Organic Reactions

VOLUME VII

PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able

to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

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CHAPTER 1

THE PECHMANN REACTION

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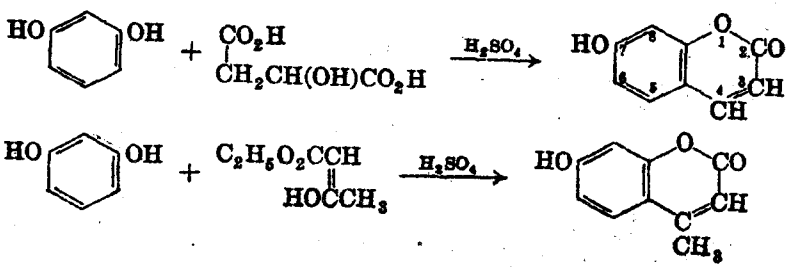
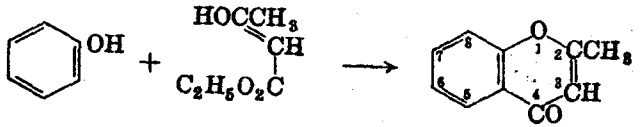
INTRODUCTION

H. v. Pechmann found that coumarin derivatives are formed when malic acid [1] or β-ketonic esters [2] are condensed with phenols in the presence of concentrated sulfuric acid. This reaction, which is commonly known as the Pechmann reaction, has found extensive application.



Simonis and his co-workers [3,4,5] used phosphorus pentoxide as the condensing agent in place of sulfuric acid and demonstrated that with the same reactants chromones rather than coumarins resulted. It was



shown later, however, that chromones were not always the reaction products. The condensation of a phenol and β-ketonic ester in the presence of phosphorus pentoxide is sometimes called the Simonis reaction,

[1] v. Pechmann, *Ber.*, **17**, 929 (1884).
[2] Pechmann and Duisberg, *Ber.*, **16**, 2119 (1883).
[3] Petschek and Simonis, *Ber.*, **46**, 2014 (1913).
[4] Simonis and Lehmann, *Ber.*, **47**, 692 (1914).
[5] Simonis and Remmert, *Ber.*, **47**, 2229 (1914).

but it is actually merely a variation of the Pechmann reaction and will be so considered in this chapter. Other condensing agents that have been used are phosphorus oxychloride, phosphoric acid, zinc chloride, aluminum chloride, hydrogen chloride, ferric chloride, stannic chloride, titanic chloride, sodium acetate, sodium ethoxide, and boric anhydride.

By condensing appropriately substituted phenols and β-ketonic esters, coumarins can be synthesized with substituents either in the benzene nucleus or in the heterocyclic ring or in both. These compounds can then be used for the preparation of other products like coumarino-α-pyrones, coumarino-γ-pyrones, furocoumarins, chromenes, coumarones, and 2-acylresorcinols.[6] The Pechmann reaction has also been employed in the syntheses of several naturally occurring coumarins [6,7] and in the investigations of natural products like rotenone [8] and cannabinol.[9,10]

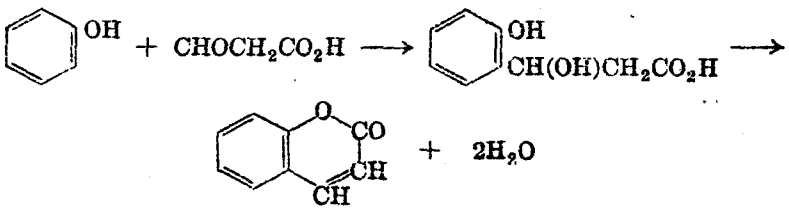
The course of this reaction depends on all of the three factors: the nature of the phenol, the nature of the β-ketonic ester, and the condensing agent.

MECHANISMS OF THE REACTIONS

Condensation of Malic Acid with Phenols. The condensation of malic acid with phenols takes place according to Pechmann [1] in three stages. The malic acid is first converted into malonaldehydic acid and formic acid, which is decomposed into water and carbon monoxide.

