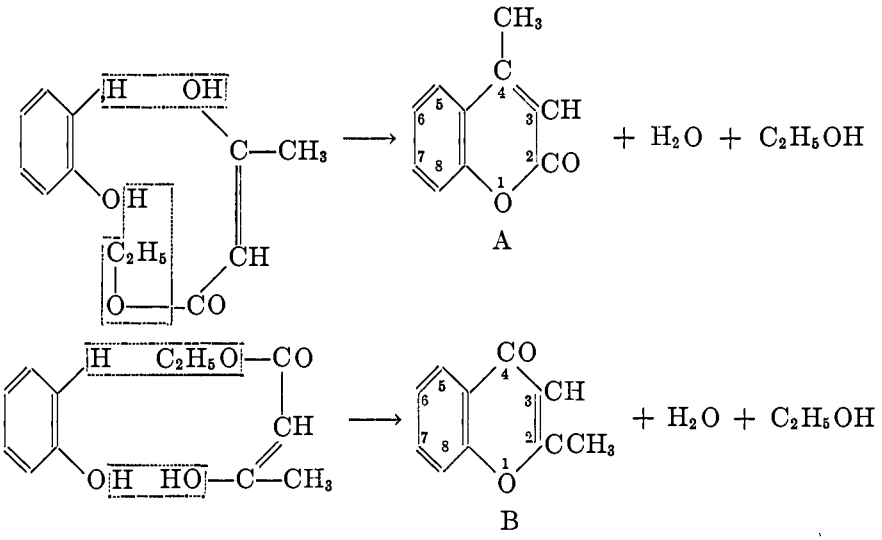
The substituent $-CH(OH)CCl_3$, considered in relation to a simple α-ethyl group in acetoacetic ester, appears to be more reactive, judging from the experimental results. The reaction in the case of resorcinol and similar phenols is completed within a shorter period: *p*-cresol condenses only at lower temperature; *o*- and *m*-cresols condense, though the reaction takes a different course. These observations are interesting, as the $-CH(OH)CCl_3$ group is a very heavy substituent compared to ethyl. The increased reactivity of ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate may be attributed to the presence of OH and CCl_3 groups in the alkyl chain.

While various α-substituted acetoacetates have been investigated, recently Kotwani, Sethna, and Advani (122, 123) have made a systematic attempt to study the reactivity of γ-substituted acetoacetic esters in the Pechmann condensation. They find that ethyl γ-phenylacetoacetate condenses with various phenols, giving 4-benzylcoumarins. The same authors, on condensing ethyl butyroacetate (ethyl γ-ethylacetoacetate), found that the γ-substituent has a considerable inhibiting effect and that in some cases it is even more inhibitory than the corresponding α-substituent or even a negative γ-substituent like the carbethoxyl group, as in ethyl acetonedicarboxylate, which may be regarded as ethyl γ-carbethoxyacetoacetate.

B. CONDENSING AGENTS

In the foregoing section, we have reviewed the work done on the effect of substituents in the phenolic nucleus as well as in the β-ketonic ester molecule. We shall now turn to the rôle of condensing agents in the course of the Pechmann reaction.

There are two possibilities in the reaction between a β-ketonic ester and a phenol, one giving rise to a coumarin derivative (A) and the other giving rise to a chromone derivative (B):



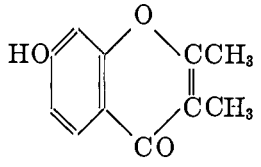
Phosphorus pentoxide and sulfuric acid as condensing agents

Simonis and his collaborators (212) condensed β-ketonic esters with phenols in the presence of phosphorus pentoxide instead of sulfuric acid, as used by Pechmann, and claimed to have obtained chromones instead of coumarins in all the cases. Jacobsen and Ghosh (110) claimed to have obtained chromones in some cases even when sulfuric acid was used as condensing agent. This work of Jacobsen and Ghosh has been contradicted by Baker (14) and by Baker and

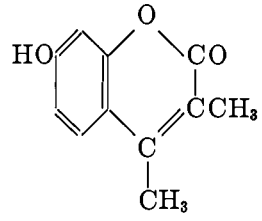
Robinson (19). They definitely proved, by synthesizing chromones by unambiguous methods, that the so-called γ-pyrones or chromones of Jacobsen and Ghosh were really coumarins or 1,2-benzopyrones.

It would therefore appear that the condensation of phenols with ethyl acetoacetate and its substituted derivatives would lead to the formation of coumarins in the presence of sulfuric acid, whereas, with phosphorus pentoxide, chromones would be formed. To settle this point, the Simonis reaction has been the subject of extensive investigation by several workers.

In connection with their work on the benzoylation of ketones from phloroglucinol, Canter, Curd, and Robertson (32) thought of the procedure of the Simonis reaction as a convenient solution of the problem of independently synthesizing chromones for purposes of comparison. They found that the condensation of phloroglucinol and ethyl α-methylacetoacetate with phosphorus pentoxide as condensing agent proceeds readily but that it results in the formation of the coumarin derivative in place of the expected chromone. Furthermore, the dimethyl ether of phloroglucinol and the same ester in the presence of phosphorus pentoxide also gave the dimethyl ether of the above coumarin. In view of the unexpected behavior of phloroglucinol, they extended the reaction to resorcinol. Simonis and Remmert (214) had studied this condensation and assigned to the condensation product obtained the constitution 7-hydroxy-2,3-dimethyl-1,4-benzopyrone (I). Robertson and coworkers found that Simonis' so-called chromone was identical with 7-hydroxy-3,4-dimethylcoumarin (II).



I



II

Robertson and coworkers extended the investigation to other phenols with similar results; they found that resorcinol, phloroglucinol, pyrogallol (33), and α-naphthol (173) always gave coumarins, irrespective of the condensing agent used. Robertson and coworkers (175) studied different phenols with a view to investigating whether coumarins or chromones are formed in the presence of phosphorus pentoxide. They concluded that the Simonis reaction depends entirely on the nature of the phenol and is independent of the nature of the ester, a view which was modified by them later on.

Simultaneously, Chakravarti (37) also showed that resorcinol reacts with β-ketonic esters to form coumarins and not chromones, even in the presence of phosphorus pentoxide. He also studied the condensation of pyrogallol, phloroglucinol, *m*- and *p*-cresols, and α- and β-naphthols with various β-ketonic esters in the presence of both of the condensing agents and obtained results essentially similar to those of Robertson and coworkers.

Dey and Lakshminarayanam (68) supported the earlier view of Robertson by studying the condensation of β-naphthol and acetoacetic ester. They found that in the case of β-naphthol even sulfuric acid gives a mixture of coumarin and chromone. The statement, "Those phenols which readily give coumarins with β-ketonic esters in presence of sulphuric acid also give coumarins and not chromones in presence of phosphorus pentoxide; those phenols which give coumarins in poor yield or do not react at all, produce chromones with phosphorus pentoxide in good yield", has been supported by numerous experimental facts obtained by both Robertson and Chakravarti and their collaborators.

The following generalization can be made on this point:

(*1*) Sulfuric acid as a condensing agent always gives a coumarin derivative, provided the reaction takes place. There is, however, a remarkable exception to the above generalization in the case of β-naphthol, which gives a mixture of coumarin and chromone even in the presence of sulfuric acid. Recently, Adams and Mecorny (1a) have reported the exclusive formation of a chromone in the Pechmann condensation of ethyl acetoacetate with 4-chloro-3,5-dimethylphenol.

(*2*) Phenols which react readily in the presence of sulfuric acid, e.g., resorcinol, pyrogallol, orcinol, α-naphthol, etc., also give coumarins by the Simonis reaction, i.e., in the presence of phosphorus pentoxide.

(*3*) Phenols which do not form coumarins at all or form them in poor yields with sulfuric acid, give chromones by the Simonis reaction, i.e., in the presence of phosphorus pentoxide.

(*4*) β-Ketonic esters with an α-alkyl substituent favor chromone formation in the Simonis reaction, but the substituent if too heavy retards and inhibits the reaction. Negatively substituted esters give coumarins in good yield, but if the substituent is of a strongly negative character, it is eliminated.

(*5*) Phosphorus pentoxide is the only condensing agent which promotes chromone formation. This singular behavior of phosphorus pentoxide is noteworthy. It may be mentioned, however, that Robertson and Goodall (171) have recently shown that phosphoryl chloride acts like the pentoxide in the condensation of *p*-xylenol, giving rise to chromones identical with the respective chromones obtained by the phosphorus pentoxide method.

Some other condensing agents

Besides the two common condensing agents, several others have been used to a greater or less extent. Pechmann used anhydrous zinc chloride in some condensations. Carl Bülow (31) condensed resorcinol and other phenols with ethyl *o*-carboxyphthalylacetoacetate and ethyl *o*-carboxybenzylacetoacetate in the presence of dry hydrogen chloride in glacial acetic acid solution and obtained coumarin derivatives. Appel (9) introduced absolute alcohol in place of acetic acid as the solvent. Various acidic and basic agents, like phosphoric acid, sodium ethoxide, boric anhydride, and sodium acetate, have been tried by Chakravarti (39) in place of sulfuric acid. Horrii (107) has investigated the use of ferric chloride, stannic chloride, and titanium chloride.

Naik, Desai, and Trivedi (146) introduced the use of phosphoryl chloride as the condensing agent to condense α-naphthol with α-benzylacetoacetate, as

sulfuric acid fails in this case. It has also been found to be successful in effecting the condensation of resacetophenone and other 4-acylresorcinols (60, 61) with acetoacetic ester to give 7-hydroxy-6-acyl-4-methylcoumarins, sulfuric acid failing to bring about this condensation.

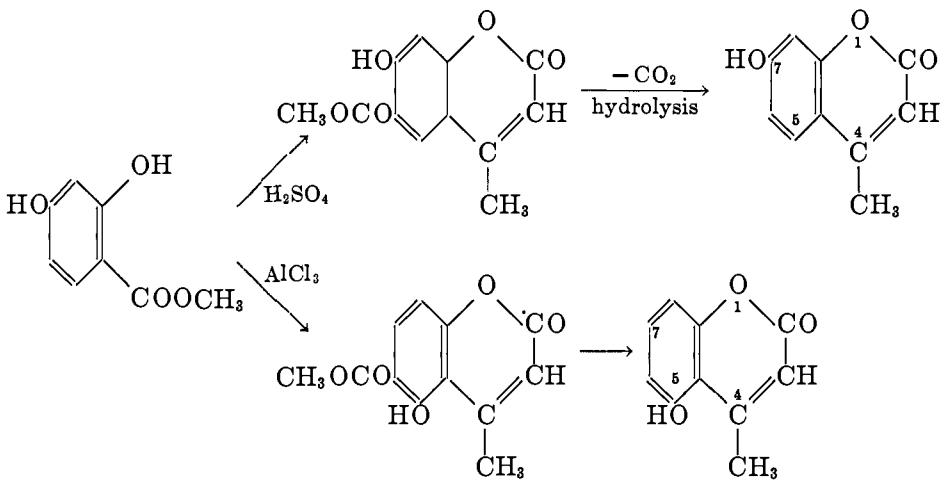
It has been found that the above condensing agents do not yield results of any particular value or interest, except in the case of phosphoryl chloride. In all cases coumarins are obtained, as with sulfuric acid, with some variations in the yields. Hydrogen chloride and phosphoric acid appear to be cleaner agents, as they do not produce highly colored and pasty products, but they have failed to promote the condensation where sulfuric acid has failed. Phosphoryl chloride, however, promises to be of interest, as already indicated above.

Anhydrous aluminum chloride as condensing agent

In exploring the use of other condensing agents, Sethna, Shah, and Shah (194) have in recent years introduced the use of a new condensing agent—namely, anhydrous aluminum chloride—which has proved to be of great value in the condensation of phenols with β-ketonic esters. The condensation is generally carried out in the presence of a solvent—anhydrous ether, in which aluminum chloride dissolves readily (206), or generally in dry nitrobenzene where elevated temperatures have to be used. The results obtained, which are unique in some respects, are outlined below:

(*a*) *Simple phenols*—The same coumarins are obtained as with sulfuric acid, in some cases with higher yields. In no case has a chromone been obtained. The reagent is of particular value in the case of slightly reactive monohydric phenols: phenol uniformly gives a yield of 30–40 per cent of 4-methylcoumarin (193), the recorded yield in the literature being 3 per cent; *o*-cresol, which does not condense in the presence of sulfuric acid, readily gives 4,8-dimethylcoumarin.

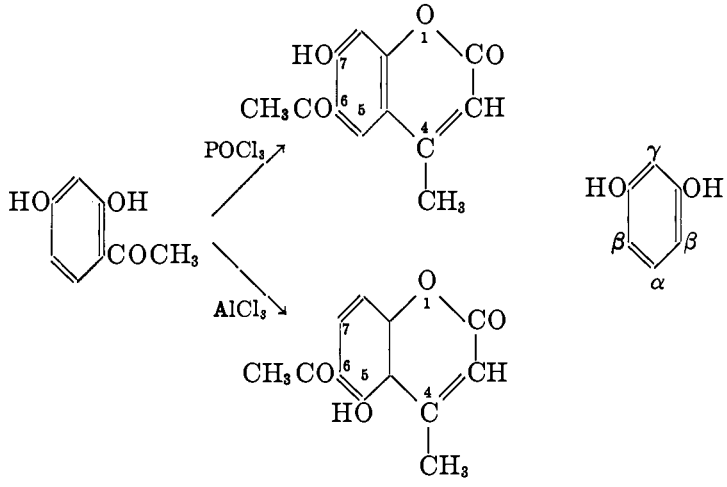
(*b*) *Phenolic esters*—Mention has already been made in another connection of the fact that methyl β-resorcylate condenses with acetoacetic ester in the presence of sulfuric acid, giving a 7-hydroxy-4-methylcoumarin-6-carboxylate. The



same condensation in the presence of aluminum chloride affords mainly the isomeric 5-hydroxycoumarin derivative (194), from which by hydrolysis and subsequent decarboxylation 5-hydroxy-4-methylcoumarin is readily obtained. Methyl 2,4-dihydroxy-5-ethylbenzoate (196) and methyl phloroglucinolcarboxylate (192) were also successfully condensed with acetoacetic ester in the presence of this condensing agent.

(*c*) *Phenolic ketones*—It has already been pointed out that resacetophenone does not condense with ethyl acetoacetate in the presence of sulfuric acid or sodium ethoxide. However, it readily undergoes the condensation in the presence of aluminum chloride, the product obtained in high yield being 5-hydroxy-6-acetyl-4-methylcoumarin (194). Orcacetophenone and 2,4-dihydroxybenzophenone react similarly, giving the corresponding 5-hydroxycoumarins. 2-Acetylresorcinol gives 7-hydroxy-8-acetyl-4-methylcoumarin in better yield than with sulfuric acid. *o*-Hydroxyacetophenone, quinacetophenone, and gallacetophenone do not condense (204). Shah and coworkers (47, 56) have extended the reaction to several 4-acylresorcinols and have obtained 5-hydroxy-6-acylcoumarins which are almost inaccessible by the hitherto known methods.

Desai and Hamid (61) were able to condense resacetophenone and other 4-acylresorcinols, using phosphoryl chloride as the condensing agent. 7-Hydroxy-6-acylcoumarins were obtained.



A reference has been made earlier to the fact that Chakravarti (41, 43) condensed 4-nitroresorcinol with acetoacetic ester, using sulfuric acid as condensing agent, and obtained 7-hydroxy-6-nitro-4-methylcoumarin. The same condensation with aluminum chloride was carried out by Parekh and Shah (150), who obtained 5-hydroxy-6-nitro-4-methylcoumarin.

Deliwala and Shah (57) condensed various substituted resacetophenones with acetoacetic ester in the presence of aluminum chloride and found that the presence of negative groups like —NO_2, —$COOCH_3$ and —$COCH_3$ in the resacetophenone nucleus has a deactivating effect and therefore prevents the condensation, while positive groups like —C_2H_5 have no such effect, the reaction readily taking

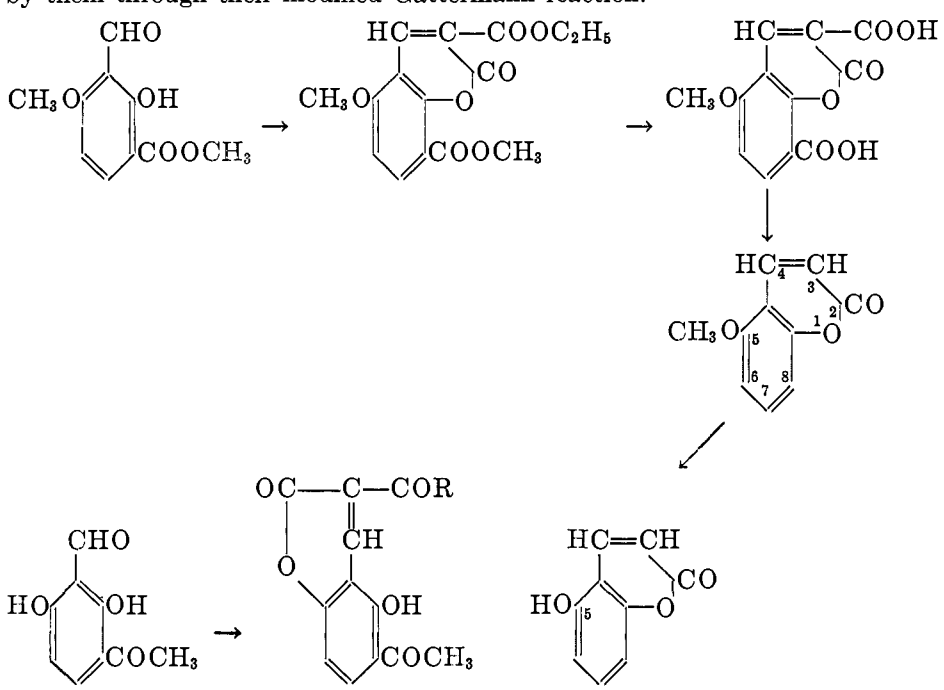
place. They (58) have also studied the condensation of resacetophenone with ethyl α-alkylacetoacetates. A negative substituent in the α-position has a completely inhibitory effect on the reaction. A positive substituent has less inhibitory effect, but as the bulk of the substituent increases, the reactivity diminishes; thus, ethyl α-propylacetoacetate did not condense. It may be mentioned here that resacetophenone could not be condensed even with ethyl α-methylacetoacetate with phosphoryl chloride as condensing agent. Thus the introduction of an α-alkyl substituent is not so inhibitive if aluminum chloride is used.

The striking feature of aluminum chloride as the condensing agent lies in the fact that, whereas other condensing agents give 7-hydroxycoumarins from resorcinol derivatives, this reagent modifies the course of the reaction with the production of 5-hydroxycoumarins, the condensation taking place in the usually inaccessible γ-position of the resorcinol nucleus.

The above results indicate that if the β-position in the resorcinol molecule is occupied by groups like carbethoxyl, carboxyl, acyl, benzoyl, and nitro, then the product obtained depends upon the condensing agent used.

5-Hydroxycoumarin, which cannot be obtained by the aluminum chloride method, has been synthesized by Shah and Shah (199) from methyl 2-hydroxy-3-formyl-4-methoxybenzoate by its Knoevenagel condensation with ethyl malonate and subsequent hydrolysis, followed by decarboxylation and demethylation of ethyl 5-methoxy-8-carbomethoxycoumarin-3-carboxylate.

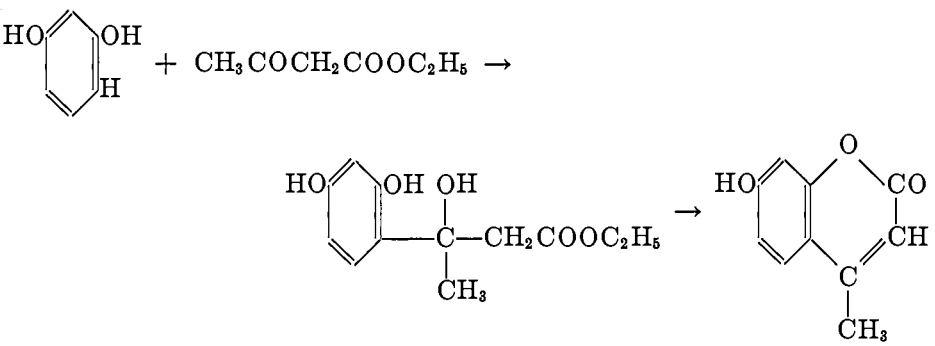
Several substituted 5-hydroxycoumarin derivates have been synthesized by Shah and his coworkers (200, 207) from 3-formylhydroxyphenyl ketones by the application of the Knoevenagel method, the formyl ketones being easily obtained by them through their modified Gattermann reaction.



IV. Mechanism of Reaction between β-Ketonic Esters and Phenols

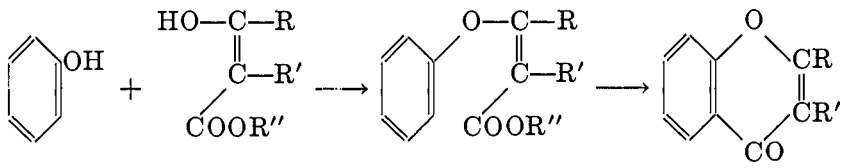
Two different views have been advanced with regard to the mechanism of coumarin formation by the Pechmann reaction. Robertson and coworkers (175) conclude from experimental evidence that cinnamic acid is formed as an intermediate. They observed that 2-methoxy-β,4-dimethylcinnamic acid was converted into 4,7-dimethylcoumarin by 86 per cent sulfuric acid and, further, that *m*-tolyl methyl ether and *o*,*o*-dimethylresorcinol gave rise to 4,7-dimethylcoumarin and 7-methoxy-4-methylcoumarin, respectively.

Ahmed and Desai (3) offer the explanation that the reactive hydrogen of phenol coördinates readily with the carbonyl group of the β-ketonic ester. This hydrogen is in the ortho position to the hydroxyl group and should be sufficiently reactive; otherwise, the tendency for the formation of the additive product will be little or nil.



The additive product then undergoes dehydration and cyclization to coumarin. The substituent in the β-ketonic ester will facilitate or retard the formation of the additive product, and the effect will be partly polar and partly steric.

With regard to the mechanism of the Simonis reaction, Robertson and collaborators consider that the first stage in the reaction is the formation of the phenoxy acid (or its ester) by the interaction of the enolic form of the ester and phenol with the removal of elements of water, the phenoxy compound then undergoing ring closure with the formation of chromone.

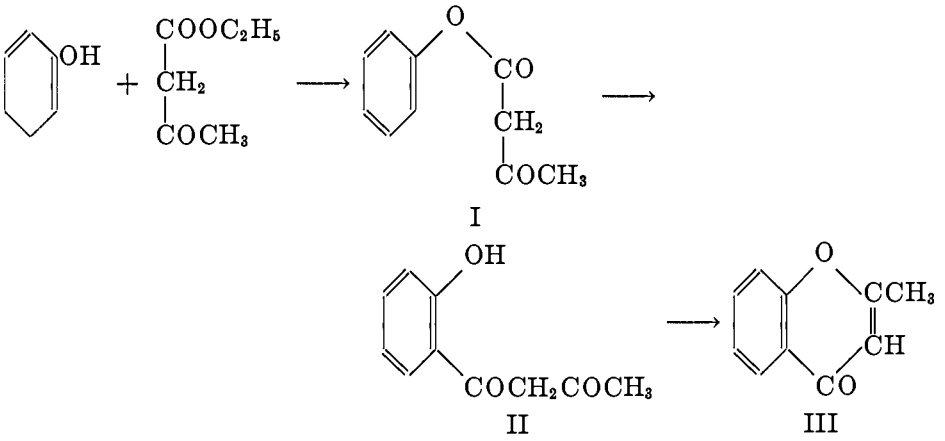


(R = CH_3; R′ = H or alkyl; R″ = C_2H_5)

In support of this mechanism, Robertson and collaborators cite as evidence the synthesis of 1,4-pyrones from phenoxyfumaric acid and from β-phenoxycinnamic acids by Ruhemann and coworkers (177).

Ahmed and Desai consider that, since only those phenols which do not contain a reactive hydrogen ortho to the hydroxyl group give chromones by the Simonis reaction, the reactive hydrogen belongs to the hydroxyl group, which interacts

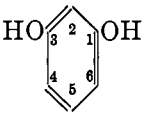
with β-ketonic esters giving rise to aryl esters of these acids (I). These aryl esters then undergo an isomeric change analogous to the Fries migration, forming *o*-hydroxybenzoylacetylmethane (II), which is dehydrated to the chromone derivative (III).



The specific condensing action of phosphorus pentoxide, according to Ahmed and Desai, is to facilitate the formation of I or II or both, as the conversion of II into III may be accomplished with the help of any dehydrating agent. The intermediate formation of diketone (II) in the Kostanecki acylation has been proved by Baker (15). Ahmed and Desai consider that it is also produced in the course of the Simonis reaction.

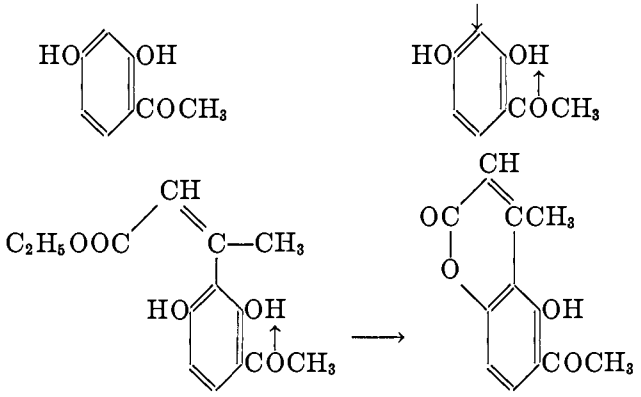
Of the two essentially similar views described above regarding coumarin formation, that of Robertson and coworkers is simpler and appears more plausible than that of Ahmed and Desai, whose assumption of additive compound formation, though ingenious, is not based on any experimental evidence. With regard to chromone formation, the two views are fundamentally different. Robertson and coworkers assume the condensation of phenolic hydroxyl with acetoacetate, the point of attack being the =C(OH)— part of the ketonic ester. Ahmed and Desai assume the condensation of phenolic hydroxyl with the carbethoxyl group of the ester, with the elimination of an alcohol molecule. This is not very likely, as the —C(OH)= group is usually more reactive than $—C_2H_5$ in the acetoacetic ester molecule. Ahmed and Desai further assume the transformation to be analogous to the Fries migration in the presence of phosphorus pentoxide, which has been quite recently found by Schönberg and Mustafa (180) to be effective in the Fries reaction on phenolic esters. No definite opinion is possible till further evidence is forthcoming.

The formation of 5-hydroxycoumarin derivatives in the condensation of resacetophenone, methyl β-resorcylate, etc., with aluminum chloride as condensing agent, obviously depends upon the reactivity in the 2-position in the resorcinol nucleus. Resorcinol derivatives easily undergo various substitutions and condensations in the 4-position in preference to the 2-position, which is usually inaccessible.

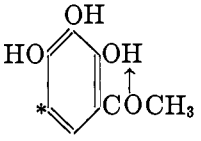


The reactivity in the 2-position in the present case becomes explicable in the light of the view that in these *o*-hydroxyacyl ketones one of the Kekulé forms becomes stabilized, owing to chelation between hydroxyl and acyl groups which requires the fixation of double bonds in the benzene nucleus between the carbon atoms bearing these two groups. Such a view of fixation of double bonds in the benzene nucleus was first put forward by Mills and Nixon (142) for compounds in which another ring is fused on to the benzene ring, and has been applied by Baker and his collaborators (16, 18) to substitution in resorcinol derivatives.

The formation of 5-hydroxycoumarins in the present case also depends upon the stabilization of one of the Kekulé forms by the fixation of double bonds. Thus, for example, in resacetophenone, owing to the existence of a chelate bond between the hydroxyl and acetyl groups, the double bonds are fixed and the point of attack is the carbon atom joined by a double bond to that bearing the other hydroxyl group; the condensation therefore takes place here, with subsequent ring closure to give 5-hydroxy-6-acetyl-4-methylcoumarin.



The non-condensation of gallacetophenone can also be satisfactorily explained by the application of the above views. It will be seen that the carbon atom marked with an asterisk, where the condensation may be expected to take place,



is not reactive, as it is united by a single bond to the carbon atom bearing the hydroxyl group. Baker states that aluminum chloride may prevent the chelation, but since 5-hydroxycoumarins are exclusively formed in good yields, it appears that this reagent does not prevent chelation and may even promote it.

This view also finds support in the work of Shah and Shah (200) on the formylation of 4-acylresorcinols, wherein it is found that the formyl group also enters the γ-position.

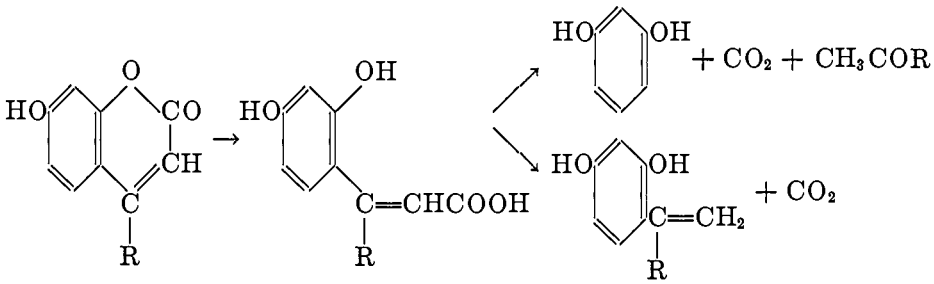
The formation of 5-hydroxycoumarins from methyl β-resorcylate and 4-nitroresorcinol in the presence of aluminum chloride can also be similarly explained. Two points bearing on the mechanism require to be mentioned. Whereas, in the case of resacetophenone and other 4-acylresorcinols, it is generally accepted that chelation between OH and —COR groups requires the double bond bearing these groups to be fixed, in the case of β-resorcylic acid and its ester, no definite conclusion seems to have been arrived at, as no case of 3-substitution in these compounds was previously known. Again, Baker is of the opinion that the presence of aluminum chloride must prevent chelation, owing to the formation of an addition product. However, in the present case it appears that aluminum chloride has a specially favorable action in promoting chelation, as other condensing agents produce 7-hydroxycoumarin derivatives. The view advanced above that the γ-position in methyl β-resorcylate is activated by the fixation of double bonds finds support in the work of Shah and Laiwalla (207), who found that the formyl group can be conveniently introduced in the γ-position in methyl β-resorcylate by the use of aluminum chloride in the Gattermann reaction.

V. Methods for Distinguishing Coumarins and Chromones

Much of the confusion that prevailed following the work of Simonis was due to the absence of any definite method by which a coumarin or chromone could be identified. At present, however, a number of methods are available. These can be divided into two groups: (*1*) those based upon the hydrolysis of the compound by alkaline reagents, and (*2*) those based upon the preparation of some special derivative. Earlier workers mainly depended upon hydrolytic methods, which often led to erroneous conclusions. The initial action of alkali on a coumarin is to open the pyrone ring, with the formation of a salt of coumarinic acid which on acidification regenerates the original coumarin. Although coumarinic or *cis-o*-hydroxycinnamic acids are as a class unstable, there are a few exceptions of moderately stable coumarinic acids, such as those derived from 8-nitrocoumarin (141), 3-acetyl-4,5,7-trimethylcoumarin-6,8-dicarboxylic ester (113), 6-nitro-$\alpha\beta$-1,2-naphthopyrone, and 6-nitro-$\alpha\beta$-1,2-naphthopyrone-4-acetic acid (64), and a few others. It will be noticed that, in all these cases, the coumarinic acid is stabilized by the entrance of acidic groups, the effect being more marked when the acidic radical is in position 8 of the coumarin ring system. Dey and Krishnamurthi (66) devised a method of separating a mixture of 6-nitro- and 8-nitro-coumarins by taking advantage of the superior stability of the coumarinic acid formed from the latter.