$$HO_2CCH(OH)CH_2CO_2H \rightarrow HCO_2H + CHOCH_2CO_2H$$

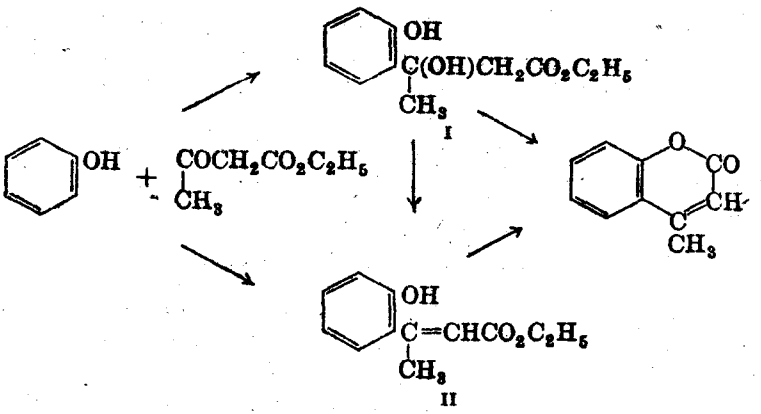
In the second stage, the union of the aldehyde with the phenol results in the formation of an unstable addition product. Two molecules of water are then eliminated, and the coumarin derivative is formed. Malonaldehydic acid contains a carbonyl group in the β position and resembles ethyl acetoacetate in its reaction with a phenol to give a coumarin.



[6] Sethna and Shah, *Chem. Revs.*, **36**, 30 (1945).
[7] Späth, *Ber.*, **70A**, 83 (1937).
[8] Bridge, Crocker, Cubin, and Robertson, *J. Chem. Soc.*, **1937**, 1530.
[9] Ghosh, Todd, and Wilkinson, *J. Chem. Soc.*, **1940**, 1121.
[10] Adams and Baker, *J. Am. Chem. Soc.*, **62**, 2405 (1940).

Condensation of β-Ketonic Esters with Phenols. To explain the formation of coumarins from β-ketonic esters and phenols, Pechmann and Duisberg[2] suggested that the reactive hydrogen of the phenol in the *ortho* position to the hydroxyl group adds to the carbonyl of the β-ketonic ester to give an intermediate hydroxy ester (I). Ring closure may then take place with the elimination of a molecule of water and one of ethanol.

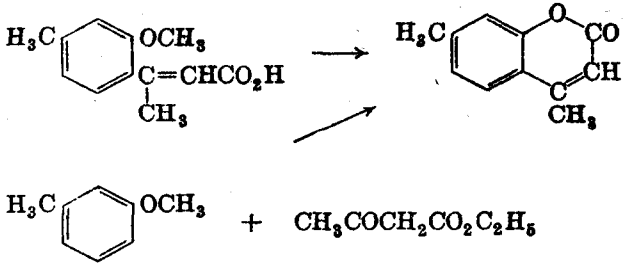
Ahmad and Desai[11] have pointed out that the effectiveness of such condensations depends on the reactivity of the hydrogen in the *ortho*



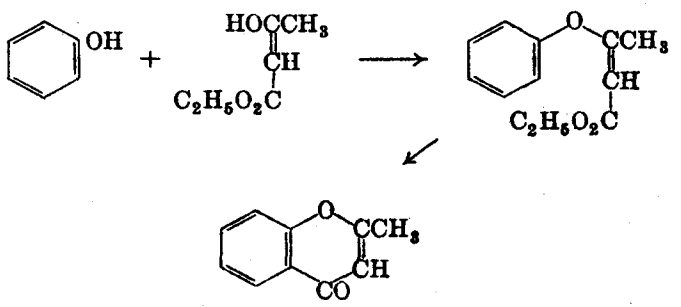
position to the hydroxyl group and on the substituents in the β-ketonic ester. The feeble tendency of phenol itself to condense is enhanced by the presence of electron-donating groups such as CH_3, OH, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, and halogens in the *meta* position to the hydroxyl group but is depressed or almost eliminated by electron-attracting groups such as NO_2, SO_3H, CO_2H, CO_2CH_3, $COCH_3$, CN, and CHO in the same position.[12] Since no intermediates have been isolated this course for the reaction is purely speculative.

A slightly different view has been advanced by Robertson and his co-workers.[13] They observed that 2-methoxy-β,4-dimethylcinnamic acid was converted into 4,7-dimethylcoumarin in the presence of 86% sulfuric acid and, further, that *m*-tolyl methyl ether and the dimethyl ether of resorcinol gave rise to 4,7-dimethylcoumarin and 7-methoxy-4-methylcoumarin, respectively. From this experimental evidence they conclude that the cinnamic acid derivative (II) is formed as an intermediate product.

[11] Ahmad and Desai, *Proc. Indian Acad. Sci.*, **6A**, 6 (1937) [*C. A.*, **32**, 559 (1938)].
[12] Desai and Ekhlas, *Proc. Indian Acad. Sci.*, **8A**, 567 (1938) [*C. A.*, **33**, 3356 (1939)].
[13] Robertson, Waters, and Jones, *J. Chem. Soc.*, 1932, 1681.