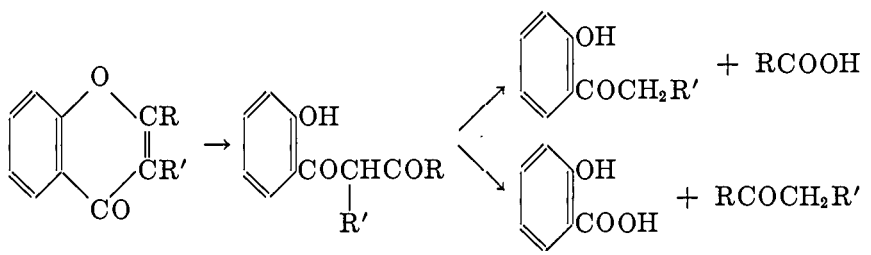
The entrance of alkyl groups, on the other hand, is found to produce the opposite effect. However, Dey, Rao, and Sankaranarayanan (71) have found certain $\beta\alpha$-1,2-naphthopyrone derivatives which give stable coumarinic acids, notwithstanding the presence of alkyl groups and the absence of any acidic substituent in the coumarin ring.

If the action of alkali is prolonged under suitable conditions, the stable coumaric acid is formed (85, 88). Sometimes the action of alkali results in the complete elimination of the pyrone ring, leading to the formation of a phenol (267, 128) or a styrene derivative (153).



Limaye and Kulkarni (133) have exhaustively studied the effect of substituents in 7-hydroxycoumarin on the elimination of the pyrone ring by caustic alkali.

In the case of chromone, according to Simonis (211), the hydrolysis occurs in two stages: the β-diketone is first formed and breaks up to yield either an *o*-hydroxy acid or an *o*-hydroxy ketone; the acid may further decompose giving a phenol.



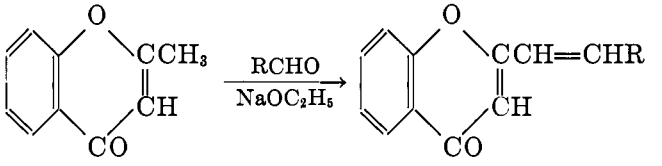
What type of splitting a chromone will undergo will depend upon the nature of the chromone and of the hydrolyzing agent and the conditions of the hydrolysis, or both. The action of sodium ethoxide on chromones generally leads to the acid type of splitting (268).

Information concerning a substance supposed to be a coumarin or a chromone may be obtained by consideration of the product of its hydrolysis: (*i*) If an *o*-hydroxy diketone is obtained, the substance is definitely a chromone. (*ii*) If a coumaric acid is obtained, the substance is definitely a coumarin. Some exceptions, however, have been recorded where the hydrolysis takes an abnormal course: 7-hydroxy-4,5-dimethylcoumarin (198) and 4-isopropyl-1,2-α-naphthopyrone (5) have been found to give orcacetophenone and 1-hydroxy-2-naphthoic acid, respectively, on hydrolysis. (*iii*) If an *o*-hydroxy ketone or *o*-hydroxy acid is obtained, the substance must be a chromone. Exceptions have been known, such as those mentioned above. (*iv*) If a phenol is obtained, no definite conclusion can be drawn. It must be made clear that negative results in any of the above cases do not indicate the absence of a coumarin or chromone.

The results have to be carefully considered if the confusion arising out of the wrong interpretations, as happened in the case of Jacobsen and Ghosh, is to be avoided.

Canter and Robertson (34) have devised an elegant method for the identification of coumarins. It consists in hydrolyzing the coumarin and preventing the closure of the lactone ring by subsequent methylation by dimethyl sulfate to get an *o*-methoxycinnamic acid derivative. The formation of the *o*-methoxycinnamic acid is a sure indication that the substance is a coumarin derivative. This method has been modified by Shah and Shah (205), who found that by dissolving the substance in acetone and then adding dimethyl sulfate and finally alkali, the formation of the methoxycinnamic acid was rendered more facile; in several cases where the Robertson method fails the modified method was found satisfactory.

An elegant method for distinguishing 2-methylchromones is due to Heilbron and coworkers (99), who from considerations of valency showed that the methyl group in the 2-position of a chromone should be reactive. This was realized experimentally, as 2-methylchromones condense with aromatic aldehydes in the presence of sodium ethoxide, giving styrene derivatives. Several workers, notably Chakravarti (42) and Robertson (119), have used styrene formation as a characteristic reaction of 2-methylchromones. Coumarins do not give styrene derivatives.

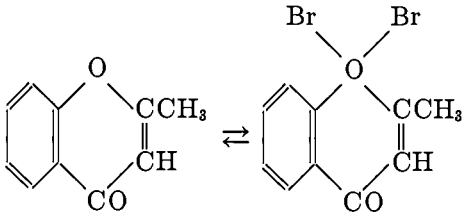


It has been observed that 2-methylchromones with certain substituents, e.g., $-OCH_3$, $-OCOCH_3$, $-OCH_2C_6H_5$, etc., in the 5- and 7-positions, as well as 3-acylated chromones, do not yield styrene derivatives (93, 132). Hence no definite conclusion can be drawn from a negative result in this test.

In the Kostanecki acylation of *o*-hydroxy ketones, the formation of a 3-acyl derivative is taken to be indicative of chromone formation. In view of the recent work of Sethna and Shah (197) on the Kostanecki–Robinson acylation of orcacetophenone, where 4-acylcoumarins have been obtained, the production of an acylpyrone as a criterion of chromone formation may be regarded with some doubt.

Lastly, mention may be made of Wittig's method (268) of separating a mixture of coumarin and chromone. The mixture is treated with sodium ethoxide; on acidification the coumarin is regenerated, but the β-diketone is unaffected and can be extracted with alkali, from which the chromone can be obtained. This method has been utilized by Heilbron and coworkers in several cases. Its success depends on two factors: (*i*) the absence of hydroxycoumarins and (*ii*) the fact that the chromone ring opens on treatment with sodium ethoxide and is not closed again on acidification along with the coumarin ring.

Desai (59) has evolved a diagnostic test for coumarins and chromones. When a glacial acetic acid solution of bromine is added to a solution of coumarin or chromone in the same solvent, the former gives invariably the soluble 3-bromo derivative, while the latter gives an insoluble perdibromide from which the original chromone is regenerated by treatment with sulfurous acid solution. If the chromone contains a hydroxyl group, the action of bromine gives a bromochromone.



VI. Substitution in the Coumarin Ring System

The coumarin ring system, which comprises a benzenoid part and the heterocyclic α-pyrone part, can give several derivatives with substituents in either component of the ring system. This can be realized either by condensing substituted phenols with different β-ketonic esters—as already discussed under the synthetic methods—or by substitution in the simple coumarin derivatives. The latter work is discussed in this section.

Several halogen, nitro, amino, and sulfonic acid derivatives have been obtained. There are, however, many difficulties in the preparation of alcohols, aldehydes, ketones, and carboxylic acids of the coumarin series. It may be mentioned that the benzene nucleus of the coumarin ring system is not so reactive as that of a simple benzene derivative.

Acyl- and formyl-coumarins

With a view to the preparation of acetylcoumarins, Desai and Hamid (61) tried the Friedel–Crafts reaction on 7-hydroxy- and 7-methoxy-4-methylcoumarins but it proved unsuccessful. However, the synthesis of hydroxyacetylcoumarins was realized by Limaye (130), by applying the Fries migration to 7-acetoxy-4-methylcoumarin with the help of anhydrous aluminum chloride, a process which resulted in the formation of 7-hydroxy-8-acetyl-4-methylcoumarin in quantity, along with a small amount of 7-hydroxy-6-acetyl-4-methylcoumarin. The Fries migration of acyloxy- or aroyloxy-coumarins to yield the acyl- or aroylhydroxycoumarins has been studied by various workers. Several 7-hydroxy- as well as 5-hydroxy-6-acylcoumarins have been directly synthesized by the condensation of resacetophenone and other 4-acylresorcinols with acetoacetic ester in the presence of either phosphoryl chloride (61) or aluminum chloride (194). Similarly, carboxylic acids of the coumarin series have been synthesized.

The Gattermann reaction on coumarins is unsuccessful, but Späth and Pailer (242) were able to introduce the formyl group in 7-hydroxycoumarin by means of hexamethylenetetramine, the 8-aldehydrocoumarin being obtained in poor yield. Rangaswamy and Seshadri (166) prepared aldehydohydroxy-coumarins,

-chromones, and -flavones by the same method. Sen and Chakravarti (185) prepared 6-aldehydocoumarin.

Nitration

Clayton (50) observed that coumarin was found to resist strongly the introduction of more than one nitro group, but this resistance diminishes very appreciably with the introduction of alkyl groups in the molecule: he found that when 8-nitrocoumarin is nitrated, the second nitro group goes to the 6-position, and that when 6-nitrocoumarin is nitrated, 3,6-dinitrocoumarin is obtained. The presence of a nitro group in the 3-position is shown by the reaction with alkali. When the substance is boiled with alkali, preferably concentrated ammonia solution, it dissolves and on subsequent acidification yields the corresponding salicylaldehyde derivative. This remarkably easy rupture of the lactone ring is found to be a property of all 3-nitrocoumarins. Clayton studied the nitration of various substituted coumarins and from the results concluded that there can be no doubt that the difficulty of obtaining higher nitration products of coumarin is due to the general acidity conferred on the molecule by the lactone ring; the introduction of methyl groups gradually weakens this acidity and makes the molecule more susceptible to the action of nitric acid.

Pechmann and Obermiller (158) investigated the nitration of 7-hydroxy-4-methylcoumarin and its methyl ether. They obtained 8- and 6-nitro compounds, respectively. This is in agreement with the similar reactivity exhibited by the same coumarin in other reactions: e.g., the formation of 8-aldehydo and 8-acyl compounds, the formation of angular α-pyrones, and the transformation of 7-allyloxycoumarin to 7-hydroxy-8-allylcoumarin.

The nitration of coumarin was found to proceed in the first place with exclusive substitution in the 6-position. Dey and Krishnamurti (66) revealed the formation also of small quantities of 8-nitrocoumarin in the process. The nitration of coumarin by benzoyl nitrate gives 5-nitrocoumarin in quantitative yield (83).

Fries and Lindemann (86) nitrated 8-chloro- and 8-bromo-7-hydroxy-4-methylcoumarins and obtained 8-chloro-6-nitro- and 8-bromo-3,6(or 5,6)-dinitro-7-hydroxy-4-methylcoumarins, respectively.

Dey and Kutti (67) have investigated the nitration of 8-methoxy- and 8-hydroxy-coumarins and obtained 8-methoxy-5-nitrocoumarin and 8-hydroxy-7-nitrocoumarin, respectively. Thus hydroxyl and methoxyl groups direct the nitro groups to different positions.

Recently, Parekh and Shah (149) have studied the nitration of 5-hydroxy-4-methylcoumarin and 5-hydroxy-4-methylcoumarin-6-carboxylic acid and its methyl ester. The nitration of the coumarin at lower temperature gave the 8-nitro derivative and at higher temperature the 6,8-dinitro derivative, while the acid and its ester afforded 8-nitro derivatives.

Halogenation

In the halogenation of coumarins, the halogen atom enters the pyrone ring initially in the 3-position and then enters the benzene nucleus. Thus, Simonis

and his coworkers (213, 215) found that the bromination of 4-methylcoumarin gave 3-bromo-4-methylcoumarin. By the action of bromine in carbon disulfide solution in a sealed tube, 3,6-dibromo-4-methylcoumarin was obtained, and 3,6,8-tribromo-4-methylcoumarin resulted when the reaction was carried out under pressure. In the case of hydroxycoumarins, bromination is not restricted to the pyrone ring alone but proceeds to the benzene ring as well (223). This difficulty is overcome by protecting the hydroxyl group by acetylation (115), methylation, or carbethoxylation (87). The presence of an acyl group in the benzene ring in the position ortho to the hydroxyl group seems to have a similar effect. For example, the bromination of 6-acetyl-5-hydroxy-4-methylcoumarin yields the monobromo derivative mixed with the dibromo derivative. To get a good yield of the 3-bromo derivative only, the bromination of the acetyl derivative was carried out, the deacetylation taking place during the reaction. Dey and Kutti (67) have found that in the halogenation of 8-methoxycoumarin, in contrast to the usual rule of halogen entering the pyrone ring first, halogenation proceeds with substitution in the benzene ring. In the bromination of 4-methyldaphnetin, Sakai and Kato (178) obtained 3-bromo- and 3,4-dibromo-4-methyldaphnetins.

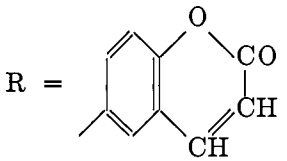
In the halogenation of coumarin-4-acetic acids, Dey and Radhabai (70) observed that the methylene group in the side chain in the 4-position was attacked and that 4-halogenocoumarinacetic acids were obtained. Addition of the halogen to the double bond of the pyrone ring was observed in the case of $\beta\alpha$-1,2-naphthopyrone-4-acetic acid only.

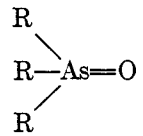
Sulfonation

Perkin (161) carried out the sulfonation of coumarin but did not establish the constitutions of the products obtained. Sen and Chakravarti (183) have sulfonated coumarin and 6-nitrocoumarin and obtained coumarin-6-sulfonic acid, coumarin-3,6-disulfonic acid, and 6-nitrocoumarin-3-sulfonic acid, the constitutions of which were proved by oxidation of the pyrone ring with alkaline potassium permanganate to yield the known salicylic acid derivatives.

Arsonation

Goswami and Das-Gupta (92) made the first attempts to introduce arsenic into the coumarin ring system. By applying Bart's reaction to 6-aminocoumarin, they obtained tricoumarylarsenic oxide (I). The reaction was extended to other coumarin derivatives, which yielded only mono derivatives (II).





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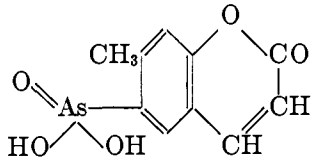
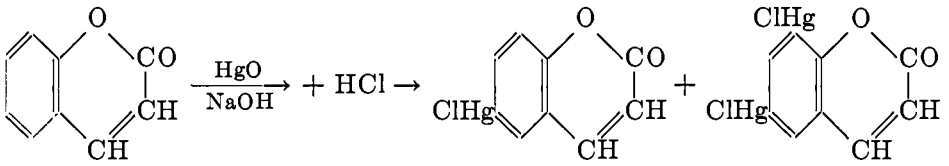


II

Mercuration

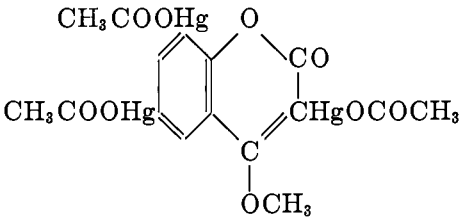
Sen and Chakravarti (184) were successful in introducing mercury into coumarins. They found that the usual reagents effectively employed in the mercuration of organic compounds failed to mercurate coumarin in aqueous, alcoholic, or acetic acid solution. When, however, the lactone ring was broken open and the masked hydroxyl group brought to prominence, mercuration readily took place with mercuric oxide or with mercuric acetate. By boiling the dilute solution of coumarin in alkali with yellow mercuric oxide, monochloro- and dichloro-mercuricoumarins were obtained. If the 6-position was occupied, no mercury compound was formed but geometrical inversion to *o*-coumaric acid derivatives took place.



Mercuration by mercuric acetate in alkaline solution gave diacetoxymercuric derivatives.

Naik and Patel (147) have studied the effect of substituents in the mercuration of coumarins. Ahmed and Desai (2) have mercurated coumarins obtained from cyclic β-ketonic esters, using the method of Sen and Chakravarti. The coumarins from resorcinol, orcinol, and phloroglucinol gave diacetoxymercuro derivatives. The coumarins from α-naphthol did not undergo mercuration.

Seshadri and Rao (190) have investigated the reaction of mercury salts on coumarins. They found that mercuric acetate in methyl alcoholic solution reacts with the double bond of the coumarin and further mercurates the benzene ring if the 6- and 8-positions are free, giving 3,6,8-triacetoxymercuro-4-methoxymelilotic anhydride:

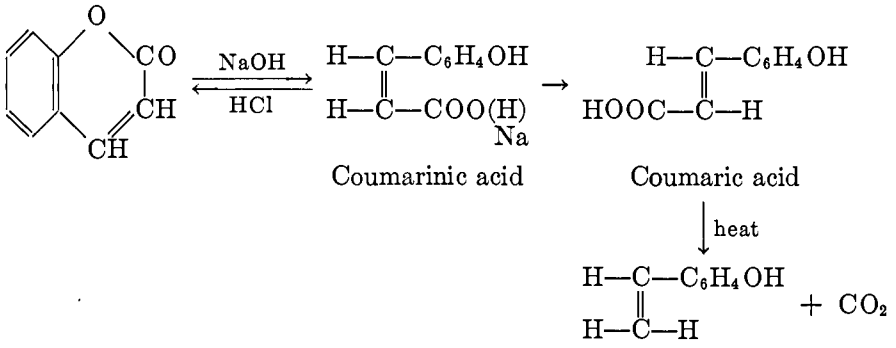


Mercuric chloride also adds to the double bond of coumarin and of 7-methylcoumarin.

Geometrical inversion in the acids derived from coumarins

Coumarins, being the lactones of *o*-hydroxycinnamic acids, give on treatment with alkali the salts of the corresponding coumarinic acids, which on acidification immediately revert to the coumarins; therefore the coumarinic acids are the

cis compounds. They are incapable of free existence, though some stable *cis* acids are known (page 23). If the action of alkali is prolonged under suitable conditions, *cis*-to-*trans* inversion takes place.



In this reaction, the initial formation of the alkali salt of coumarinic acid takes place, which then undergoes inversion under the influence of the reagent. This change is greatly facilitated by the addition of some reagent which acts as an addendum at the double bond of the pyrone ring. Methods have been devised in which substances like sodium hydrogen sulfite (74, 79) or mercury compounds (187) have been successfully employed to effect the inversion to the *trans* isomer.

The *trans* acids—coumaric acids—are capable of free existence and on heating decompose into carbon dioxide and hydroxystyrenes (72, 78). They undergo inversion to the *cis* forms under the influence of sunlight and are then readily converted into coumarins, the esters inverting even more readily than the free acids.

Among other methods of producing the *trans*-to-*cis* change, concentrated sulfuric acid at 100°C. has been sometimes used. Seshadri and Rao (191) found that this method gives only a poor yield; a saturated solution of hydrogen chloride in alcohol was superior to sulfuric acid in some cases. They have shown that a satisfactory method of *trans*-to-*cis* inversion is to boil the *trans* isomer with mercuric chloride solution.

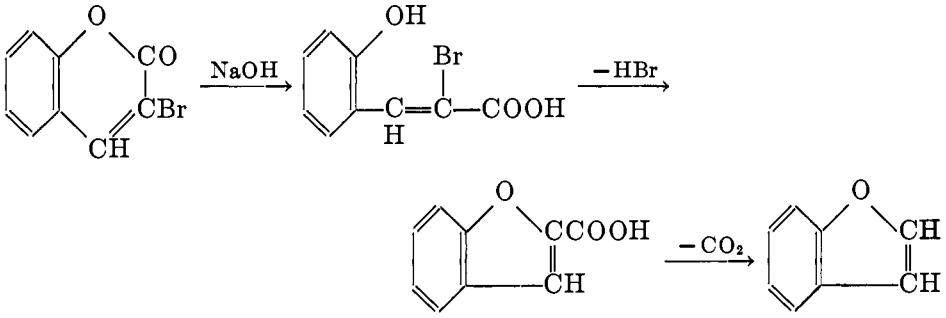
VII. Synthetic Uses of Coumarins

Coumarin and its derivatives are substances of much potential value for synthetic purposes. Their easy accessibility opens the way through suitable reactions to the synthetic preparation of various other heterocyclic compounds, such as coumarones, furanocoumarins (or furocoumarins), chromono-α-pyrones, flavono-α-pyrones, and chromenes, as well as natural products containing such ring systems.

Coumarones

3-Halogenated coumarins are converted into the corresponding coumarilic acids by treatment with alkali. The pyrone ring opens and loses a molecule of halogen acid, with the subsequent formation of coumarilic acid, which on

heating breaks down into carbon dioxide and yields coumarone. This is known as Fittig and Ebert's reaction.

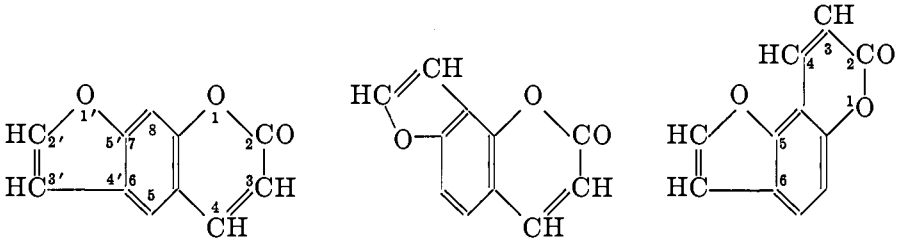


This method, which works well with simple coumarins, is not directly applicable to hydroxycoumarins, as bromination of these coumarins is not restricted to the pyrone ring but proceeds to the benzene ring; hence, bromo-free coumarones are not obtained. This difficulty is overcome by protecting the hydroxyl group and carrying out the bromination to get the monobromo derivative.

Thus, coumarone is a degradation product of coumarin in which the five-membered ring is obtained from the pyrone ring. Several coumarones have been prepared from coumarins in this way. Coumarones are used in industry for the manufacture of coumarone resins.

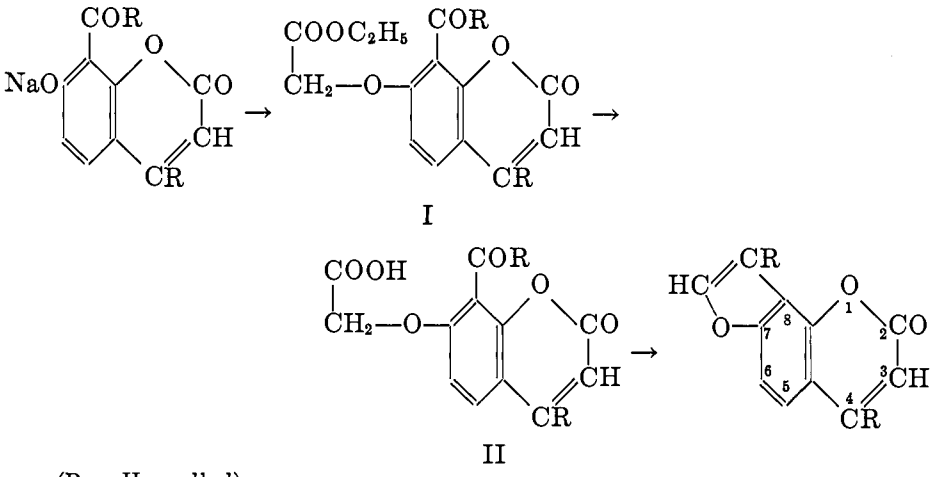
Furanocoumarins (or furocoumarins)

If the furan ring is built on a suitably substituted coumarin or chromone derivative, it leads to the synthesis of coumaronocoumarins or coumaronochromones, generally known as furanocoumarins or furanochromones. Alternatively, one can start with an appropriate coumarone and build up the α-pyrone or γ-pyrone ring, leading to the same furanocoumarins or furanochromones. Depending upon the position of the furano ring, several isomeric forms of furanocoumarins are possible: for instance,



The above three types are theoretically derivable from resorcinol.

In recent years, several furanocoumarins have been synthesized by Limaye (130) and his coworkers (131) by treating the dry sodium salt of an *o*-acylhydroxycoumarin or the coumarin in sodium ethoxide with bromoacetic ester; the resulting *O*-acetate (I) was hydrolyzed and the *O*-acetic acid (II) cyclized to the furan ring by treatment with acetic anhydride.



I

II

(R = H or alkyl)

An *o*-hydroxyacylcoumarin required for this synthesis is easily available by the Fries migration of acyloxycoumarins. Späth and Pailer (242) substituted bromoacetic ester by bromoacetal, while Ray, Silooja, and Vaid (170) used chloroacetone or bromoacetone in alkaline solution in the above condensation and cyclized the resulting product.

The above synthesis from 7-hydroxy-8-acylcoumarins leads to the formation of the furan ring between the 7- and 8-positions of the coumarin ring; such furanocoumarins are known as the angular type of furanocoumarins. If the ring is between the 6- and 7-positions of the coumarin, it will be the linear type, as obtained by Ray *et al.* All the types of these furanocoumarins shown above have been synthesized.

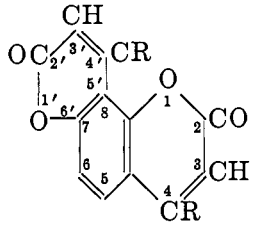
Shah and Shah (201) synthesized unsubstituted furanocoumarins from 5-hydroxycoumarin derivatives. In this case the sodium salt method was found unsatisfactory; hence the bromoacetic ester was condensed in dry acetone solution in the presence of potassium carbonate. This modification has been found to be satisfactory, and several furanocoumarins from 6-acyl-5-hydroxy-4-methylcoumarins have been synthesized by Chudgar and Shah (unpublished work).

Coumarino- and chromono-α-pyrones

Hantzsch and Zurcher (95) condensed a few umbelliferones with malic acid in the presence of sulfuric acid and obtained the first representatives of the coumarino-α-pyrones in poor yield. They did not prove their constitutions. Sen and Chakravarti (186) prepared some other members of the same class. Rangaswami and Seshadri (166) showed that when umbelliferone is condensed with malic acid, two isomeric compounds are formed: angular coumarino-7,8-α-pyrone (I; R = H) is the major product; the second compound, obtained in small quantity, is taken to be the linear compound, coumarino-7,6-α-pyrone (II; R = H). Under the same conditions, 4-methylumbelliferone gives only one coumarino-α-pyrone, *viz.*, 4-methylcoumarino-7,8-α-pyrone. 4-Methyl-

umbelliferone and ethyl acetoacetate also give 4,4′-dimethylcoumarino-7,8-α-pyrone (I; R = CH_3), which is obtained in good yield when resorcinol is condensed with an excess of the ester in the presence of alcoholic hydrochloric acid. Coumarino-α-pyrones are prepared by the Perkin reaction on *o*-hydroxyformylcoumarins, which are obtainable with difficulty.

Another way of synthesizing these compounds is to subject an *o*-hydroxyacyl- or aroyl-coumarin derivative to the Kostanecki acylation. This will give either chromono-α-pyrones or coumarino-α-pyrones. Shah and coworkers (194, 204, 56) have synthesized several of these types of compounds from 6-acyl-5-hydroxycoumarins.



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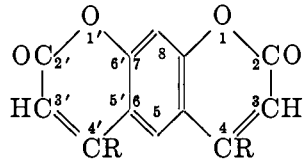

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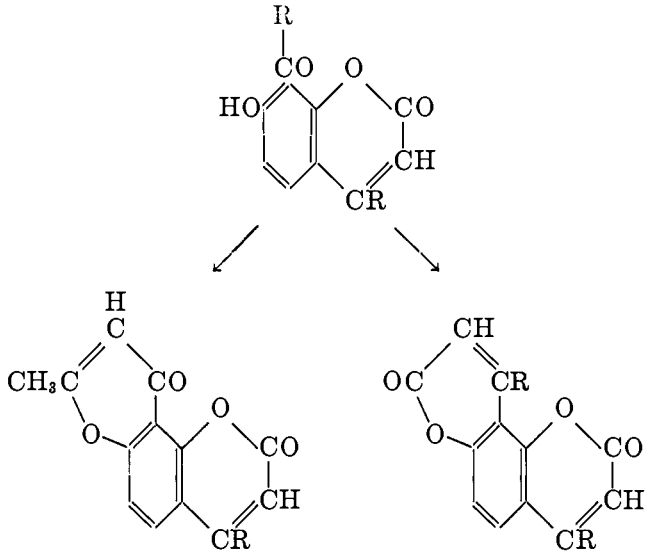
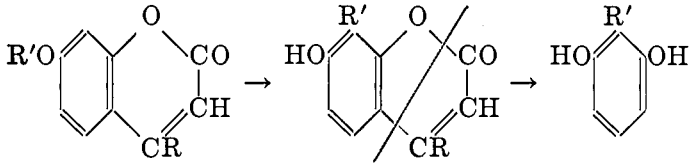


Chromono-α-pyrone

2-Acylresorcinols

The introduction of an acyl or aroyl group into the γ-position of the resorcinol nucleus was difficult until Limaye (128, 129) developed an elegant method for this synthesis. Starting with a 7-hydroxycoumarin derivative, its acyloxy or aroyloxy compound is prepared, which on Fries migration gives mainly an 8-acyl-7-hydroxycoumarin derivative, from which the pyrone ring is eliminated

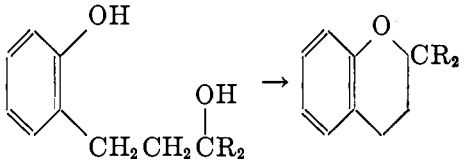
by boiling with aqueous alkali, the resulting product being a 2-acyl- or 2-aroyl-resorcinol. This method, named the Nidhone process by the author, has been extensively applied for the preparation of various 2-acyl- and 2-aroyl-resorcinols.



(R' = acyl or aroyl; R = H or alkyl)

Action of Grignard reagents on coumarins

When Grignard reagents react with dihydrocoumarins, carbinols (I) are obtained which on ring closure give 2,2-dialkylchromans (221).

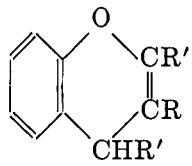


I

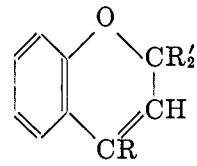
The action of Grignard reagents on coumarins, however, is much more complicated because of the presence of the conjugated double bonds, and a variety of products is obtained depending upon the conditions of the reaction. Decker and Fellenburg (54, 55) have shown that the interaction of coumarin and Grignard reagents under carefully specified conditions leads to the production of monoalkyl pyrylium salts. Willstätter and his coworkers (266) have used this reaction for the synthesis of anthocyanidins from 3-methoxycoumarins.

Houben (108), Löwenbein, Pongráez, and Spiess (136), and Shriner and Sharp (210a) have recorded a number of investigations leading to the formation of substituted chromenes and have suggested a mechanism for the course of the reaction employing a large excess of the Grignard reagent.