Two different mechanisms for chromone formation have been proposed. Robertson and his co-workers suggest that the first stage in the reaction results in a phenoxy acid (or its ester) by the interaction of the enolic form of the ester and phenol with the removal of a molecule of water. The phenoxy derivative then undergoes ring closure to a chromone. In support of this mechanism they cite the synthesis of

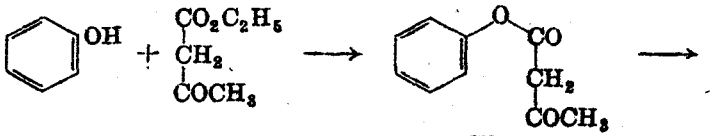


chromones from phenoxyfumaric acid and β-phenoxycinnamic acid by Ruhemann and co-workers.[14]

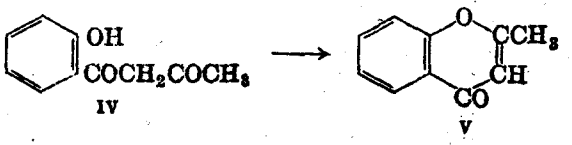
According to Ahmad and Desai,[11] in the formation of chromones, the reactive hydrogen of the phenolic hydroxyl reacts with the ethoxyl of the β-ketonic ester to give an aryl ester of the acid (III). This assumption is based on the evidence that only those phenols that do not contain a reactive hydrogen *ortho* to the hydroxyl group give chromones in the presence of phosphorus pentoxide as condensing agent. The aryl ester then undergoes an isomeric change analogous to the Fries migration forming an *o*-hydroxybenzoylacetone (IV) which is dehydrated to the chromone derivative (V). They assume the transformation to be possible in view of the work of Schönberg and Mustafa[15] on Fries rearrangements with phosphorus pentoxide. They suggest also that the specific action of phosphorus pentoxide is to facilitate the formation

[14] Ruhemann and co-workers, *J. Chem. Soc.*, **77**, 984, 1119 (1900); **79**, 470, 918 (1901).
[15] Schönberg and Mustafa, *J. Chem. Soc.*, **1943**, 79.

of III or IV or both since the conversion of IV into V may be accomplished with the help of any dehydrating agent. The formation of the



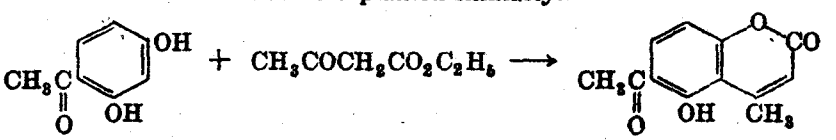
III



IV V

intermediate diketone IV in the syntheses of chromones by the Kostanecki acylation of *o*-hydroxyketones has been proved by Baker.[16]

Formation of 5-Hydroxycoumarin Derivatives in Presence of Anhydrous Aluminum Chloride. The formation of 5-hydroxycoumarin derivatives in the condensations of resacetophenone, 4-nitroresorcinol, and methyl β-resorcylate in preference to the 7-hydroxycoumarin derivatives is obviously due to the greater reactivity of the usually inaccessible 2-position of the resorcinol nucleus in these compounds. Shah and Shah[17] have explained this on the basis of chelation between the hydroxyl group and the *ortho*-substituted group, thus fixing the double bonds.[18,19,20] The point of attack is consequently the carbon atom joined by a double bond to that bearing the other hydroxyl group; resacetophenone and ethyl acetoacetate condense with the formation of 5-hydroxy-6-acetyl-4-methylcoumarin. The formation of a 5-hydroxycoumarin from methyl β-resorcylate and 4-nitroresorcinol in the presence of aluminum chloride can be explained similarly.



Baker[19] believes that aluminum chloride may prevent chelation; but, since 5-hydroxycoumarins are formed mainly or exclusively in good yields in the above condensations, it appears that this reagent not only fails to prevent chelation but may even promote it, for other condensing

[16] Baker, *J. Chem. Soc.*, **1933**, 1381.
[17] Shah and Shah, *J. Chem. Soc.*, **1935**, 1424.
[18] Mills and Nixon, *J. Chem. Soc.*, **1930**, 2510.
[19] Baker, *J. Chem. Soc.*, **1934**, 1684.
[20] Baker and Lothian, *J. Chem. Soc.*, **1935**, 628.

agents generally produce derivatives of 7-hydroxycoumarin. This view also finds support in the work on the formylation of methyl β-resorcylate[21] and 4-acylresorcinols;[22,23] the Gattermann reaction in the presence of anhydrous aluminum chloride in dry ether leads to formylation in the 2 position, in the case of resacetophenone yielding 2-formylresacetophenone.