Heilbron and Hill (104, 105) investigated the action of Grignard reagents on substituted coumarins with the object of synthesizing flavylium chlorides containing methoxyl and hydroxyl groups in the 4-position, compounds of the latter type being expected to lose hydrogen chloride and pass into flavones. They obtained only diaryl products. A detailed investigation of 3- and 4-substituted coumarins led to the conclusion that the production of either a Δ^2- or a Δ^3-chromene is influenced solely by the position of the substituent in the pyran ring. They also found that when dilute solutions under the conditions employed by Willstätter are used with 3-methyl-, 3-phenyl-, and 3-methoxycoumarins, the reaction proceeds smoothly and gives good yields of the corresponding 2-phenylbenzopyrylium salts, but that when more concentrated solutions are employed, Δ^3-chromenes are obtained.



2,4-Diaryl-Δ^2-chromene



2,2-Diaryl-Δ^3-chromene

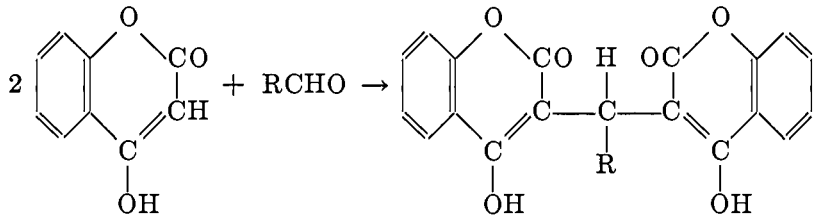
The formation of 2,2-dialkyl- and 2,2-diaryl-Δ^3-chromenes, directly or through the isolation of the intermediate unsaturated carbinols, has been utilized by many workers (26, 30, 137) for the synthesis of such derivatives. The formation of chromonols in the reaction between Grignard reagents and coumarins has also been noted.

Kartha and Menon (116) have studied the condensation of methoxymethylumbelliferone with an excess of Grignard reagents: α-naphthocoumarin has been condensed with phenylmagnesium bromide. All the condensation products are assigned the Δ^3-chromene structure, in conformity with the general conclusions of Heilbron: i.e., when the 4-position is occupied by a substituent, the product is the Δ^3-compound.

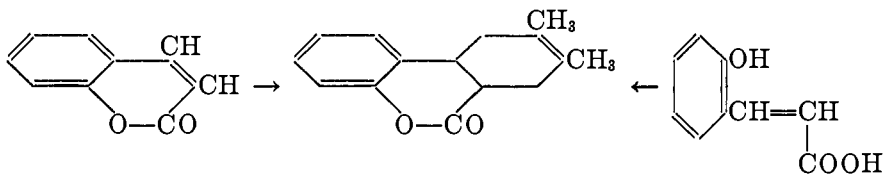
Other reactions

Row and Seshadri (176) synthesized coumarino-7,8-furanones by the Fries reaction on the chloroacetoxy derivatives of 7-hydroxycoumarins.

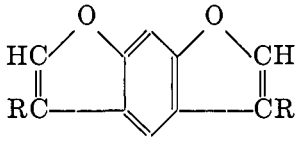
Two molecular equivalents of 4-hydroxycoumarin condense with formaldehyde, giving 3,3′-methylenebis(4-hydroxycoumarin), the causative agent of the hemorrhagic sweet clover disease of cattle. The reaction has been extended to other aliphatic and aromatic aldehydes (250); the products obtained have been dehydrated to form the substituted 1,4-pyran derivatives, 3,3′-alkylidene- or 3,3′-arylidene-4,4′-epoxydicoumarins, by means of acetic anhydride in pyridine.



Adams and coworkers (1) added 2,3-dimethylbutadiene to coumarin and some substituted cinnamic acids. With coumarin they obtained 8,9-dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone in poor yield. *trans-o*-Hydroxycinnamic acid added the same diene more readily to give the same pyrone.

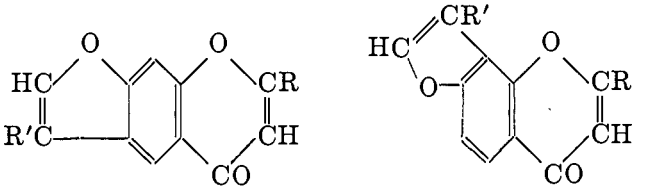


Furocoumarones (dicoumarones) have been synthesized by Hanztsch (96), Algar and coworkers (4), and recently by Limaye and Panse (134).

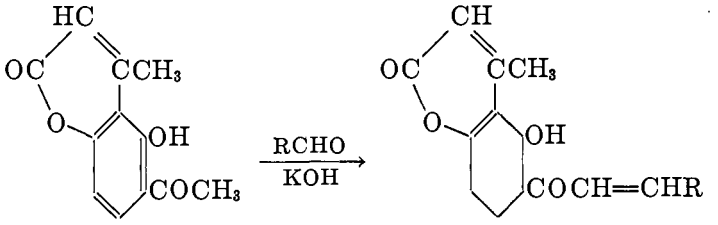


Limaye and Sathe (135) have described a synthesis of some members of the furanochromone class by building up a furan ring on a suitably substituted chromone derivative. The other possibility of synthesizing the γ-pyrone ring on a suitable coumarone derivative has not yet been realized. The synthesis of the hydroxyacylcoumarone required as the starting material is being attempted.

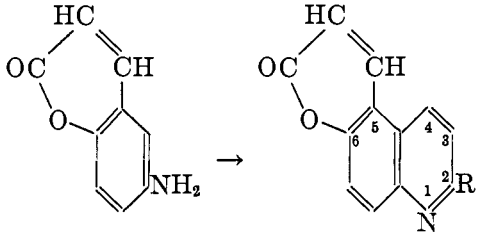
Recently Shah (202) synthesized coumarinochalcones from 6-acetyl-5-hydroxy-4-methylcoumarin. Though a considerable amount of work has been published on chalcones, this appears to be the first instance of the formation of chalcones from heterocyclic ketone derivatives.



Furanochromones

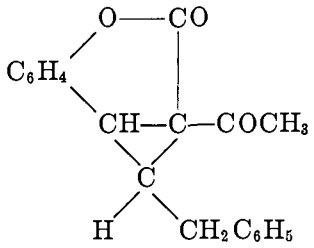


By applying the Doebner–Miller reaction to 6-aminocoumarin and 6-amino-4-methyl-α-naphthopyrone, Dey, Sarkar, and Seshadri (75) have synthesized a class of 2-methylquinolino-6,5-α-pyrones; the simple quinolino-α-pyrones have been obtained by Dey and Goswami (65) by the application of the Skraup reaction.



(R = H or CH_3)

Widman (265) has prepared a new type of coumarin in which a cyclopropane ring forms a part of the nucleus by condensing 3-acetylcoumarin with ω-chlorobenzophenone in cold alcoholic solution.



VIII. Physicochemical and Other Properties of Coumarins

Tasaki (253) investigated the absorption spectra of several coumarin derivatives in 0.001 *M* alcoholic solution for wave numbers (λ^{-1} in centimeters) from 2000 to 5000. Coumarin shows two absorption maxima in this region, at 3200 Å. and 3600 A. When hydroxyl groups are introduced, the substance shows only one absorption maximum.

E. Rakower (164) has described and discussed the spectra of methyl 3-cinnamoylacetylcoumarin-7-carboxylate, dicinnamoylmethane, and coumarin.

The fluorescence and absorption spectra of 7-hydroxycoumarin-3-carboxylic acid and methyl 7-hydroxy- and 7,8-dihydroxy-coumarin-3-acetates have been investigated by Czapska-Narkiewiez (52). The fluorescence maxima are at 4596, 4727, and 4679 Å. and the absorption maxima are at 3300, 4314, and 4517 Å., respectively.

The Raman spectra of coumarin in the solid state as well as in solution in different solvents have been examined by Seshadri (188) with reference to (*1*) the C=C and (*2*) the C=O frequencies. Of the three frequencies belonging to (*1*), which are fairly constant throughout, the two lower ones represent the aromatic double bonds of the benzene ring and the third represents the ethylene double bond of the pyrone ring. The C=O frequency is considerably low in the solid state as well as in the solutions with certain polar solvents, possibly owing to the weakening of the C=O bond by the formation of hydrogen bonds through coördination. Mookerjee and Gupta (143) have also investigated the Raman spectra of some coumarin derivatives and chromone in the solid state and in solution with reference to shifts in C=O frequency.

The dipole moment of coumarin at 20°C. (4.51×10^{-19} E.S.U.) has been measured and indicates a state of resonance between the normal and excited states (169).

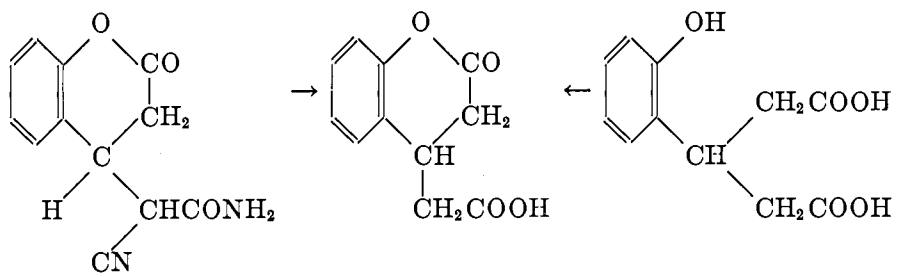
The crystal structure of coumarin has been investigated by Ramaswamy (165). An exhaustive study of the structural influences governing the fluorescence exhibited by coumarin derivatives has been made by Seshadri and coworkers (20, 167, 168). They have studied several hydroxycoumarins as well as chromones with respect to their fluorescence. A number of umbelliferone derivatives with different substituents in the 3-position have also been examined in this respect. The presence of carbethoxyl, carbonyl, or acetyl in the 3-position of

7-hydroxy- and 7-methoxy-coumarins enhances the fluorescent property of the compounds to such an extent that they exhibit bright fluorescence even in neutral alcoholic solutions, whereas the same groups in the 4-position produce no such effect. 7-Hydroxycoumarins produce bright fluorescence in neutral or alkaline media, but the intensity is considerably diminished in acid media. The fluorescence of 7-hydroxycoumarins is blue, whereas their methoxy derivatives show fluorescence more on the violet side. 3-Benzoyl compounds are yellow in the solid state as well as in solution and exhibit no visible fluorescence under any conditions.

Dihydroumbelliferone and its derivatives in which there is no ethylenic double bond do not give fluorescence. 5-Hydroxycoumarins dissolve in alkali with a deep yellow non-fluorescent color.

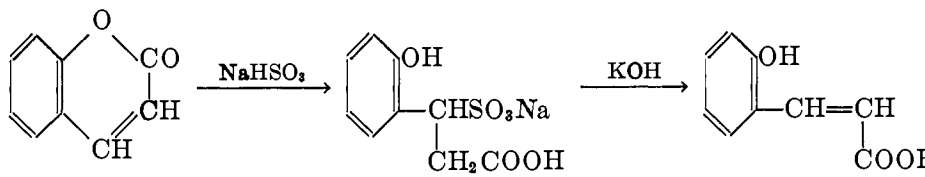
The possibility of resonance as the result of electron mobility is now recognized as the essential cause of absorption, and this may also be considered as one of the deciding factors for fluorescence emission. The results are explained on this basis.

A large amount of work has been done on the reactivity of the double bonds in coumarins. The unsaturated center in coumarins seems to differ greatly in reactivity from the double bond in related compounds. The double bond between carbon atoms 3 and 4 in the coumarin nucleus is highly reactive; it adds bromine (162), hydrogen cyanide, and sodium bisulfite with great facility. Seshadri (189, 190) investigated this reactivity of the double bonds in coumarins in comparison with α,β-unsaturated carbonyl compounds, and found that coumarin condensed easily with cyanoacetamide and yielded I, which on hydrolysis gave the acids II and III, the latter being converted into II.



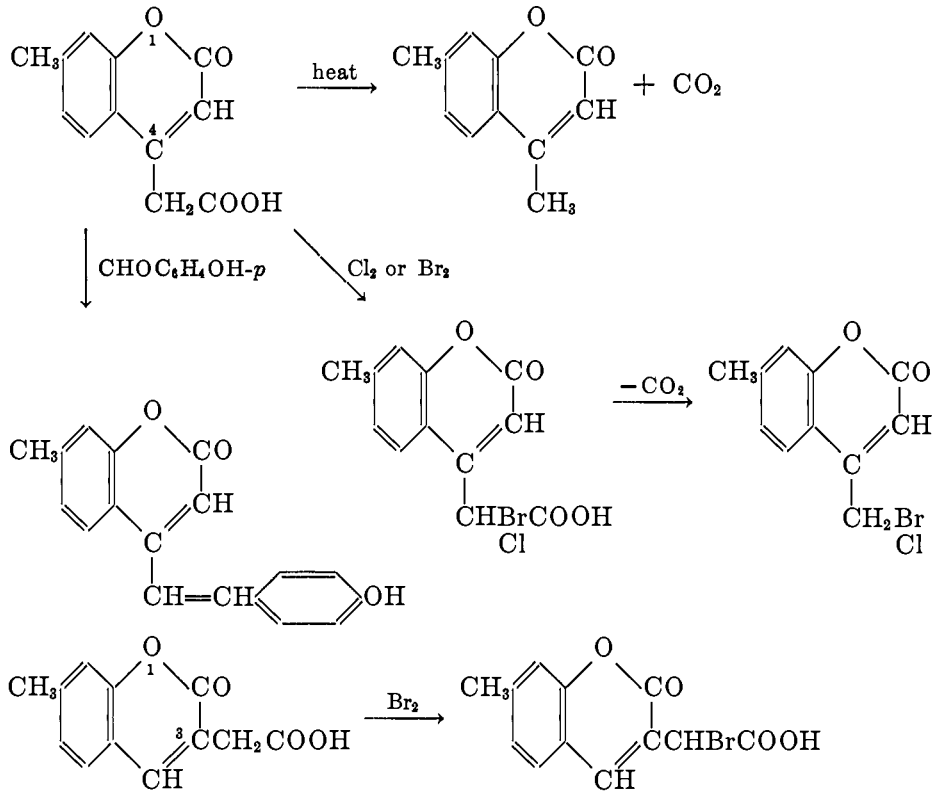
I II III

Dey and Rao (73), as well as Dodge (79), found that sodium hydrogen sulfite reacts with coumarin to give a β-sulfonic acid, which on being boiled with concentrated caustic potash solution gives *o*-coumaric acid. This reaction furnishes a convenient method of converting coumarins into their coumaric acids.



Coumarin-3- and 4-acetic acids comprise within their molecules a double bond between carbon atoms 3 and 4 in the pyrone ring and a reactive methylene group attached to either of these atoms. Dey and Row (74) and Dey and Seshadri (77) have shown that coumarin-4-acetic acids resemble malonic acid in decomposing smoothly and quantitatively into 4-methylcoumarins and carbon dioxide. Further, coumarin-4-acetic acids and their esters readily condense with aromatic aldehydes both by Perkin's and by Knoevenagel's methods, giving rise to 4-coumarylphenylethylene and 4,3-dicoumaryl derivatives. Coumarin-3-acetic acids, on the other hand, are more stable and do not decompose even on heating at high temperatures; they are less reactive, as they do not undergo the Knoevenagel reaction.

Dey and Radhabai (70) have studied the action of halogens on the above acids. They found that halogen does not attack the double bond in the pyrone ring, as usually happens, but substitutes one of the methylene hydrogen atoms, a considerable amount of decarboxylation taking place. $\beta\alpha$-1,2-Naphthopyrone-4-acetic acid forms a solitary exception to the above generalization.



The hydrogenation of some substituted coumarins has been investigated with a view to obtaining information regarding the mechanism of formation of chroman derivatives (25a).

IX. Natural Coumarins

Coumarins either in the free or in the combined condition are found to occur in different parts of the plant. The coumarin-bearing part, after suitable preliminary treatment, is extracted with a solvent and the extract is then subjected to various processes for isolation.

Isolation

A simple coumarin having no interfering group in the molecule and not in combination with glucose as glucoside can be isolated on treatment with dilute aqueous alkali solution (0.5 per cent). This treatment removes acids and other phenolic substances present in the extract. It is then treated with 5 per cent aqueous alkali alcoholic solution (caustic potash) for some time. By this treatment the coumarins are transformed into the potassium salts of the corresponding coumarinic acids as the lactone ring opens. Other reactions also occur simultaneously, e.g., any fatty material present is saponified. The mixture is then diluted with water and extracted with ether, whereby other substances (if any) are removed. The alkaline layer is then acidified; the acidic substances (if any) and coumarins are liberated. This mixture is taken up with an excess of ether and treated dropwise with dilute aqueous alkali; the acids dissolve and the coumarins remain behind. This process is repeated, whereby the acids along with a fraction of the coumarin are removed. Further separation is effected by vacuum distillation and/or sublimation. The coumarin is then purified by crystallization, chromatographic analysis, or other suitable method.

If the original plant material contained any hydroxycoumarins, they are carried down in the aqueous portion by initial treatment with aqueous alkali. That fraction is worked up; it is acidified, and extracted with ether, and separated from other fatty substances by extraction with petroleum ether. It is then distilled in a high vacuum and further purified by crystallization. To ascertain the presence of hydroxycoumarin, a portion of the liquid after acidifying is treated with diazomethane and then subjected to the treatment described above. If a methoxycoumarin is found to be present, a hydroxycoumarin was present in the original material. It may be mentioned here that prolonged treatment with alkali should be avoided, as it brings about the change of hydroxycoumarin into coumaric acid to a small extent.

Esters of hydroxycoumarins, if present, are found along with non-hydroxylic coumarins, but they may suffer in the course of separation on account of hydrolysis. Hydroxycoumarins are produced and separated along with them; they are to be worked out as described above.

Coumarin glucosides are detected thus: the soluble fraction after the treatment with alcoholic alkali is freed from impurities by extraction with ether; the glucoside is then decomposed by treating with dilute sulfuric acid, and the resulting aglucone is tested for coumarin. A quantitative estimation of simple coumarins is of possible interest in the scheme of separation of coumarins (114).

Classification

The coumarins isolated from plants and so far investigated can be grouped as shown below:

1. Coumarin and its simple derivatives.
2. Hydroxy- and methoxy(alkoxy)-coumarins and their glucosides. The hydroxy or alkoxy group may be present in the benzene or the pyrone ring.
3. Hydroxy- or methoxy-coumarins with an alkyl group in any part of the ring system.
4. Furanocoumarins (furan ring fused to benzene ring) with (*i*) an unsubstituted furan ring and (*ii*) a substituted furan ring.
5. Coumarins with a 2,2-dimethyl-1,2-chromene ring.

Several natural coumarins are so diversely substituted that they may be classified under more than one of the above subgroups. In such a case, the coumarin should be placed in that group which emphasizes a prominent point with regard to its constitution. The above classification is not final and will have to be modified or altered as our knowledge of the chemistry of natural coumarins advances.

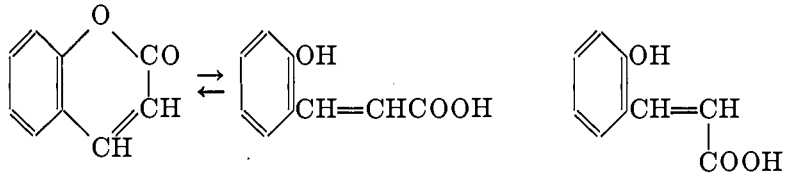
At present about fifty natural coumarins are known and their chemical constitutions established. Thanks to Späth and coworkers, the natural coumarins have been extensively studied in recent years, and interest has been created in the subject.

Structure and occurrence

We shall now consider some reactions which have been used to prove the structure of natural coumarins.

Let us first consider coumarins having no acidic groups such as hydroxyl. A simple proof is that these non-hydroxylic coumarins are difficultly soluble in water and do not dissolve in alkali immediately, but when kept for a long time or when heated, dissolve completely with a yellow color, the corresponding alkali salt of the coumarinic acid being formed: if carbon dioxide is now passed into the alkaline solution or the solution is acidified, the acid is set free and, being unstable, immediately changes into a coumarin.

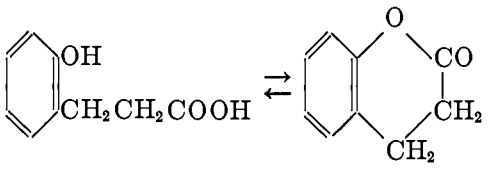
The transformation of coumarinic acid formed by the opening of the pyrone ring into coumaric acid—the *trans* isomer of coumarinic acid—is characteristic of the presence of the coumarin structure. The *trans* isomer can be changed into the *cis* form by the action of light or treatment with acids; the experimental realization of these isomeric changes is in many cases beset with difficulties.



Coumarin Coumarinic acid Coumaric acid

To decide whether a compound is a coumarin or not, hydrogenation is helpful. If a coumarin is present, one can introduce two hydrogen atoms into the coumarin structure by catalytic hydrogenation with palladium black or animal

charcoal. The resulting hydrocoumarin (I) is then changed into its hydroxy acid (II) by opening the lactone ring; the acid has no tendency to form the ring



II Melilotic acid

I Dihydrocoumarin

at ordinary temperature, in contrast to the hydroxycinnamic acids which easily change into coumarins. The hydrocoumarinic acids can be isolated in their free condition and converted into hydrocoumarins by distilling in a vacuum at higher temperatures.

The hydrocoumarin or hydrocoumarinic acid, on treatment with oxidizing agents such as nitric acid and potassium permanganate, gives succinic acid, which arises from the hydrogenated pyrone ring. This reaction is easily carried out, but it may be mentioned here that succinic acid can also arise from the side chain if any; therefore the above important reaction should always be considered in relation to other results. Dihydrocoumarins are dehydrogenated to coumarins in very good yield by the method of Späth and Galinovsky (230).

By the action of dimethyl sulfate on an alkaline solution of a coumarin, a methoxycinnamic acid is obtained. This method is a good one for distinguishing a coumarin structure, as stated previously.

An important method for determining the structure of a coumarin is to convert it into a benzene derivative of unambiguous constitution by cautiously oxidizing the *o*-methoxycinnamic acid. Hydroxycoumarins yield complicated results; on methylation, the disturbing factors are suppressed.

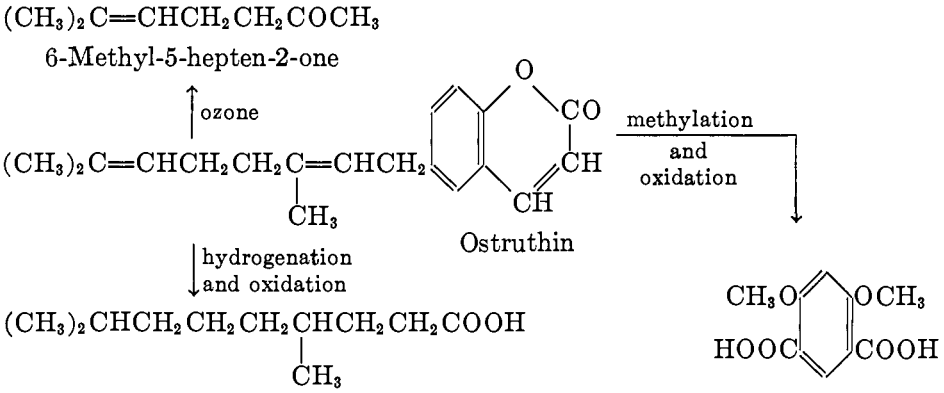
Glucosides of coumarins must first of all be hydrolyzed by dilute acids, and the resulting aglucones treated as described above.

With regard to the position of the hydroxyl group in the benzene nucleus of the coumarin, it has been found that in several cases, by fusion with potash, the heterocyclic ring and the side chain, if any, are split off and the simple phenol is obtained. By the action of nitric acid on a coumarin derived from resorcinol, styphnic acid, $C_6H(OH)_2(NO_2)_3$, is obtained; the methoxycoumarins on oxidation yield methoxybenzoic acids. A clue to the position of the group in the coumarin nucleus is thus obtained. In the case of a polyhydroxy coumarin, only an unambiguous synthesis can settle the constitution. Bargellini (24) has made an interesting observation that coumarins on oxidation with potassium persulfate are hydroxylated in the 6-position.

The number of double bonds can be easily estimated by quantitative hydrogenation, which has nowadays been developed even on a micro scale. As a rule, a coumarin double bond in the 3- and 4-positions is always more difficultly hydrogenated than a double bond in an unsaturated aliphatic side chain.

The structure and position of a side chain can be ascertained by the investi-

gation of oxidation products from the hydrogenated coumarins; an aliphatic carboxylic acid is obtained. The carbon atom of the carboxyl group comes from the nucleus; the other carbon atoms are from the hydrogenated side chain. The position of double bonds in the side chain is indicated by examining the oxidation products of the coumarin: aldehydes, ketones, and acids with a different number of carbon atoms are produced. All these reactions are illustrated below:



The presence of an unsubstituted furan ring is also determined by the oxidation of a furanocoumarin in alkaline solution, the furandicarboxylic acid being obtained.

Ethers of hydroxycoumarins and unsaturated alcohols containing the chain $-OCH_2CH=C(CH_3)_2$ undergo decomposition into their phenolic and alcoholic constituents by the action of glacial acetic acid to which a few drops of sulfuric acid have been added; the products can then be easily investigated.

We shall now briefly consider some natural coumarins.

The long-known sources of coumarin are the tonka bean, white clover, woodruff (*Asperula odorata*), etc. It is widely distributed in the plant kingdom and is found to be present in over sixty plants belonging to about twenty-four natural orders. It is often found as a glucoside or as a derivative of melilotic acid. Melilotoside is a crystalline glucoside of coumaric acid.

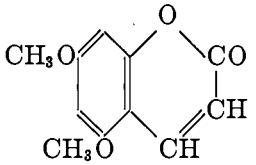
Out of the simple monohydroxycoumarins having the hydroxyl group in the benzene nucleus, only 7-hydroxycoumarin (called umbelliferone) has been long known. 5-, 6-, or 8-hydroxy-coumarins have not yet been found in plants. 7-Hydroxycoumarin was called umbelliferone, as it was obtained by the dry distillation of umbelliferous resin. It also occurs in the free condition in several plants. Various derivatives of umbelliferone are extensively distributed in the plant kingdom and await investigation.

Dihydroxycoumarins in which both the hydroxyl groups are in the benzene nucleus, as well as their glucosides, are frequently found in plants. The hydroxyl groups are in the 5,7-, 6,7- and 7,8-positions. Of the two hydroxyl groups, the one in position 7 generally takes part in the formation of glucosides or ethers. This has been found to hold good even in complex coumarins. 5, 6-, 5,8-, and 6,8-dihydroxycoumarins have not yet been found to occur in nature.

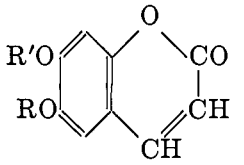
5,7-Dimethoxycoumarin, known as citropten or limettin, is present in citron oil and similar essential oils.

Esculetin (or aesculetin) was known as a product of the decomposition of the glucoside esculin. This coumarin has also been found to occur in the free condition in the bark of horse chestnut and other plants. The constitution 6,7-dihydroxycoumarin is assigned to it. The esculin isolated from the horse chestnut is 6-β-glucosidoesculetin, while cichoriin, an isomeric glucoside of esculetin present in the leaves of the chicory plant, is its 7-glucoside.

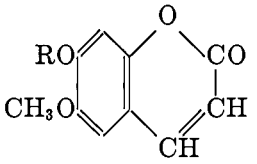
Scopoletin, or 7-hydroxy-6-methoxycoumarin (97), occurs in its free form as well as in the form of its glucoside, scopolin, in belladonna and other plants.



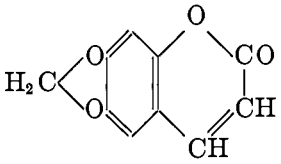
Citropten (limettin)



Aesculetin (R = R′ = H)
Aesculin (R = $C_6H_{11}O_5$; R′ = H)
Cichoriin (R = H; R′ = $C_6H_{11}O_5$)



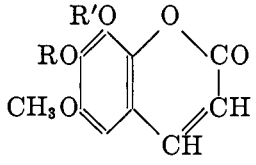
Scopoletin (R = H)
Scopolin (R = $C_6H_{11}O_5$)



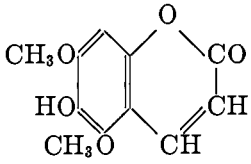
Ayapin

Ayapin, found in the leaves of *Eupatorium ayapana* Vent., is the methylene ether of esculetin and is the first instance of a methylenedioxycoumarin found in nature (226). Daphnetin, 7,8-dihydroxycoumarin, occurs in the form of its glucoside, daphnin, found in the plants of the Thymelaeceae order.

As a trihydroxycoumarin, fraxetin has been known since 1857. It was obtained from its glucoside fraxin, which is present in various species of ashwood. Its constitution has been proved to be 7,8-dihydroxy-6-methoxycoumarin (263). The glucose molecule in fraxin is combined with the hydroxyl group in the 8-position.



Fraxetin (R = R′ = H)
Fraxidin (R = CH_3:R′ = H)
Isofraxidin (R = H; R′ = CH_3)
Fraxin (R = H; R′ = $C_6H_{11}O_5$)



Fraxinol

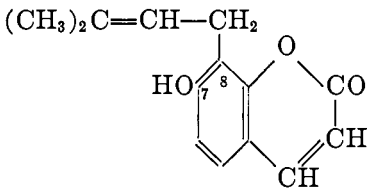
Recently, Späth (234) has found that a series of trihydroxycoumarins are present in the form of their glucosides in the fresh bark of German ashwood. Of these, the coumarins fraxidin and isofraxidin are related to fraxetin. Fraxetin, fraxidin, and isofraxidin are the derivatives of 1,2,3,4-tetrahydroxybenzene, while fraxinol is a derivative of 1,2,3,5-tetrahydroxybenzene.

Coumarins with hydroxyl groups in the pyrone ring have not yet been found as natural products, but 4-hydroxy-7-methoxycoumarin is produced by the thermal decomposition of neutral constituents of ammonia gum (125).

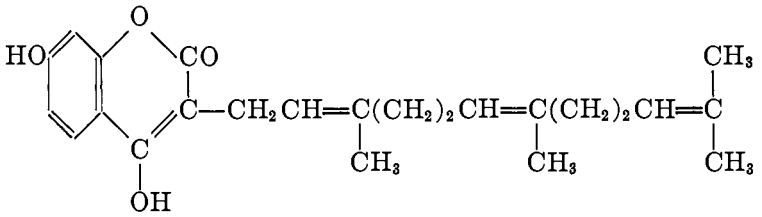
Osthol, osthenol, ostruthin, ammoresinol, and toddalolactone belong to the group of hydroxy- and methoxy-coumarins with alkyl or alkylene groups. Osthol, found to occur in umbelliferous plants, is the methyl ether of osthenol, which is 7-hydroxy-8-(γ,γ-dimethylallyl)coumarin (243). Späth has investigated various plant materials to find other coumarins with constitutions analogous to that of osthol.

Another interesting coumarin belonging to this group is ostruthin, occurring in imperatoria rhizhomes as a main coumarin (237).