SCOPE AND LIMITATIONS

The reactivity of the various simple and substituted phenols and β-ketonic esters in the Pechmann reaction, with sulfuric acid as the condensing agent, will be discussed first, and the role of the condensing agents second.

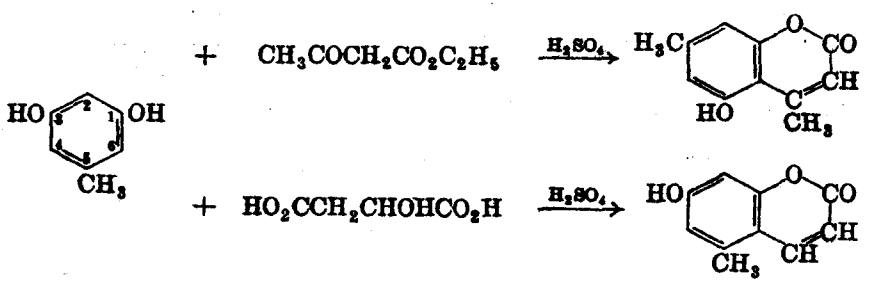
Reactivity of Phenols. It is found that, of the simple mono-, di-, and tri-hydric phenols, resorcinol is the most reactive, and it condenses with many substituted and cyclic β-ketonic esters. Almost equal in reactivity are phloroglucinol, α-naphthol, and pyrogallol. Phenol, quinol, and β-naphthol, however, usually give low yields of products. Phenol, for example, gives only about a 3% yield of 4-methylcoumarin on condensation with ethyl acetoacetate in the presence of sulfuric acid,[24] and it does not condense at all with many other β-ketonic esters. Catechol does not condense even with ethyl acetoacetate.

Among the substituted phenols it is found that the reactivity depends both on the nature and on the position of the substituent in the phenol. Alkyl groups in general have very little inhibiting effect in the Pechmann reaction; halogens exert somewhat more. When substituents like the nitro and the carboxyl groups are present, the reactions may not take place at all.[25,26] This is exemplified by the non-reactivity of *o*-, *m*-, or *p*-nitrophenol and simple phenol carboxylic acids with ethyl acetoacetate and other β-ketonic esters. The rate and degree to which a coumarin is produced depend, however, on the position of the substituent. *m*-Cresol condenses very readily with ethyl acetoacetate and a number of other β-ketonic esters,[27,28] *p*-cresol less readily,[2,28] and *o*-cresol not at all, even with ethyl acetoacetate.[29] *m*- and *p*-Chlorophenols react with ethyl acetoacetate, but *o*-chlorophenol does not react.[25] *m*-Dimethylaminophenol condenses with acetonedicarboxylic acid, but the *ortho* and *para*

[21] Shah and Laiwala, *J. Chem. Soc.*, **1938**, 1828.
[22] Shah and Shah, *J. Chem. Soc.*, **1939**, 132.
[23] Shah and Shah, *J. Chem. Soc.*, **1940**, 245.
[24] Pechmann and Kraft, *Ber.*, **34**, 421 (1901).
[25] Clayton, *J. Chem. Soc.*, **93**, 2016 (1908).
[26] Dey, *J. Chem. Soc.*, **107**, 1606 (1915).
[27] Fries and Klostermann, *Ber.*, **39**, 871 (1906).
[28] Fries and Klostermann, *Ann.*, **362**, 1 (1908).
[29] Chakravarti, *J. Indian Chem. Soc.*, **9**, 31 (1932).

compounds are inert.[26] Thus in many monohydric phenols a substituent in the *ortho* position has the maximum inhibiting effect, less if the same substituent is in the *para* position, and least when it is in the *meta* position.

The influence of substituents in the resorcinol nucleus on the Pechmann reaction has been investigated. In molecules where substituents in the 4 position cause the reaction to take place with some difficulty, the same substituents in the 2 position have less effect. Resorcinols with alkyl groups in the 2 or 4 position react as readily as resorcinol. Even 4-hexadecylresorcinol condenses smoothly with ethyl acetoacetate in the presence of sulfuric acid.[30] Alkyl groups in the 5 position change the course of the reaction, and, instead of the 7-hydroxycoumarin derivatives, the 5-hydroxy isomers are obtained; an exception is in the condensation with malic acid. Thus orcinol [26,31–35] and other 5-alkylresorcinols [36–38] with ethyl acetoacetate and other β-ketonic esters give 5-hydroxycoumarin derivatives. Orcinol with malic acid gives a 7-hydroxycoumarin.[39,40,*]



4-Chlororesorcinol condenses smoothly with a number of β-ketonic esters like ethyl α-alkylacetoacetates, ethyl benzoylacetate, and diethyl

[30] Chudgar and Shah, *J. Univ. Bombay*, **12**, Pt. 3, 18 (1944) [*C. A.*, **39**, 4078 (1945)].