The isolation and investigation of the constituents of umbelliferous resins which are reputed to be drugs is a difficult task, which is yet in its initial stage. Casparis (35) has devised a process by which a crystalline product called ammoresinol is obtained as a main constituent from ammonia rosin of *Dorema ammoniacum* Don., and it has been assigned the following constitution:

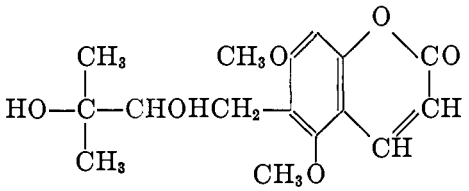


Osthenol

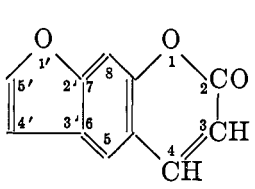


Ammoresinol

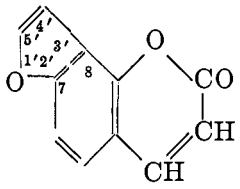
The optically active toddalolactone, isolated from the root-bark of *Toddalia aculeata* (Rutaceae) by Dey and Pillai (69), has been assigned the following constitution by Späth, Dey, and Tyray (229):



Furanocoumarins of type I have been found in nature. Depending upon the position of fusion of the furan ring, several isomers are possible, two of which have been found to occur in nature,—angelicin (II) and psoralene (I). These



I
Psoralene



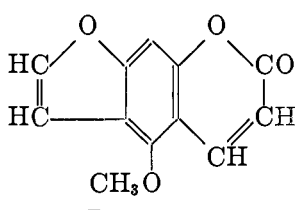
II
Angelicin

are the parent substances of several natural furanocoumarins. The ring system of angelicin is present in isobergaptene and pimpinellin, while that of psoralene is found in bergaptol, bergaptene, xanthotoxol, xanthotoxin, isopimpinellin, imperatorin and isoimperatorin, oxypeucedanin, and ostruthol.

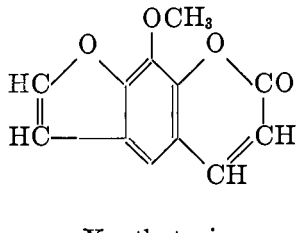
Angelicin was first detected in *Angelica archangelica* (Umbelliferae) and is also found to occur in an Indian leguminous plant, *Psoralea corylifolia* L. Angelicin has been proved to be furano-2′,3′,7,8-coumarin (II) (244).

Psoralene, isomeric with angelicin, was found by Manjunath (111) in the same leguminous plant and its constitution established as furano-2′,3′,7,6-coumarin (I) (241). Psoralene is also found in the leaves of the fig and appears to be widely distributed.

Bergaptene and xanthotoxin contain a methoxyl group with the psoralene ring structure. Both of them are thus monomethoxy derivatives of psoralene. They occur in *Fagara* (Rutaceae) and other plants. The determination of the correct structure for xanthotoxin from several suggested possible formulae is due to Thoms (254).



Bergaptene

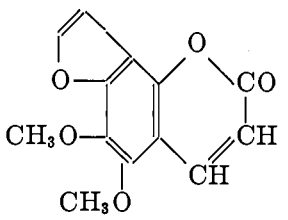


Xanthotoxin

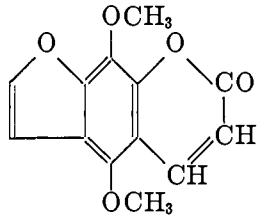
Bergaptol, the hydroxy derivative of bergaptene, is found to occur along with bergaptene in bergamot oil; xanthotoxol, the hydroxy derivative of xanthotoxin, was isolated from the seeds of *Angelica archangelica*. These phenolic furanocoumarins give on methylation bergaptene and xanthotoxin, respectively; thus their constitutions are beyond doubt.

Isobergaptene was found as a constituent in the roots of burnet saxifrage (*Pimpinella saxifraga*) and is 5-methoxyangelicin (264a).

Pimpinellin and isopimpinellin are dimethoxyfuranocoumarins obtained from the roots of burnet saxifrage. The synthesis of isopimpinellin from 5,8-dihydroxypsoralene settles its constitution out of a plethora of suggested formulae (264).



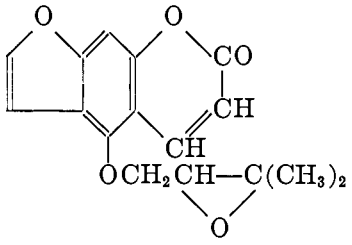
Pimpinellin



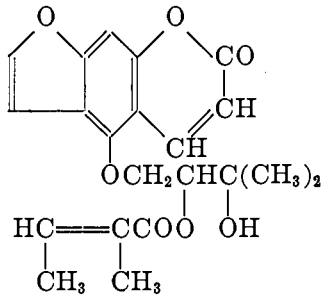
Isopimpinellin

Sphondin and sphondylin, found in the roots of bear's breech (*Acanthus mollis*), are methoxyfuranocoumarins whose constitutions have not been settled (246).

A number of complex furanocoumarins are present in master-wort (imperatoria) rhizome. Of these, imperatorin, isoimperatorin, oxypeucedanin, and ostruthol have been completely investigated. Imperatorin and isoimperatorin are isomeric (233, 239). Oxypeucedanin, present in the roots of *Peucedanum officinale* (Umbelliferae) and known for nearly a century, has been investigated only in recent years (236). Its name is misleading, as it would indicate that the substance is related to peucedanin, a furanocoumarin belonging to an entirely different group. Ostruthol has been established as a furanocoumarin related to oxypeucedanin (227).



Oxypeucedanin

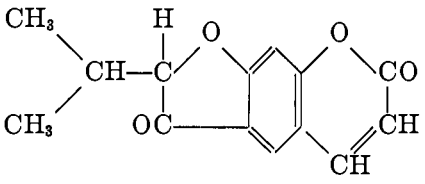


Ostruthol

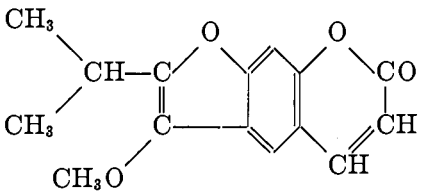
All the above furanocoumarins are unsubstituted in the furan ring. We shall now refer to a group of furanocoumarins with substituents in the furan ring, *viz.*, peucedanin, oreoselone, nodakenin, and nodakenetin. In 1833, the presence of peucedanin in the rhizomes of *Peucedanum officinale* was noted, but Späth (238) took up the investigation of the structure of this product only a decade ago. This work gave him an incentive for his future work in the field of natural coumarins.

Peucedanin contains one methoxyl group more than oreoselone, while oreo-

selone has no free hydroxyl group; therefore Späth has put forward the following formulae for them:



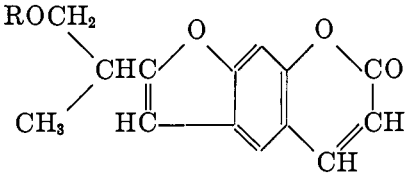
Oreoselone



Peucedanin

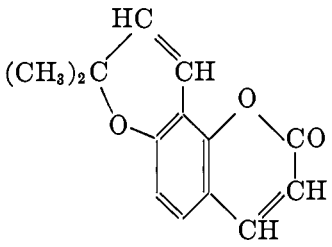
Peucedanin is the enolic methyl ether of oreoselone, a fact which easily explains the hydrolysis of peucedanin to oreoselone.

Nodakenin is a coumarin glucoside found in a Japanese species of *Peucedanum decurvisum* Max., which on hydrolysis gives nodakenetin and *d*-glucose. Nodakenetin was also obtained in a minute quantity by Späth from the same plant (235).



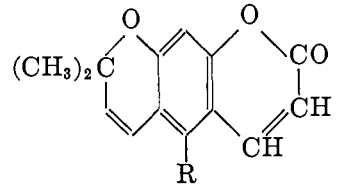
Nodakenetin (R = H)
Nodakenin (R = $C_6H_{11}O_5$)

Späth, Bose, and others (225) have isolated seselin from *Seseli indicum* and have assigned the following structure to it. The same coumarin is also obtained from Japanese *Skimmia japonica*.



Seselin

Xanthoxyletin (or xanthoxylin N) and xanthyletin, occurring in the bark of the plant *Xanthoxylum americanum* (Rutaceae), belong to the group of coumarins with a 2,2-dimethyl-1,2-chromene ring. At present two coumarins are known in this group. Xanthoxyletin has now been found to occur in *Luvunga scandeus* Ham. Robertson (174) has done much work on these coumarins, and assigned the following structures to them:



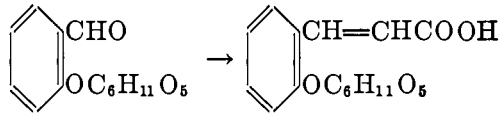
Xanthyletin (R = H)
Xanthoxyletin (R = OCH_3)

Synthesis

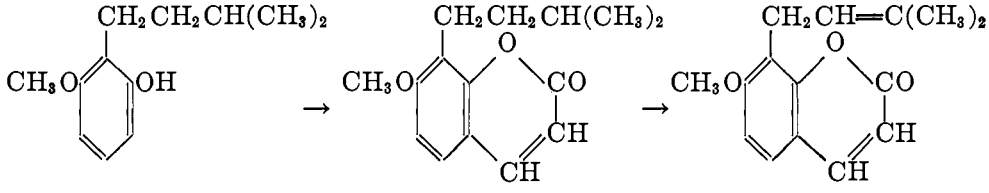
The natural coumarins, umbelliferone, herniarin, citropten, esculetin, and daphnetin, were long ago synthesized by the well-known methods of Perkin and Pechmann. The synthesis of these coumarins presented some difficulties, as the necessary starting materials were not easily available then. During the last few years, Seka (182) and Robertson (25) have synthesized scopoletin from 2,4-dihydroxy-5-methoxybenzaldehyde; Späth and Jerzmanowska (234) have obtained fraxinol from 3,6-dihydroxy-2,4-dimethoxybenzaldehyde.

For synthesizing the glucosides of phenolic coumarins, the reaction with acetobromoglucose has been found to be fruitful in several cases. Seka (181) and Merz (140) synthesized cichoriin from esculetin; Merz (140; also 138) prepared a pure specimen of scopolin. Mauthner (139) has prepared a synthetic umbelliferone glucoside isomeric with skimmin. Leone (127) obtained a daphnetin glucoside isomeric with natural daphnin. From helicin, a glucoside of salicylaldehyde, Shinoda and Imaida (210) have synthesized melilotoside by condensation with malonic acid.

In the group of alkylated hydroxycoumarins, Späth and coworkers (247) have carried out the synthesis of osthol by subjecting the product of the action of γ,γ-dimethylallyl bromide on the sodium salt of 2-hydroxy-4-methoxybenzaldehyde to the Perkin reaction. By the action of malic and sulfuric acids on the monomethyl ether of 2-isoamylresorcinol, dihydroösthol is obtained, from which osthol has been prepared. Hailer and Acree (94) also carried out a similar synthesis.



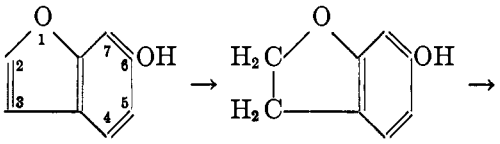
Melilotoside

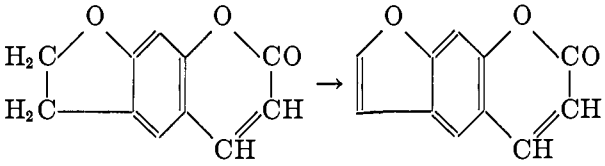


Dihydroösthol Osthol

With regard to the synthesis of natural furanocoumarins, Späth prepared angelicin in low yield by treating the sodium salt of umbelliferone with bromoacetal at a high temperature. Späth and Pailer improved the yield by building the furan ring on umbelliferone-8-aldehyde. Limaye (131) synthesized angelicin from 4-hydroxycoumarone.

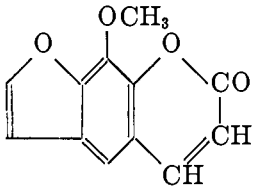
Psoralene has been synthesized by Späth, Manjunath, Pailer, and Jois (241) from 6-hydroxycoumarone. The coumarone does not undergo the Pechmann reaction, but the 6-hydroxycoumaran, when treated with malic and sulfuric acids, formed the coumarin ring; the dihydropsoralene thus obtained was dehydrogenated to psoralene.





Dihydropsoralene Psoralene

Späth and Pailer synthesized xanthotoxol from 6,7-dihydroxycoumaran, which on condensation with malic acid in the presence of sulfuric acid gave dihydroxanthotoxol; dehydrogenation of this substance yielded xanthotoxol. To get xanthotoxin, either xanthotoxol was methylated or dihydroxanthotoxol was first methylated and then dehydrogenated.

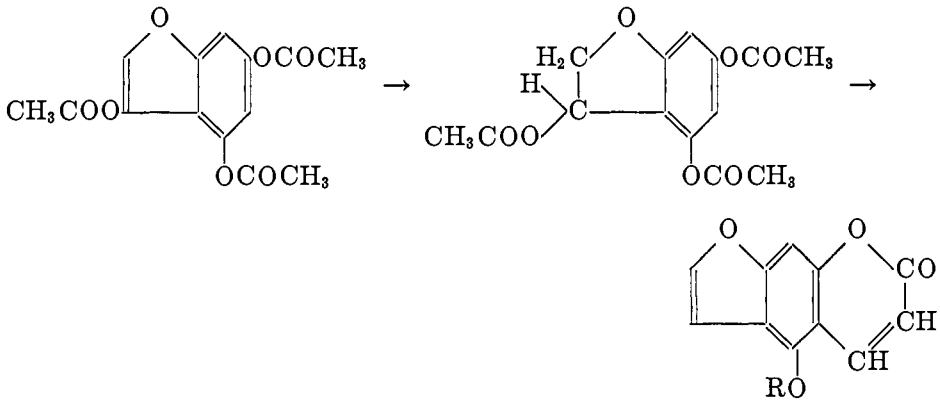


Xanthotoxin

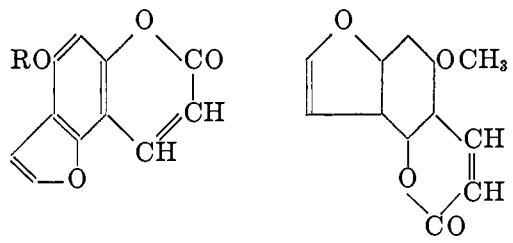
Späth, Wessely, and Kubiczek (248) have synthesized bergaptol, starting with 3,4,6-triacetoxycoumarone. This substance was hydrogenated, and the coumaran treated with ethyl sodioformylacetate in alkaline solution. Deacetylation took place, and the resulting hydroxy compound condensed with the forma-

tion of two products, allobergaptol and bergaptol, which on methylation gave allobergaptene and bergaptene, respectively. Isobergaptene is produced by the opening of the pyrone ring of bergaptol, partial methylation of the resulting product, and new ring formation in another position (240).

Howell and Robertson (109) have synthesized bergaptene starting with apoxanthoxyletin: 7-hydroxy-5-methoxy-6-formylcoumarin condensed with bromoacetic ester to yield a product which on hydrolysis gave the acid which, on cyclization and simultaneous decarboxyation, yielded bergaptene. Foster, Howell, and Robertson (82) have synthesized allobergaptene.



Bergaptol (R = H)
Bergaptene (R = CH_3)

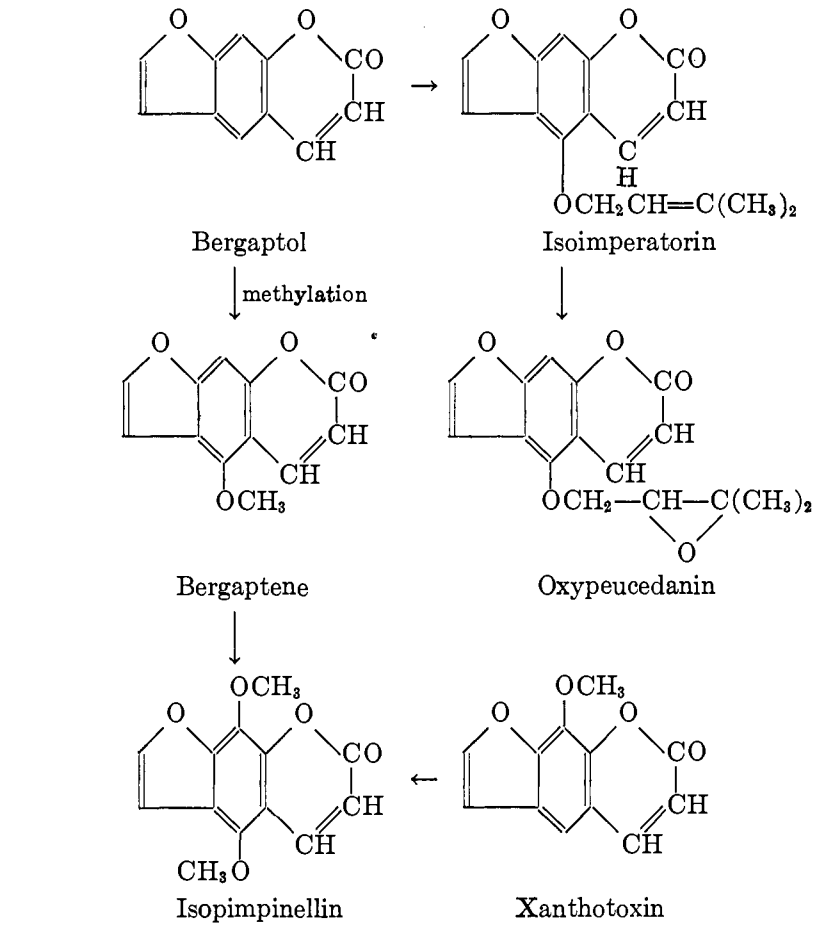


Allobergaptol (R = H)
Allobergaptene (R = CH_3)

Isobergaptene

By the action of perbenzoic acid on isoimperatorin, Späth and Holzen (232) obtained oxypeucedanin. By the condensation of prenyl bromide with bergaptol in the presence of sodium methylate, Späth and Dobrovolny (228) prepared isoimperatorin, thus establishing a total synthesis of oxypeucedanin.

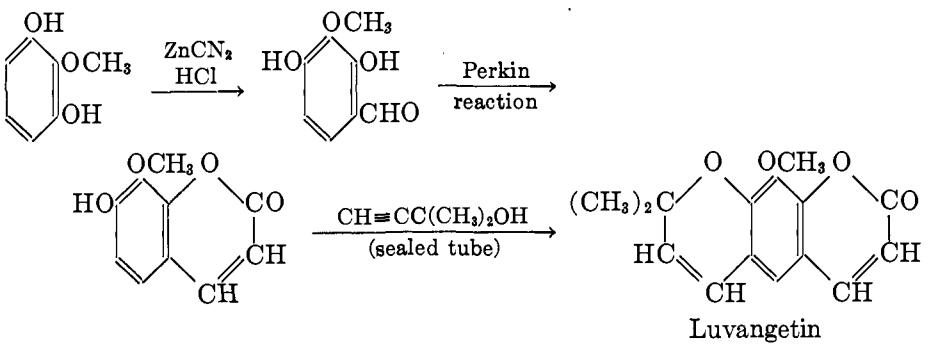
Wessely and Nadler (264a) have carried out a synthesis of isopimpinellin. Starting with bergaptene and xanthotoxin, they prepared their nitro derivatives;



from these derivatives quinones were prepared, which on reduction and subsequent methylation gave isopimpinellin.

Späth and Hillel (231) have obtained seselin by heating umbelliferone with 2-methyl-3-butyn-2-ol.

Späth and Schmid (245) have recently synthesized luvangetin from 1,3,2-$C_6H_3(OH)_2OCH_3$.



X. Physiological Action of Coumarins

Coumarins have been found to be physiologically effective for animals as well as men. Levaditti, Ellinger, Bergstrom, Rai, and Trendenburg have done the main work in this field. A collective bibliography of the relevant literature is available in E. Merck's *Jahresbericht* (262).

It has been observed that coumarin acts as a narcotic for rabbits, frogs, earthworms, and many other animals. It is a sedative and hypnotic for mice. In men as well as dogs its toxic action is predominant. A dose of about 5 g. kills a sheep; the fatal dose for horses and cattle is about 40 g.

Wasicky has investigated the action of naturally occurring coumarins such as pimpinellin, peucedanin, and ostruthin on the mouse, rat, and guinea pig. They have been found to possess a little toxicity. It was also observed that they promote the intestinal absorption of other substances. Priess, Rost, and Sieburg have studied the action of natural coumarins on fish. Incidental to their purely chemical work on natural coumarins, Späth and Kuffner have carried out a number of experiments on fresh-water fish (*Lebistes reticulatus*). They found that these coumarins are highly effective substances in spite of the low concentration of solutions employed (owing to the fact that most of them are sparingly soluble). Initially they are strong stimulants but then the action becomes moderate. Fish gradually lose their balance, and remain steady or swim on their backs; movement is then suspended, and finally they die. The concentration of the dose by which the lethal effect set in after some hours was decidedly dependent on the constitution of the coumarin used. Whereas coumarin itself was first lethal in a concentration of 1 g. in 6800 cc. of water, the same effect was observed for the methyl ether of alloimperatorin in a concentration of 1 in 100,000. The absolute quantity of the coumarins which produced the effect on the fish used in these experiments was extraordinarily small. Altogether forty coumarins have been tested. Many of them show a poisonous effect like that of picrotoxin. The hydroxycoumarins have been found to be less effective, though toxicity increases considerably on methylation.

Coumarin, 3-chlorocoumarin, and particularly angelicin show a strong narcotic action on fish. In about 30 to 100 sec. after the administration of the dose, the fishes turned on their backs, remained without any recognizable injury for about 12 hr., gave response to stimulus when knocked, but again returned to their normal positions in fresh water.

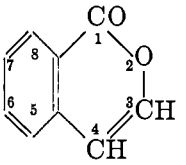
For human beings, coumarin has a slight toxic effect. The first dose, to the extent of 4 g., produces the symptoms of illness and weakness. It has no definite injurious effect on the heart; it checks the reactivity of the sympathetic nerves and paralyzes the flat muscles. Dihydrocoumarin, *o*-hydroxyphenylpropyl alcohol, and chroman have a narcotic action. Werder has synthesized over one hundred derivatives of coumarin-3-carboxylic acids. (These acids have not yet been found to occur in the vegetable kingdom.) He has investigated their utility as medicines. They are sedative in small doses and hypnotic in large doses. Among the derivatives of these acids, the diethylamide has proved to be a good drug in general nervous diseases and in various neurasthenic and hysterical ailments.

Mannich has found that some hydroxycoumarins possessing the power of absorbing ultraviolet light are extensively used as medicinals in skin diseases. Recently β-methylesculetin has been used as an expectorant.

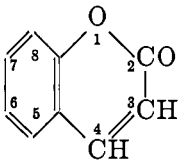
Asai (10) has published an interesting investigation on the action of daphnin for plants. He has shown that the leaves of the plant *Daphne odora* Thu. contain varying quantities of daphnin according to the period of vegetation. The falling leaf-buds contain 21–7 per cent of daphnin (on the basis of the dried material), while the developed buds contain only 6–7 per cent; the value finally declines to 1–3 per cent and remains constant until the leaves fall. Asai concludes that daphnin in the plant plays the important rôle of protecting the plant from the harmful effects of the short-wave radiations.

XI. Isocoumarins and Thiocoumarins

Isocoumarins, the lactones of benzenecarboxylic acids with a hydroxylated side chain unsaturated in the β-position, are isomeric with coumarins, the lactones of *o*-hydroxycinnamic acids.

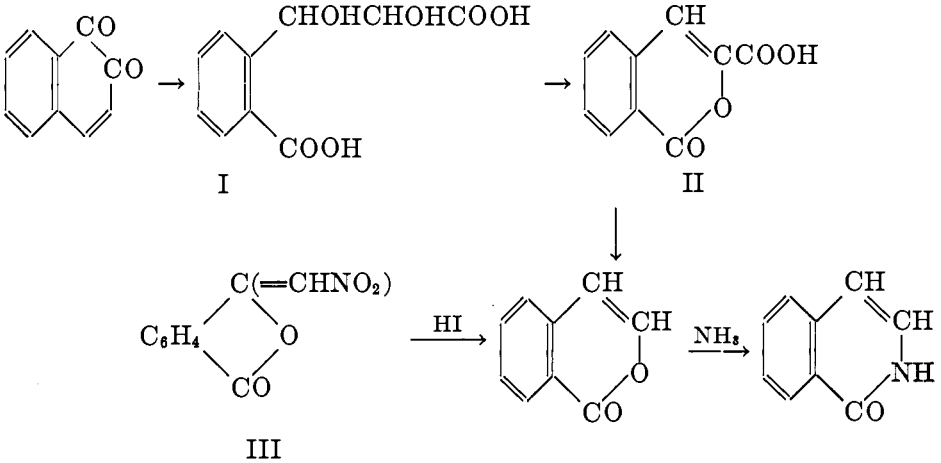


Isocoumarin



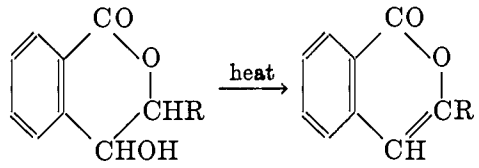
Coumarin

There is hardly any general method for the synthesis of isocoumarins, yet a good amount of work has been carried out and a number of isocoumarin derivatives have been synthesized. Bamberger and his coworkers (21, 22) obtained isocoumarin from β-naphthoquinone by oxidation with bleaching powder; *o*-carboxyphenylglyceric acid (I) was formed, which on heating with hydrochloric acid gave isocoumarin-3-carboxylic acid (II), the silver salt of which when heated yielded isocoumarin. Working along similar lines, Zincke (271) also obtained isocoumarin. Gabriel (90) synthesized isocoumarin in small quantity from nitromethylenephthalide (III) by boiling it with hydriodic acid.



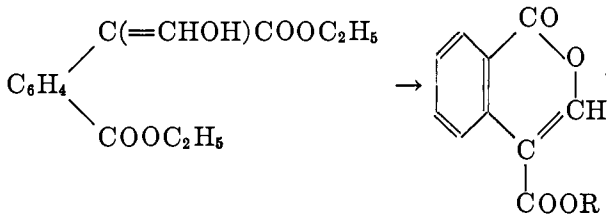
Isocoumarins are useful materials for synthesizing isocarbostyrils, since on treatment with ammonia, the oxygen of the heterocyclic ring is easily replaced by the =NH group.

Jowett and Pyman (112), during the course of their investigations on the physiological action and chemical constitution of tropeines, synthesized isocoumarincarboxyltropeine in a manner analogous to that of Bamberger.



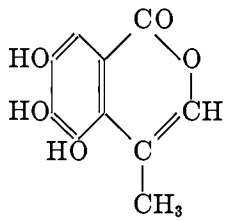
(R = $-COC_8H_{14}ON$)

Dieckmann and Meiser (80) obtained ethyl isocoumarin-4-carboxylate and its free acid by heating ethyl hydroxymethylenehomophthalate:

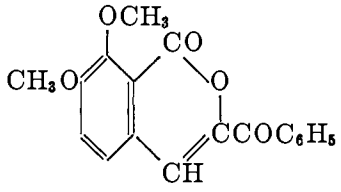


(R = C_2H_5 or H)

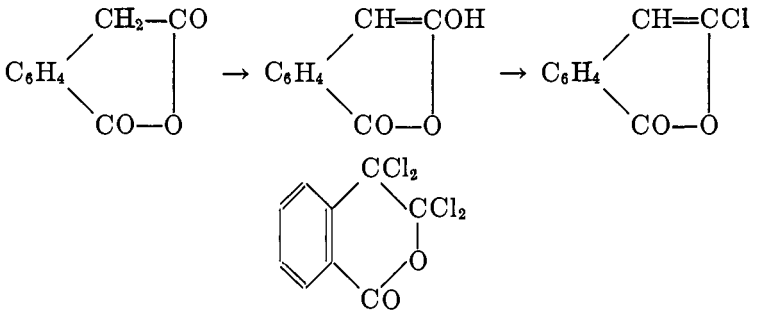
Fritsch (89) synthesized trihydroxymethylisocoumarin from gallacetol, the condensation product of gallic acid and chloroacetone, by treating it with concentrated sulfuric acid.



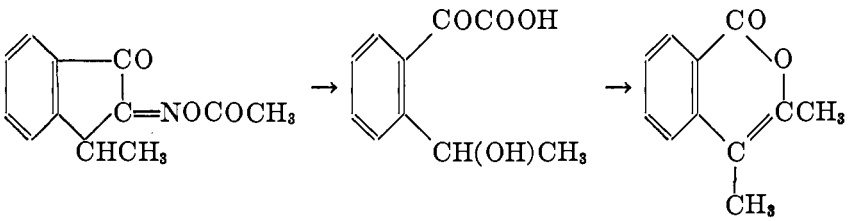
Bain, Perkin (Jr.), and Robinson (13) tried to develop a general method of isocoumarin synthesis depending upon the hydrolysis of the condensation product of hippuric acid with *o*-aldehydo acids, using acetic anhydride as condensing agent, but the hydrolysis did not occur in the manner expected. However, they were able to obtain 3-benzoyl-7,8-dimethoxyisocoumarin by the alkaline hydrolysis of *ω*-opianoylacetophenone:



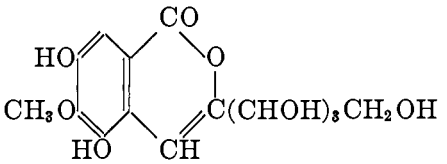
Davies and Poole (53), during their studies on homophthalyl chloride, obtained 3-chloroisocoumarin and 3,3,4,4-tetrachloro-3,4-dihydroisocoumarin by the action of phosphorus pentachloride on homophthalic acid, the explanation of its production being the existence of homophthalic anhydride in the enolic form.



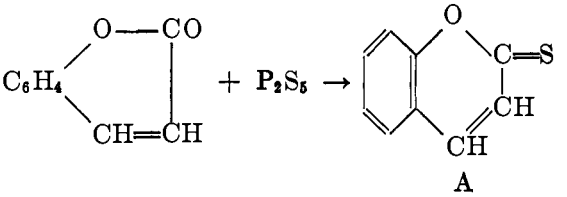
By the action of alkali on acetylated or benzoylated 3-methylindan-1,2-dione oxime, Heller (98) obtained an acid which on treatment with acetic anhydride and sodium acetate gave 3,4-dimethylisocoumarin.



A characteristic isocoumarin derivative called berganin was isolated by Tschitschibabin (259) from the root stems of various members of the saxifrage family. The following formula has been proposed for it:

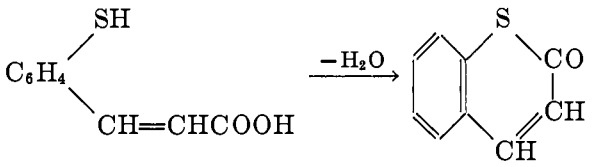


If either of the two oxygen atoms of the heterocyclic ring of the coumarin derivative is replaced by a sulfur atom, a thiocoumarin is formed. Tiemann (255) heated a mixture of coumarin and phosphorus pentasulfide at 120°C. and isolated thiocoumarin (A):



A

Aldringen (11) extended this reaction to several coumarins and obtained similar thiocoumarins. Clayton (49) prepared various thiocoumarins in a similar manner. Chmelewski and Friedlander (46) synthesized *o*-thiolcinnamic acid and dehydrated it to thiocoumarin (B).



B

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