[31] Krishnaswamy, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, **19A**, 5 (1944) [*C. A.*, **39**, 1153 (1945)].

[32] Pechmann and Hancke, *Ber.*, **34**, 354 (1901).

[33] Chakravarti, *J. Indian Chem. Soc.*, **8**, 407 (1931).

[34] Shah and Shah, *J. Indian Chem. Soc.*, **19**, 481 (1942).

[35] Kotwani, Sethna, and Advani, *Proc. Indian Acad. Sci.*, **15A**, 441 (1942) [*C. A.*, **37**, 624 (1943)].

[36] Russell, Todd, Wilkinson, Macdonald, and Woolfe, *J. Chem. Soc.*, **1941**, 169.

[37] Russell, Todd, Wilkinson, Macdonald, and Woolfe, *J. Chem. Soc.*, **1941**, 826.

[38] Adams, Loewe, Jelinek, and Wolff, *J. Am. Chem. Soc.*, **63**, 1971 (1941).

[39] Pechmann and Welsh, *Ber.*, **17**, 1646 (1884).

[40] Sastry, *J. Indian Chem. Soc.*, **19**, 403 (1942).

* 7-Hydroxy-4,5-dimethylcoumarin, which cannot be obtained by the direct condensation of orcinol with ethyl acetoacetate, has been prepared by the decarboxylation of 7-hydroxy-4,5-dimethylcoumarin-8-carboxylic acid formed by the condensation of *p*-orsellinic acid with ethyl acetoacetate. Sethna and Shah, *J. Indian Chem. Soc.*, **17**, 211 (1940).

acetosuccinate, and with acetonedicarboxylic acid.[41,42] 4-Bromoresorcinol reacts similarly.[43] The condensation of resorcinols with halogen substituents in the 2 and 5 positions has not been studied.

2-Nitroresorcinol forms coumarins with ethyl acetoacetate and ethyl α-methylacetoacetate but not with higher α-alkylacetoacetates.[41] 4-Nitroresorcinol, however, does not condense with ethyl α-methylacetoacetate.[44] It is thus obvious that the nitro group has a greater inhibiting effect on the reaction in the 4 position than in the 2 position.

Compounds with a carbomethoxyl group in the 4 position react more readily than those with a carboxyl group; β-resorcylic acid will condense with ethyl acetoacetate,[45] but methyl β-resorcylate reacts smoothly not only with ethyl acetoacetate but also with ethyl α-alkylacetoacetates and several other β-ketonic esters.[42,45-48] This suggests that coumarin carboxylic acids with a carboxyl group in the benzene nucleus may be prepared preferably through the ester of the phenolic acid and subsequent hydrolysis of the coumarin ester. The only example of the use of resorcinol derivatives with the carboxyl or carbomethoxyl groups in the 2 and 5 positions is that of 2-resorcylic acid, which condenses smoothly with ethyl acetoacetate.[49]

An acyl group in the 4 position completely prevents the Pechmann reaction, for resacetophenone does not react with ethyl acetoacetate in the presence of sulfuric acid.[50] 2-Acyl- or 2-aroyl-resorcinols present no such difficulty, for 2-acetyl-[17] and 2-benzoyl-resorcinol [54] with ethyl acetoacetate give an acetyl- and benzoyl-coumarin, respectively. 4-Ethyl-2-acetylresorcinol also condenses with several ethyl α-alkylacetoacetates and with ethyl benzoylacetate.[55]

[41] Chakravarti and Ghosh, *J. Indian Chem. Soc.*, **12**, 622 (1935).
[42] Shah and Shah, *J. Indian Chem. Soc.*, **19**, 486 (1942).
[43] Chakravarti and Mukerjee, *J. Indian Chem. Soc.*, **14**, 725 (1937).
[44] Chakravarti and Banerjee, *J. Indian Chem. Soc.*, **14**, 37 (1937).
[45] Shah, Sethna, Banerjee, and Chakravarti, *J. Indian Chem. Soc.*, **14**, 717 (1937).
[46] Sethna and Shah, *J. Indian Chem. Soc.*, **17**, 37 (1940).
[47] Sethna and Shah, *J. Indian Chem. Soc.*, **15**, 383 (1938).
[48] Desai, Gaitonde, Mehdi Hasan, and Shah, *Proc. Indian Acad. Sci.*, **25A**, 345 (1947) [*C. A.*, **42**, 1913 (1948)].
[49] Limaye and Kulkarni, *Rasayanam*, **1**, 251 (1943) [*C. A.*, **38**, 4264 (1944)].
[50] Agarwal and Dutt, *J. Indian Chem. Soc.*, **14**, 109 (1937), reported the formation of coumarin derivatives in the condensation of resacetophenone with malic acid, ethyl acetoacetate, and ethyl α-alkylacetoacetates in the presence of sulfuric acid. This work has been completely disproved by a number of workers, and it has been shown that condensation does not take place. See refs. 51, 52, and 53.
[51] Limaye, *Rasayanam*, **1**, 101 (1937) [*C. A.*, **32**, 2099 (1938)].
[52] Chakravarti and Chakravarty, *Science and Culture*, **3**, 244 (1937) [*C. A.*, **32**, 1255 (1938)].
[53] Sethna, Shah, and Shah, *J. Chem. Soc.*, **1938**, 228.
[54] Limaye, *Ber.*, **67**, 12 (1934).
[55] Desai and Mavani, *Proc. Indian Acad. Sci.*, **14A**, 100 (1941) [*C. A.*, **36**, 1599 (1942)].

The capacity of hydroquinone to undergo the Pechmann reaction is not great. When a chlorine atom is present in the hydroquinone the reaction takes place even less readily, and the presence of a bromine atom or acetyl group prevents the reaction completely. On the other hand, greater reactivity is observed when a methyl or ethyl group is substituted in the hydroquinone. 2-Methyl- and 2-ethyl-hydroquinone form coumarins with ethyl benzoylacetate and ethyl α-alkylacetoacetates; but quinacetophenone and 2-bromohydroquinone do not condense even with ethyl acetoacetate, and 2-chlorohydroquinone reacts with difficulty. Hydroquinone, its 2-chloro- and 2-bromo-derivative, and quinacetophenone do not condense with ethyl benzoylacetate.[56]

Of the trihydroxy compounds, 4-ethylpyrogallol and ethyl pyrogallolcarboxylate condense readily with ethyl acetoacetate, ethyl α-alkylacetoacetates, and ethyl benzoylacetate. Gallic acid, its methyl and ethyl esters, pyrogallolcarboxylic acid, and gallacetophenone do not undergo the coumarin condensation with these same β-ketonic esters.[57]

Phloroglucinol and many of its derivatives, methylphloroglucinol,[58] dimethylphloroglucinol,[58] methyl phloroglucinolcarboxylate,[59] phloroacetophenone, and phlorobenzophenone give coumarins with ethyl acetoacetate. The reaction with other β-ketonic esters has not been studied.

1,2,4-Triacetoxybenzene and ethyl acetoacetate in the presence of 75% sulfuric acid condense to give 6,7-dihydroxy-4-methylcoumarin.[60] No condensation of a substituted 1,2,4-trihydroxybenzene with a β-ketonic ester has been reported.

α-Naphthol derivatives with chlorine or bromine in the 4 position react with ethyl α-alkylacetoacetates and other β-ketonic esters like ethyl benzoylacetate, diethyl acetonedicarboxylate, and diethyl acetosuccinate. 4-Bromo-α-naphthol appears to be less reactive than 4-chloro-α-naphthol.[61] In the condensation of 4-acetyl-, 4-propionyl-, and 4-butyryl-α-naphthol with β-ketonic esters, the acyl group is eliminated.[12] Substituted β-naphthols have not been studied.

Attempts to condense cyclohexanol and dimethyl dihydroresorcinol with acetonedicarboxylic acid did not succeed.[26]

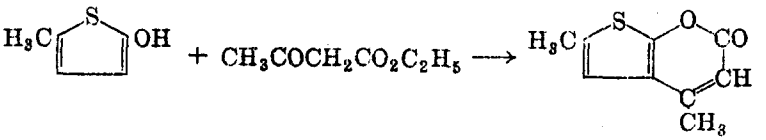
Certain miscellaneous compounds not included in the previous discussion have been condensed with malic acid and β-ketonic esters in the presence of sulfuric acid. Resorcinol and other polyhydroxyphenols

[56] Desai and Mavani, *Proc. Indian Acad. Sci.*, **15A**, 11 (1942) [*C. A.*, **36**, 6151 (1942)].
[57] Desai and Mavani, *Proc. Indian Acad. Sci.*, **15A**, 1 (1942) [*C. A.*, **36**, 6150 (1942)].
[58] Fujise and Maruyama, *J. Chem. Soc. Japan*, **55**, 1013 (1934) [*C. A.*, **29**, 4008 (1935)].
[59] Sethna, *J. Univ. Bombay*, **9** (pt. 3), 104 (1940) [*C. A.*, **35**, 6948 (1941)].
[60] Vliet, *Org. Syntheses*, **4**, 45 (1924).
[61] Chakravarti and Bagchi, *J. Indian Chem. Soc.*, **13**, 649 (1936).

will not react satisfactorily with two molecules of ethyl acetoacetate or malic acid simultaneously, but the pure hydroxycoumarins formed by the condensation of one molecule of ethyl acetoacetate or malic acid will react with a second molecule of ethyl acetoacetate or malic acid to produce coumarino-α-pyrones.[62, 63] The condensation of hydroxycoumarins with malic acid takes place more readily than with ethyl acetoacetate, though the condensation of many simpler aromatic hydroxy compounds with malic acid is more difficult than with ethyl acetoacetate. The dihydroxycoumarins derived from pyrogallol and ethyl acetoacetate will react with malic acid [63] but not with ethyl acetoacetate.

Hydroxychromones do not undergo condensation with malic acid.[64]

Hydroxythiophene derivatives react with β-ketonic esters to yield thiocoumarin derivatives.[65, 66]



Reactivity of Malic, Maleic, and Fumaric Acids. The condensation of malic acid with phenols leads to coumarins which are unsubstituted in the pyrone ring. This procedure is therefore an alternative method for the synthesis of coumarins that are difficult to obtain by Perkin's method from *o*-hydroxy aromatic aldehydes. There are, however, limitations in the preparation of coumarins by this method: malic acid does not condense with many substituted phenols, and, when it does condense, the yields are often low and tarry products are obtained. Malic acid condenses only in the presence of sulfuric acid; other condensing agents fail.

Fumaric and maleic acids have been found to condense with *p*-cresol in the presence of sulfuric acid to give 6-methylcoumarin in good yield.[67, 68] The encouraging results in this condensation justify a more

[62] Rangaswami and Seshadri, *Proc. Indian Acad. Sci.*, **6A**, 112 (1937) [*C. A.*, **32**, 559 (1938)].

[63] Sen and Chakravarti, *J. Indian Chem. Soc.*, **6**, 793 (1929).

[64] Rangaswami and Seshadri, *Proc. Indian Acad. Sci.*, **9A**, 7 (1939) [*C. A.*, **33**, 4244 (1939)].

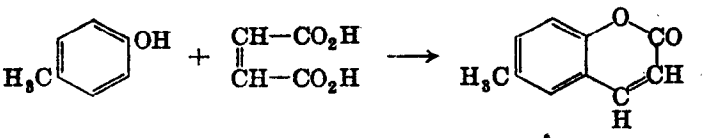
[65] Mentzer, Billet, Molho, and Dat Xuong, *Bull. soc. chim. France*, **12**, 161 (1945) [*C. A.*, **40**, 865 (1946)].

[66] Mentzer and Billet, *Bull. soc. chim. France*, **12**, 292 (1945) [*C. A.*, **40**, 2828 (1946)].

[67] Pondorff, Ger. pat. 338,737 (1921) [*C. A.*, **16**, 3488 (1922)].

[68] Thompson and Edee, *J. Am. Chem. Soc.*, **47**, 2556 (1925)

detailed investigation of the condensation of these acids with other phenols.



Reactivity of β-Ketonic Esters. Ethyl acetoacetate probably condenses in its enol form with the phenols. β-Ketonic esters with substituents likely to increase the enolization or stabilize the enolic form should therefore be more active than ethyl acetoacetate, and those with substituents that tend to decrease the enolization or lead to a less stable enol form should be less reactive. Substituents in a β-ketonic ester may be attached to the α-carbon atom or the γ-carbon atom, and they provide a means of obtaining coumarins with different substituents in the heterocyclic ring. Cyclic β-ketonic esters, and β-ketonic esters with heterocyclic rings, have also been condensed with phenols. The reactivities of these esters differ very widely.

Ethyl α-chloroacetoacetate has been condensed with a number of phenols to yield 3-chlorocoumarins.[26,32,46,69] The condensation with this ester is smooth and the reactions closely parallel those with ethyl acetoacetate. The corresponding α-bromo ester has not been studied.

In ethyl α-alkyl- and α-aryl-acetoacetates the reactivity varies with the nature of the α substituent. With methyl, ethyl, propyl, butyl, allyl, phenyl, and benzyl groups as α substituents the condensation with reactive phenols is satisfactory, but with less reactive phenols the yields are generally poor and the condensation may be inhibited completely. Thus with *m*-cresol the α-ethyl derivative of ethyl acetoacetate gives a poorer yield than the α-methyl derivative; α-propyl- and α-phenylacetoacetates do not react.[27,28] Ethyl α-allylacetoacetate, however, condenses with *m*-cresol easily.[70] β-Naphthol does not react with ethyl α-ethyl-, α-propyl-, or α-isopropyl-acetoacetate.[71] Ethyl α-(α-hydroxy-β,β,β-trichloroethyl)acetoacetate with various phenols gives satisfactory results.[72,73,74] Thus the presence of a heavy α substituent like —CH(OH)CCl_3 does not appreciably inhibit the Pechmann reaction and has less effect than an α-ethyl substituent.

The Pechmann reaction of diethyl acetosuccinate and diethyl aceto-

[69] Chakravarti and Banerjee, *J. Indian Chem. Soc.*, **13**, 619 (1936).
[70] Naik, Desai, and Desai, *J. Indian Chem. Soc.*, **6**, 83 (1929).
[71] Chakravarti, *J. Indian Chem. Soc.*, **9**, 389 (1932).
[72] Kulkarni, Alimchandani, and Shah, *J. Indian Chem. Soc.*, **18**, 113 (1941).
[73] Kulkarni, Alimchandani, and Shah, *J. Indian Chem. Soc.*, **18**, 123 (1941).
[74] Shah and Kulkarni, *J. Univ. Bombay*, **10** (pt. 3), 86 (1941) [*C. A.*, **36**, 3796 (1942)]

glutarate, which have $—CH_2CO_2C_2H_5$ and $—CH_2CH_2CO_2C_2H_5$ as substituents in the α position, with various phenols has been systematically studied. Diethyl acetosuccinate condenses with very reactive phenols and also with *m*-cresol, 2-acetyl, 2-benzoyl-, and 4-chloro-resorcinol, and 4-chloro-α-naphthol, but not with phenol, *o*-cresol, *p*-cresol, hydroquinone, catechol, 4-chlorophenol, β-resorcylic acid, resacetophenone, or gallic acid.[34, 42, 75, 76] The presence of a carbethoxyalkyl group as a substituent in the β-ketonic ester results in a molecule of greater reactivity than one in which an alkyl substituent is present; diethyl acetosuccinate is as reactive as or even more reactive than the corresponding ethyl α-alkylacetoacetates. Similar observations have been made with diethyl α-acetoglutarate.[77] With substituents such as cyano or aceto the condensation takes place with the elimination of the group and the formation of the unsubstituted coumarin.[32, 46, 78]

Other α-substituted ethyl acetoacetates that have been studied are ethyl *o*-carboxybenzylacetoacetate,[79] ethyl phthalylacetoacetate,[79] ethyl benzoylacetoacetate,[32, 46] diethyl acetylmalonate,[32] and ethyl diacetylacetate.[32] The first two have been condensed with resorcinol and a few other reactive phenols in the presence of dry hydrogen chloride in acetic acid to form coumarin derivatives. When ethyl benzoylacetoacetate and ethyl diacetylacetate react with resorcinol, the acetyl group is removed during condensation and the same coumarins result as are formed with ethyl benzoylacetate and ethyl acetoacetate, respectively. Diethyl acetylmalonate reacts with the loss of a carbethoxyl group to give the same coumarin as that obtained by the use of ethyl acetoacetate.

A number of β-ketonic esters with groups other than methyl in the γ position have been condensed with phenols. Ethyl butyroacetate,[35] which may be considered as ethyl γ-ethylacetoacetate, and ethyl γ-phenylacetoacetate [80, 81] react with resorcinol, orcinol, pyrogallol, phloroglucinol, and α-naphthol to give 4-ethyl- and 4-benzyl-coumarin derivatives, respectively, but they do not condense with phenol, β-naphthol, hydroquinone, *m*-cresol, methyl β-resorcylate, or resacetophenone. A γ substituent thus reduces the reactivity.

Acetonedicarboxylic acid and its diethyl ester have been condensed with a number of simple and substituted phenols.[26, 46, 82] Citric acid gives

[75] Banerjee, *J. Indian Chem. Soc.*, **8**, 777 (1931).
[76] Dey and Sankarnarayan, *J. Indian Chem. Soc.*, **8**, 817 (1931).
[77] Shah and Shah, *Ber.*, **71**, 2075 (1938).
[78] Held, *Compt. rend.*, **116**, 720 (1893).
[79] Bülow, *Ber.*, **38**, 474 (1905).
[80] Sonn and Litten, *Ber.*, **66**, 1512 (1933).
[81] Kotwani, Sethna, and Advani, *J. Univ. Bombay*, **10** (pt. 5), 143 (1942) [*C. A.*, **37**, 623 (1943)].
[82] Burton and Pechmann, *Ann.*, **261**, 166 (1891).